ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Covexin 10 Suspension for Injection for Sheep and Cattle

PuAR correct as of 12/06/2018 when RMS was transferred to DE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0201/001/E/001
Name, strength and pharmaceutical form	Covexin 10 Suspension for Injection for Sheep and Cattle.
Applicant	Pfizer Ltd Ramsgate Road Sandwich Kent UK CT13 9NJ
Active substance(s)	*C. perfringens* type A toxoid ≥ 0.9 U# *C. perfringens* type B & C toxoid ≥ 12.4 IU* *C. perfringens* type D (ε) toxoid ≥ 5.1 IU* *C. chauvoei* whole culture meets Ph. Eur.** *C.novyi toxoid* ≥ 1.2 IU* *C. septicum* toxoid ≥ 3.6 IU* C. tetani toxoid ≥ 2.5 IU* *C. sordellii* toxoid ≥ 0.8 U* *C. haemolyticum* toxoid ≥ 16.5 U# Adjuvant: alum 3.03 – 4.09 mg/mL Aluminium Preservative: thiomersal 0.05 – 0.18mg/mL Excipient to 1 ml: formaldehyde ≤ 0.5mg/mL *In-House ELISA ** Challenge test according to Ph. Eur # *In vitro* toxin neutralisation test based on haemolysis of sheep erythrocytes.
ATC Vetcode	QI04AB01
Target species	Sheep and Cattle.
Indication for use	For the active immunisation of sheep and

	cattle against diseases associated with infections caused by *Clostridium perfringens* type A, *C. perfringens* type B, *C. perfringens* type C, *C. perfringens* type D, *Clostridium chauvoei*, *Clostridium novyi* type B, *Clostridium septicum*, *Clostridium sordellii* and *Clostridium haemolyticum* and against tetanus caused by *Clostridium tetani*. For the passive immunisation of lambs and calves against infections caused by the above mentioned clostridial species (except *C. haemolyticum in sheep)*. The onset of immunity is two weeks after the primary course.

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	Repeat Use application in accordance with Article 32(2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	13th May 2010.
Date product first authorised in the Reference Member State (MRP only)	11th March 2003.
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain.

I. SCIENTIFIC OVERVIEW

This is a repeat use application for a combined clostridial vaccine, effective against the following: *Clostridium perfringens* type A, *C. perfringens* type B, *C. perfringens* type C, *C. perfringens* type D, *Clostridium chauvoei*, *Clostridium novyi* type B, *Clostridium septicum*, *Clostridium sordellii, Clostridium haemolyticum* and *Clostridium tetani*. The adjuvant is potash alum and the preservative is thiomersal. Covexin 10 Suspension for Injection for Sheep and Cattle is intended to generate the active immunisation of sheep and cattle against diseases caused by the bacteria described above, including tetanus caused by *C. tetani*. Lambs and calves may also be passively immunised against all the above clostridial species, apart from *C. haemolyticum* in sheep.

The vaccine is an inactivated, adjuvanted alum, a multicomponent clostridial product for use subcutaneously in lambs and calves from two weeks of age. The vaccine may also be used in adult cattle and sheep, in the late stages of pregnancy. In sheep, the initial dose is 1 ml, given again after six weeks. In cattle, the initial dose is 2 ml, repeated after six weeks. In naïve pregnant animals, the first dose should be given eight to twelve weeks prior to parturition. In sensitised pregnant animals, the booster dose should be administered two to six weeks prior to parturition.

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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains *C. perfringens* type A toxoid ≥ 0.9 U#, *C. perfringens* type B and C toxoid ≥ 12.4 IU*, *C. perfringens* type D (ε) toxoid ≥ 5.1 IU*, the *C. chauvoei* whole culture meets Ph. Eur.**, *C. novyi toxoid* ≥ 1.2 IU*, *C. septicum* toxoid ≥ 3.6 IU*, C. tetani toxoid ≥ 2.5 IU*, *C. sordellii* toxoid ≥ 0.8 U*, *C. haemolyticum* toxoid ≥ 16.5 U#. The adjuvant is alum 3.03 – 4.09 mg/mL Aluminium, thiomersal is incorporated as the preservative at 0.05 – 0.18mg/mL and excipient to 1 ml: Formaldehyde ≥ 0.05mg/mL

* In-House ELISA

** Challenge test according to Ph. Eur

In vitro toxin neutralisation test based on haemolysis of sheep erythrocytes.

The container system consists of 20 ml, 50 ml or 100 ml flexible, low density polyethelene bottles, closed with a pharmaceutical grade rubber bung, held in place with an aluminium seal. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the adjuvant, vaccine strains, inactivating agent and the presence of 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 various clostridia species are prepared by fermentation and inactivated with formaldehyde. All cultures except *C. chauvoei* are filtered and concentrated using ultrafiltration. For all bacteria, Master Seed are propagated by standard means into Working Seed cultures, prior to collection and inactivation.

C. Control of Starting Materials

The active substance consists of several established vaccine components, not described in the European Pharmacopoeia (Ph. Eur). The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline. Also not listed in the Ph. Eur are the feed components for cell cultures. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of a non-biological origin used in production comply with monographs in the Ph.Eur. Excipients are sodium chloride, alum, thiomersal, sulphuric acid, sodium hydroxide, formaldehyde, glucose monohydrate, dextrin and fructose.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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.

E. Control tests during production

The tests performed during production are described and the results of three consecutive runs, conforming to the specifications, are provided. Tests are carried out on the identity and purity of the vaccine strains, in addition to analysis of toxoid contents, combining power and non-toxicity. Inactivation tests are also performed, in addition to tests on sterility, specific toxicity and the Limes flocculation test.

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 those for non-viability, inactivation, pH adjustment and estimation of thiomersal, aluminium and free formaldehyde, in addition to safety, residual toxicity and potency tests.

The demonstration of the batch to batch consistency is based on the results of a series of 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 active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
The in-use shelf-life of the vaccine is supported by the data provided.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The in-use shelf-life of the product as packaged for sale is twenty four months. Shelf life after first opening of the immediate packaging is eight hours.

III. SAFETY ASSESSMENT

Monovalent components of a specific vaccine batch were produced and blended in a satisfactory manner. A summary of the potency of the various batches used for Safety and Effficacy trials was presented.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal was demonstrated in several studies. The first of a series of GLP-compliant studies investigated the use of the vaccine in two week old and three to four month old cattle. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. A suitable number of young cattle were given single, repeat or double doses of vaccine, on two or three occasions. Negative controls were given a placebo. At necropsy, no significant adverse reactions were seen.

In a second study, a suitable number of young sheep were subjected to the same regimen as that described for cattle above. No significant reactions were seen.

Two further studies analysed the use of the vaccine in late pregnancy. No significant adverse reactions were observed.

Effects on reproductive performance were examined. In one study, pregnant ewes were inoculated with two overdoses of vaccine, the vaccinations being six weeks apart. The first vaccination was eight to twelve weeks before the expected date of parturition. Clinical analyses demonstrated that no adverse reactions were seen in the animals, and any slight reactions are indicated in the SPC.

In cattle, pregnant cows were vaccinated with two overdoses of vaccine six weeks apart. The first vaccination was eight to twelve weeks prior to parturition. No adverse reactions attributable to the vaccine were observed, and any slight reactions observed are cited in the SPC.

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 (aluminium potassium sulphate) and residual formaldehyde have been assigned to Annex II of EEC Directive 2377/90. Based on this information, no withdrawal period is required.

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

The safety of Covexin 10 Suspension for Injection for Sheep and Cattle under field conditions was evaluated in four studies, at more than one site. In the first blind, randomised and controlled study, systemic and local tolerance to the vaccine was examined in young sheep. The first group of animals were given a placebo and the second group were given vaccine. The study was conducted at two different sites. A first dose was given, followed by a second, six weeks later. No adverse reactions were observed.

A second study was used to evaluate the vaccine for passive protection in young sheep. This was a blind, randomised and controlled study in healthy pregnant ewes, divided into two groups, one of which received the vaccine and the other a placebo. A first dose was given seven weeks before the earliest expected parturition date, with a second dose given five weeks after the first. No adverse reactions were observed.

A third study evaluated the field safety and efficacy of the vaccine in calves, at two sites. A blind, randomised and controlled study was performed in a suitable number of young cattle, which were divided into placebo or vaccinate groups. The animals were given two inoculations six weeks apart. No significant adverse reactions were seen.

In a final study, passive immunity was observed in young cattle. Pregnant animals were divided into placebo or vaccinate groups, prior to two inoculations, Five to six weeks apart. The results of any significant reactions are reflected in the SPC.

User Safety

With regard to user safety, no special precautions are necessary. In the case of accidental self-injection, medical advice should be sought, showing the physician the package leaflet.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The antigenic components of the vaccine are chemically inactive, with testing carried out on each batch of antigen to ensure inactivation. There is no infectious hazard from these components. Levels of other partially toxic chemicals are low and consequently present little risk. 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

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the product is safe for use in the target species. Laboratory trials were conducted which investigated six and twelve months duration of immunity in sheep and cattle.

A series of studies were performed in sheep. Firstly, different formulations of Covexin 10 Suspension for Injection for Sheep and Cattle were compared in a large number of seronegative sheep over a period of six to twelve months. A second study demonstrated that when the vaccine is given twice, with six weeks between inoculations, the potency of the vaccine is maintained for six months from the second vaccination. A further two studies on the vaccine over both a six and twelve month period demonstrated that an effective ten-way product had been satisfactorily created. All animals were seronegative at vaccination. Negative controls were used, and these in general for all relevant studies had low titres of the individual strains of clostridia following a 'challenge' immunisation with the homogenous vaccine. A series of reciprocal data were also presented for cattle. Results were acceptable with specific indications highlighted in the SPC.

Field Trials

The efficacy of Covexin 10 Suspension for Injection for Sheep and Cattle was investigated in four field studies. In the first study, Covexin10 Suspension for Injection for Sheep and Cattle was administered to young sheep, in order to evaluate the serological response, and to monitor local and systemic effects. In a blind, randomised, controlled study, a suitable number of animals were divided into two groups at two different sites, and inoculated with vaccine or placebo. One group of sheep, which consisted of vaccinates and controls, were from vaccinated mothers. A second vaccination was given six weeks after the first, and serology was performed just prior to the first vaccination and then two weeks after the second. All data with regard to an appropriate immunological response were acceptable. A reduction in efficacy was noted where there had already been exposure to some of the antigens, and Covexin 10 Suspension for Injection for Sheep and Cattle is not indicated for the treatment of *C. haemolyticum* in sheep. The SPC contains a suitable indication.

A second study investigating the passive immunisation of lambs was performed at a separate site. Results were satisfactory with any implications for the indication highlighted in the SPC.

A study in young cattle analysed the product with regard to systemic and local tolerance, at two field sites. This was a blind, randomised, controlled study in which two groups of animals received either vaccine or placebo. Two vaccinations were given, six weeks apart. Results were acceptable with regard to seroconversion, with relevant specifications outlined in the SPC. A further study investigated the passive immunity of calves, and seroconversion was

analysed. Results were acceptable with relevant indications specified in the SPC.

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)