

IPAR



**Publicly Available Assessment Report for a
Veterinary Medicinal Product**

Lactovac Suspension for injection

PRODUCT SUMMARY

EU Procedure number	IE/V/417/001 (formerly UK/V/0204/001)
Name, strength and pharmaceutical form	Lactovac or Lactovac C or Bovilis Lactovac C Suspension for Injection
Applicant	Zoetis Belgium S.A. 2nd Floor, Building 10 Cherrywood Business Park, Loughlinstown Co Dublin Ireland
Active substance(s)	Inactivated bovine rotavirus, strain 1005/78 at least $10^{7.4}$ TCID ₅₀ *, inducing ≥ 1 RPU*** Inactivated bovine rotavirus, strain Holland at least $10^{7.0}$ TCID ₅₀ , inducing ≥ 1 RPU Inactivated bovine coronavirus, strain 800 at least $10^{5.8}$ TCID ₅₀ , inducing ≥ 1 RPU Inactivated <i>E.coli</i> K99/F41 250 - 260 HAU**, inducing ≥ 1 RPU
ATC Vetcode	QI02AL01
Target species	Cattle (cows and heifer during advanced pregnancy)
Indication for use	For the active immunisation of pregnant cows and heifers in order to confer passive protection to their calves (via colostrum) to reduce the severity and duration of neonatal diarrhoea caused by rotavirus, coronavirus and <i>E.coli</i> infections. Protection is conferred only while the calves are fed colostrum from vaccinated cows.
Legal basis of original application	Repeat Use application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition	23 rd September 2015
Date product first authorised in the Reference Member State (MRP only)	26 th August 1998 (UK) 9 th December 2013 (IE)
Concerned Member States	BE, BG, CY, EE, EL, FI, HR, HU, IT, LT, LU, LV, NL, RO, SI, SE, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

This was an application for a further Repeat Use Mutual Recognition procedure for Lactovac Suspension for Injection, with the intention of obtaining a Marketing Authorisation for the product in additional member states. The product was originally authorised nationally in the UK in August 1998, and subsequently went through the Mutual Recognition Procedure in additional member states, which was approved in February 2005. The product is intended for the active immunisation of pregnant cows and heifers, in order to provide passive protection to calves, (via the colostrum), to reduce the severity and duration of neonatal diarrhoea caused by rotavirus, coronavirus and *Escherichia coli* (*E. coli*) infections. The product is an

inactivated vaccine containing bovine rotavirus, strains 1005/78 and Holland, bovine coronavirus, strain 800, and *E. coli* serotype K99/F41. All cows in a herd should receive two injections of 5ml during the later stages of pregnancy, with an interval of 4-5 weeks between doses and allowing 2-3 weeks from the time of the second dose until the predicted date of calving. A booster injection of 5 ml 2-6 weeks prior to predicted calving should be administered for subsequent pregnancy. Calves then receive passive immunization via the colostrum. Refer to the SPC for detail.

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, any reactions observed are indicated in the Summary of product Characteristics (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 (production of a desired or intended result) 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

II.A. Composition

The product contains bovine rotavirus, strain 1005/78, Holland strain, bovine coronavirus, strain 800, and *E. coli* K99/F41. The excipients are thiomersal and water for injection. The adjuvants are aluminium hydroxide and Saponin/Quil A. The container/closure system consists of a cardboard box containing one Type I glass vial of 25 ml with Type I rubber stoppers sealed with an aluminium crimp cap or a cardboard box containing 10 Type I glass vials of 5 ml with type I rubber stoppers sealed with an aluminium crimp cap.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the adjuvants, vaccine strain, the presence of preservative and the inactivating agent used 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.

II.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 manufacturing method consists of: cell culture for viral or bacterial inoculation, harvesting of virus or bacteria, appropriate inactivation where required, neutralisation, sampling, dispensing into vials and suitable storage. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are established, manufactured in accordance with the principles of good manufacturing practice and in line with monographs within the Ph. Eur, and are appropriately screened for the absence of extraneous agents according to the Ph. Eur Guidelines. The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline. All excipients and adjuvants, listed or not listed in a pharmacopoeia were appropriately assessed for use.

II.C.4. Substances of Biological Origin

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.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Inactivation of virus or bacteria is carried out as appropriate.

II.E. 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 include those for identification of the active substance, the adjuvant, the excipients, sterility and purity tests and physico-chemical tests.

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

II.F. Stability

Stability data on the active substances 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 broached reconstituted vaccine is supported by the data provided.

G. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
- Shelf life after first opening of the immediate package: 10 hours.
- Store in a refrigerator (2 °C – 8 °C). Protect from frost.

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 was demonstrated via suitable studies when the product was originally authorised. Investigations were performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

In the first report, which examined the safety of the combination vaccine against bovine coronavirus, rotavirus and *E.coli* in pregnant cows, 10 animals were vaccinated with a double dose of the product, 8 weeks prior to parturition, with a single dose provided 4 weeks later. The animals received at least the minimum content components. Immune status was not analysed, but the animals were considered to be representative of those in the general cattle population. A negative control substance, (physiological saline), was provided to a proportion of the animals. Apart from a slight rise in temperature and mild injection site reactions, no adverse reactions were noted in vaccinated animals. The SPC carries suitable warnings. All vaccinated animals bore healthy calves.

The second assay involving 16 cattle included administration of the product, with subsequent monitoring of the immune response and collection of colostrum for analysis. This assay was considered to be of limited value with regard to the analysis of safety, but was assessed for the analysis of efficacy data. No adverse reactions were noted.

A third study observed the inoculation of a repeated dose (x 4 at 2 week intervals), of the product into 5 cattle. No unforeseen adverse reactions occurred that were attributable to the study.

Effects on reproductive performance were examined when the product was originally authorised, and the product is permitted for use in 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. No withdrawal period is proposed or required. The product must not be used with other vaccines or immunological products.

Field studies

Five field studies were carried out, with 1 study being of significant relevance to the assessment of safety. In the safety study, 15 pregnant cattle were vaccinated 6 and 2 weeks prior to calving with two batches of the product at the relevant titre. A further group of cows received physiological saline as negative controls. Clinical observations were made, and no severe adverse reactions were noted. Swelling at the injection site, an expected adverse reaction cited within the SPC, was seen. A study comparing the historical product with the new formulation was performed, but this was not regarded as being of significant value for the safety assessment.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that as the viral and bacterial components are inactivated, and additionally the excipients do not pose undue threat 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

Clinical Studies

Laboratory Trials

The applicant provided four laboratory studies, with suitable preliminary challenge studies having demonstrated the transfer of immunity to calves. The first study observed the vaccination of cattle with the proposed product, monitoring the immune response and collecting colostrum for analysis. 32 pregnant cattle, exhibiting low antibody titres to rotavirus, coronavirus and *E.coli* K99/F41 were divided into two groups. The first group was vaccinated with the proposed product, with 2 doses being given at an interval of 4 weeks. The other group of cattle were unvaccinated controls. The antigen content of the vaccine was the minimum content required for administration. Serum samples were collected at appropriate time points during the study, with milk and colostrum samples being collected up to 19 days post-calving. All post-vaccination serum, colostrum and milks samples were analysed for neutralising antibodies against relevant rotavirus, coronavirus and *E. coli* serotypes. Statistical analysis demonstrated that clinically significant raised antibody titres were seen.

A second study observed the efficacy of colostrum from vaccinated cattle, (with low antibody titre to the viruses contained within the challenge vaccines), testing for protection given to 22 calves challenged with *E. coli* K99/F41. The calves were manually fed the colostrum with a milk substitute. A number of negative control dams were included in the study, whose offspring did not receive the treated colostrum. None of the treated animals died, although some enteric symptoms were noted in a small proportion of the animals. It was concluded that there was a significant reduction in the instance of disease amongst the treated animals.

In a third study, the efficacy of the product in protecting calves via the colostrum from rotaviral infection was investigated. 12 calves were appropriately challenged with the product via colostrum, which contained the minimum titre of protective virus. A

number of negative control dams were not inoculated, and subsequent offspring therefore not treated. Appropriate challenge to the calves with rotavirus was performed. Clinical signs of disease were extended in the negative control group, with a reduction in disease demonstrated in the treated group.

The final study determined the efficacy of the product in protecting calves via the colostrum against coronavirus. The same protocol was followed as that used for the testing of the product in calves with regard to rotavirus. Severity and reduction of disease was noted for calves receiving colostrum from inoculated dams. The minimum protective titre was shown to be effective.

Field Trials

The results of 4 field trials were presented.

In a follow-up to one of the safety studies, (first study cited in laboratory trials in Safety section), 10 cows which had previously been vaccinated with the product twice before parturition were re-vaccinated with a single dose approximately 3 weeks before giving birth again. The vaccine batch was the same as that used before. An additional 13 cattle that had not been vaccinated previously were used as negative controls. Colostrum samples were taken at appropriate time points immediately after calving, and milk samples taken at various time points following. A significant difference was noted in the levels of serum antibodies to rotavirus and *E. coli*, between test and negative control groups, but not in serum levels of coronavirus at the time of calving. Moreover, the difference between serum antibodies at milking were initially similar for coronavirus but, this increased in vaccinates after the second milking. The serum levels of antibodies to *E. coli* and rotavirus remained high throughout the test.

A second study formed part of a multi-centre field study. Here, calves which had an existing clinical issue with diarrhoea were treated, (these animals had previously been treated with an anti-diarrhoeal vaccine). 79 pregnant cattle were randomly assigned to one of 3 groups, (2 vaccinate groups containing a total of 53 vaccinates, 1 control group of 26 animals). The vaccinates were given two doses of the product approximately 4 week intervals, at up to 1 to 2 weeks before anticipated calving. The control group was left untreated. Calves were fed milk from their dams up to day 5, thereafter receiving milk substitute. Of calves completing the study, 56.8% of calves from vaccinated dams and 95.2% of calves in the control group exhibited diarrhoea. This was a statistically significant result. A further statistically significant result was seen as 38% of faecal samples from the vaccinate group and 68% from the control group showed rotavirus. None of the samples from the vaccinates was positive for coronavirus, while 2 of the control groups were coronavirus positive. Whilst data of significance was obtained, differences were not as vast as could have been expected had there been no exposure to previous vaccinations or field transmission.

A third study did not demonstrate the efficacy of the vaccine.

A fourth study was also part of the multi-centre field study, and the study design was essentially similar to that previously described for the second study cited. 61 pregnant cattle were randomly allocated to study three groups. The vaccinate groups comprised a total of 40 cattle, and there were 21 negative controls. Vaccinates were given 2 doses of the product at an interval of approximately 4 weeks, with the second dose given 1 to 2 weeks before the anticipated calving. Control group animals were left untreated. Following calving, calves were fed for 5 days on milk from their own dam, and thereafter received milk substitute. Of calves completing the study, 47% of those born to vaccinates had diarrhoea compared to 71% of calves born to control animals. This was not statistically significant. Antibody titres in whey were noted to be significantly higher in the vaccinated animals as compare to the controls. A series of supporting studies using an older formulation contributed to the assessment of product. The product was deemed efficacious based on all the data provided.

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 of the product(s) is favourable.