Veterinary Medicines Directorate

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

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Spirovac

PuAR correct as of 17/01/2018 when RMS was transferred to IE. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0284/001/MR
Name, strength and pharmaceutical form	Spirovac
Applicant	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE
Active substance	Inactivated *Leptospira borgpetersenii* serovar Hardjo
ATC Vetcode	QI02AB03
Target species	Cattle from 4 weeks of age.
Indication for use	For active immunisation - of cattle to reduce kidney colonisation and shedding of Leptospira borgpetersenii serovar Hardjo type hardjobovis to the extent that no viable organisms can be detected by culture in the urine of vaccinated animals after challenge; a 3 weeks onset of immunity and 12 months duration of protection have been demonstrated by challenge with Leptospira borgpetersenii serovar Hardjo type hardjobovis. - of cattle persistently infected with *Leptospira borgpetersenii* serovar Hardjo type hardjobovis: to reduce urinary shedding of *Leptospira borgpetersenii* serovar Hardjo type hardjobovis without clearance of renal colonisation; this effect appears 4 weeks post vaccination and its duration is unknown. The epidemiological significance of the reduced shedding has not been demonstrated. The vaccination may not prevent abortion in cows in which placental infection has already occurred.

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	Mutual Recognition application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	10 June 2009
Date product first authorised in the Reference Member State (MRP only)	20 April 1993
Concerned Member States for original procedure	Czech Republic France Germany Hungary Ireland Poland Slovakia Additional Member States added via Repeat Use, Mutual Recognition procedure. Belgium Bulgaria Romania Portugal

I. SCIENTIFIC OVERVIEW

The product is intended to treat cattle from 4 weeks of age for *Leptospira borgpetersenii* serovar Hardjo type hardjobovis. The inactivated vaccine 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[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.

[1] SPC – Summary of Product Characteristics.

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 *Leptospira borgpetersenii* serovar Hardjo at ≥2RP (ELISA Relative Potency), and the excipients aluminium hydroxide, thiomersal, formaldehyde, sodium chloride and water for injections. The container/closure system is comprised of 50 ml (25 dose) HDPE vials or 50 ml or 10 ml (5 doses) glass Type I vials, all with a chlorobutyl stopper and aluminium over seal.

The particulars of the containers and controls performed are provided and conform to the European Pharmacopoeia monograph. The choice of the adjuvant, vaccine strain, and inactivating agent 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 using conventional manufacturing techniques. The product is manufactured in accordance with the European Pharmacopoeia, and relevant European guidelines.

C. Control of Starting Materials

The active substance is inactivated *Leptospira borgpetersenii,* serovar Hardjo, manufactured in accordance with the principles of good manufacturing practice. Starting materials of non-biological origin used in production comply with Pharmacopoeial monographs. 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 guidelines, any deviations are adequately justified. 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 and 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.

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, and any deviation from these requirements is justified. The tests include in particular sterility, inactivation, thiomersal content, free formaldehyde, pH, safety in target species, identity, aluminium content and potency of the virus. The demonstration of the batch to batch consistency is based on the results of three 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 10 hours after first opening is supported by the data provided. The shelf-life of the product as package for sale is 2 years.

- Store and transport refrigerated (2°C – 8°C).
- Do not freeze.
- Protect from light.

III. SAFETY ASSESSMENT

H. Laboratory trials

The safety of the administration of an overdose in the target animal was demonstrated. Groups of young calves which were sero-negative to *Leptospira* Hardjo *bovis* at the start of the study were administered either two times the recommended dose or a diluent, (control group), via subcutaneous injection. Clinical observations, rectal temperatures and weight were recorded for both a number of days prior to vaccination and also post-vaccination. There was some local reaction in all vaccinated animals. Although the injection site reaction appeared to persist, this was only in the form of a hard nodule, and most swelling had disappeared from Day 3 onwards.

The safety of the administration of the repeated administration of one dose in the target animal was demonstrated. Groups of young calves which were sero-negative to *Leptospira* Hardjo *bovis* at the start of the study were administered either the recommended dose or a diluent, (control group) via subcutaneous injection. Clinical observations, rectal temperatures and weight were recorded.

There were no recorded systemic signs attributable to the vaccine. There was no statistical difference in body temperature between treatment groups. Vaccinated calves gained statistically significantly more weight than untreated calves. Local reactions were observed at the injection site in all animals, and persisted from 1-

56 days. Repeat treatment appeared to increase the severity of the reaction, with hardness, swelling and pain apparently increasing with each vaccination.

The local reactions following repeat vaccination increase in size and severity. The recommended schedule is for two 2 ml doses, 4 to 6 weeks apart, followed by a single annual booster. The regimen given in the study undertaken was considerably more intensive than that recommended, with repeat doses at 4, 8 and 12 weeks, and this may have contributed to the intensity of the reaction. However, there were no systemic reactions, and the local reactions are properly and specifically reflected in the SPC:-

- A diffuse and oedematous swelling up to 10 cm in diameter, sometimes sensitive to palpation, could occur in up to 40% of animals and can last for up to 66 days after completion of vaccination. The reaction to subsequent vaccinations and the reaction in pregnant animals (see 4.7) are more marked. The injection site reaction may be sensitive to palpation the week following vaccination and may persist as a hard nodule for several weeks.

Effects on reproductive performance were examined. There were no systemic reactions to vaccination, although local reactions were large. Swelling following vaccination was more marked when pregnant, and in later trimesters compared to the first trimester. This is addressed in the SPC:-

- Can be used during pregnancy and lactation. The swelling is more marked in pregnant animals. A diffuse swelling of up to 22 cm in diameter can occur following second injection. This effect is more marked for pregnant animals in their third trimester of pregnancy.

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.

A withdrawal period of zero days is adequate as the only pharmacologically active component of the vaccine.

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

I. Field studies

Field studies were carried out to demonstrate the safety and efficacy of Spirovac. One trial involved a group of pregnant lactating cow, half were vaccinated with Spirovac the other half were administered saline, (control group), twice via subcutaneous route. Injection sites were evaluated at different intervals and milk records were analysed. There were no systemic reactions to the vaccine under field conditions. Lactation was unaffected by the administration of two doses at the recommended interval.

Another trial involved a group of cows previously vaccinated with Spirovac. These were allocated randomly to either control (saline), or vaccinated (Spirovac) groups. Two vaccinations of Spirovac (or saline for controls) were administered at an appropriate interval, by the subcutaneous route, while non-pregnant, prior to insemination. Results showed the conception rates to be similar between groups. No statistical testing was carried out. Body temperature increases were not clinically significant.

A further field trial involved a group of pregnant lactating diary cows, half were vaccinated with Spirovac twice via subcutaneous route the other half were administered saline (control group) three times at the appropriate intervals. Milk yields between the two groups were not statistically significantly different. Dimensions of the local reaction in the pregnant animal were similar to those seen in other studies. The vaccine was not associated with any reproductive abnormalities in the immediate post-vaccination period.

J. Ecotoxicity

No studies were carried out for ecotoxicity. The components of this inactivated vaccine are not considered a potential hazard. Merthioalate is approved under Annex II of Council Regulation 2377/90 for use in food producing animals.

The overall risk to the user is also very low, and no special precautions are necessary. The SPC carries the instruction:-

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

Onset of Immunity
A study demonstrated that the onset of immunity following the recommended regime of Spirovac is 20 days. This is reflected in the SPC by a claim of a 3 week onset of immunity following the primary course of vaccination.

Duration of Immunity
A study demonstrates that the duration of immunity (no kidney colonisation and no shedding) following the recommended primary course of Spirovac is at least one year. This is reflected in the SPC.

Response to Booster
The claim for annual boosting was supported. It is recommended that a single 2 ml dose be given on an annual basis.

Vaccination of Infected Animals
The indication in the SPC provides information with regard to the vaccination of infected animals.

Field Trials

Another trial involved a group of cows previously vaccinated with Spirovac. These were allocated randomly to either control (saline) or vaccinated (Spirovac) groups. Two vaccinations of Spirovac (or saline for controls) were administered at an appropriate interval, by the subcutaneous route, while cattle were non-pregnant, prior to insemination. A further field trial involved a group of pregnant lactating diary cows, half were vaccinated with Spirovac twice via subcutaneous route the other half were administered saline (control group) three times at the appropriate intervals. These studies yielded appropriate results.

A strong serological cross-reactivity post vaccination was demonstrated against *Leptospira interrogans* serovar Hardjo, a closely related species in the same serovar. This was sustained for at least 12 months following primary vaccination, and is also seen in the anamnestic response following a singe booster vaccination.

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)