ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Gudair Emulsion for Injection for Sheep and Goats

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Gudair Emulsion for Injection for Sheep and Goats
Applicant	CZ Veterinaria S.A. La Relva Porriño (Pontevedra) 36400 Spain
Active substance(s)	Inactivated *Myobacterium paratuberculosis* (strain 316F)
ATC Vetcode	QI04AB (sheep) AI03AB01 (goats)
Target species	Sheep and goats
Indication for use	For the active immunisation of sheep and goats to stimulate cell-mediated and humoral immunity against *M. avium* subspecies paratuberculosis infection, as an aid in the control of Johne's disease in those species. This is a Limited Marketing Authorisation. A full set of efficacy data are not available for this product. No information on onset of immunity or duration of immunity is available for this product.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Limited application in accordance with the Veterinary Medicines Regulations.

I. SCIENTIFIC OVERVIEW

Gudair is an inactivated bacterial vaccine for the immunisation of sheep and goats against paratuberculosis disease (Johne's disease). Johne's disease is a chronic, untreatable intestinal disease which affects mainly sheep, goats, cattle, deer and camelids.

Gudair is indicated for use in sheep and goats to stimulate immunity against paratuberculosis infection. As the product has a Limited Marketing Authorisation a full set of efficacy data are not available.

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 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

The product contains inactivated *Mycobacterium paratuberculosis* (strain 316F) as active substance and the excipients marcol 52, montanide 103, montane 80, polysorbate 80, thiomersal and phosphate buffered saline.

The container/closure system consists of 30 ml of solution for injection packaged into Type II glass bottles, or alternatively 100 ml or 250 ml packaged into high density polyethylene (HDPE) bottles and all closed with a rubber nitrile stopper and aluminium seal. The particulars of the containers and controls performed are provided and conform to the regulation.

[1] SPC – Summary of Product Characteristics

The choice of the adjuvant, vaccine strain, inactivating agent and preservative 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. Process validation data on the product have been presented in accordance with the relevant European guidelines. The product is manufactured by preparing the *M. paratuberculosis* antigen from firstly the primary seed then the secondary seed in synthetic culture medium and inactivation of the antigen, before the vaccine is prepared by blending the antigen with the excipients and finally filling the vials.

C. Control of Starting Materials

The active substance is inactivated *Mycobacterium paratuberculosis*, an active substance not described in a Pharmacopoeia. Data on the active substance have been supplied in the form of in-house data. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with the relevant Ph. Eur. 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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control tests during production

The tests performed during production are described and the results of 3 consecutive manufacturing 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. The tests include in particular potency, viscosity, conductivity, appearance and sterility.

The demonstration of the batch to batch consistency is based on the results of three batches of finished product 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 active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A shelf life for the antigen of 24 months when stored at -30ºC has been established.

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. A shelf life of 2 years for the HDPE bottle and 3 years for the glass bottles, when stored between +2ºC and +8ºC, is supported.

The in-use shelf-life of the broached vaccine, 35 days, is supported by the data provided.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the product as packaged for sale:
  - HDPE bottle: 2 years
  - Glass bottle: 3 years
- Shelf life after first opening the immediate packaging: 35 days
- Store and transport between +2ºC and +8ºC.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one has been demonstrated in sheep and goats. One study injected 1ml of vaccine subcutaneously in 8 lambs 4-6 weeks old, and repeated the vaccination process 28 days later. This was compared to a control animal which received no injection. The lambs were monitored after the single dose and again after the repeated dose. After both injections local reactions occurred at the injection site in all lambs, with several lambs having ruptured abscesses 10-14 days after the injection. This occurred less often after the second injection.

An overdose study was also performed in sheep. Subcutaneous injections of 2 ml of vaccine were given to 8 lambs aged 3-6 weeks, with a ninth lamb not receiving any injections to act as control. No systemic effects were seen in any lambs, however injection site lesions developed in all treated lambs, and were roughly twice the size of lesions in lambs dosed with 1 ml of the vaccine.

A study assessing the safety of the vaccine in single dose, repeat dose and overdose was also performed in goats. Kids aged 3-9 weeks were divided into two groups of 5, one group received 1 ml of vaccine injected subcutaneously which was repeated with an interval of 28 days, whilst the other group received

one subcutaneous injection of 2 ml of vaccine. The results indicate that overdose led to an increase in body temperature 4 hours after vaccination whilst following repeat dose small elevations in temperature were indicated and no changes were seen after a single dose. All kids had injection site lesions after injection which increased in size up to day 28 and local lymph nodes were enlarged in some goats. Following the repeat dose 2 kids developed discharging lesions whilst the lesions in the overdosed kids were larger and 2 of 5 from this group also developed discharging lesions.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. The report concludes that overall goats are more reactive to the vaccine than sheep. However all reactions had disappeared or were negligible by 2 months post vaccination and no systemic effects were seen. Adequate warnings have been included in Section 4.6 Adverse Reactions in the SPC:

- The vaccine produces swelling at the injection site which gradually becomes a persistent, fibrous and cold nodule that does not affect the general health status of the animal. This event is very common. Nodule can be detected at 1-2 weeks post vaccination with medium size of approximately 2 cm in sheep and goats, reaching a mean maximum size of 3.5 cm in sheep and 4 cm in goats at 2 months post vaccination, decreasing until 1 year after vaccination. Occasionally, the diameter can reach values greater than 5 cm at 2 months after vaccination. Palpable lesions can be observed in the 20-25% of the sheep at 4 years post vaccination.
- Nodules can rupture and discharge.
- An average increase of body temperature in sheep can occasionally be observed varying between 0.5 and 1.0 °C. It lasted no longer than 48-96 hours.

No investigation of effect on reproductive performance was conducted because the product has a Limited Marketing Authorisation and the SPC includes the statement ‘The safety of the veterinary product has not been established during pregnancy or lactation’.

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 lacking in pharmacological activity. 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.

Field studies

Two field studies have been submitted. The first field trial involved three clinically diseased flocks of sheep, one disease free flock of sheep and one clinically diseased flock of goats and was conducted in Spain. Diseased sheep were aged

3-4 months, disease free sheep were aged 15-20 days and diseased goats were aged 3 and 10 months. Animals from each group were vaccinated with the product; a number of animals from each group received a competitor vaccine instead of Gudair. In all animals local reactions were seen which increased in size until up to 100 days post vaccination, in all but two animals nodules had reduced in size but were still visible one year after vaccination. No systemic reactions were observed and there was no statistically significant difference in body weight between animals vaccinated with either product.

A second field trial was conducted in Australia where 200 lambs, from 3 farms, were vaccinated with 1 ml Gudair, whilst a further 200 lambs were inoculated with 1 ml saline to act as controls. The lambs were all 1-4 months old and vaccination was administered subcutaneously behind the ear. General reactions were monitored the first day after the injection and then weekly, the size of local reactions was measured at 2, 6, 9, 12, 15 and 18 months post vaccination. Injection site lesions were observed in 50% of the vaccinated sheep 2 months post-vaccination, in 20-25% of vaccinates these persisted for at least 4 years. In the first 2 months after vaccination burst abscesses occurred at an incidence of 7%. A small but statistically significant reduction in weight gain was observed in vaccinates compared to control animals in the first 12 months, however there were not consistent differences in adult sheep.

The results of the field studies support the effects observed during laboratory studies. Some large local reactions were observed and adequate warnings have been included in the SPC.

Ecotoxicity

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 as Gudair is an inactivated vaccine, which requires no handling before administration, it poses minimal risk to the environment. 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

Gudair is an inactivated vaccine, administered subcutaneously, for immunisation of sheep and goats against Johne's disease. The product is indicated for single vaccination and the efficacy claim is to stimulate cell-mediated and humoral immunity against *M. avium* subsp. paratuberculosis infection, as an aid in the control of Johne's disease in those species.

The product has been granted a Limited Marketing Authorisation and a full set of efficacy data are not available for this product.

Laboratory Trials

Laboratory trials have been performed. Two studies were performed following the same protocol but one was in sheep and the other goats. In the studies lambs and kids, over 1 month old and free from paratuberculosis, were vaccinated with either Gudair, an experimental inactivated vaccine or a live control vaccine from the VLA Weybridge. There were 5 groups: 5 lambs received Gudair subcutaneously, 2 lambs received Gudair intramuscularly, 5 lambs received the experimental vaccine subcutaneously, 2 lambs received the experimental vaccine intramuscularly and 2 lambs received the live vaccine subcutaneously. There was no challenge. Blood samples were collected pre- and post-vaccination, and CMI (skin tests) were also performed at these times. The results indicate the vaccine stimulates an immune response similar to that obtained with the live vaccine, when administered by the subcutaneous route. The skin tests indicate the vaccine induces a strong CMI response and this suggests the Gudair vaccine could slow disease progression. The results indicate that Gudair is able to produce a strong and lasting immune response in both target species.

In a third study the effect of vaccination on the development of granulomatous lesions in sheep was investigated. Eight pairs of 15 day old twins were used, 1 twin received the Gudair vaccination via the subcutaneous route and the other twin was not vaccinated to act as the control. Two challenges were given on Day 50 post vaccination and then to only 2 lambs from each group on day 270 post vaccination. The challenge was *M avium* sub sp *paratuberculosis* and was administered orally. Three of the challenged lambs were sacrificed and histology was performed after the first challenge. Histology on the lambs showed that vaccinated animals had granuloma restricted to intestinal lymphoid tissue whilst non-vaccinates had spread of granulomatous lesions to other areas of intestinal wall. Therefore it was concluded that vaccination reduces the extent of the lesions and also modifies the type to regressive granulomatous lesions.

Field Trials

Field trials were performed. One field trial involved three clinically diseased flocks of sheep, one disease free flock of sheep and one clinically diseased flock of goats and was conducted in Spain. Diseased sheep were aged 3-4 months, disease free sheep were aged 15-20 days and diseased goats were aged 3 and 10 months. Animals from each group were vaccinated with the product; a number of animals from each group received a competitor vaccine instead of Gudair. The parameters studied were serology, CMI skin test and gamma interferon all tested post vaccination as well as serology being performed on day 0. The results showed all animals had seroconverted within one month of vaccination and 37 -75% were still positive a year post vaccination. No cases of paratuberculosis appeared in vaccinated animals in the 7 years after vaccination.

A second five year field trial was conducted in Australia where 200 lambs, from 3 farms, were vaccinated with 1 ml Gudair, whilst a further 200 lambs were inoculated with 1 ml saline to act as controls. The lambs were all 1-4 months old and vaccination was administered subcutaneously behind the ear. Older sheep with suspected OJD were put in with the trial animals and therefore presented a natural challenge. In this study the parameters observed were the humoral

response, CMI, mortality rate due to OJD and the presence of *M. paratuberculosis* in pooled and individual faeces. The results indicate that vaccination reduced mortalities as a result of the disease and there was a 90% reduction in sheep excreting *M. paratuberculosis.* Humoral and CTS testing indicated the vaccine stimulated a cell-mediated and humoral immune response whereas non-vaccinates had an increase in positive immune reactions thought to be due to the prevalence of OJD in control animals. The conclusion from this trial was that vaccinating youngstock with the product stimulates specific immune responses, significantly reduced OJD and *M. paratuberculosis* excretion, as well as protecting the economic life of the sheep.

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)