IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

BOVIGEN SCOUR Emulsion for injection for cattle

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0341/001/DC
Name, strength and pharmaceutical form	Bovigen Scour Emulsion for injection for cattle
Active substance(s)	Bovine rotavirus strain TM-91 serotype G6P1 (inactivated) Bovine coronavirus strain C-197 (inactivated) *Escherichia coli* strain EC/17 (inactivated) expressing Adhesin F5 (K99)
Applicant	FORTE Healthcare Limited Cougar Lane Naul Co. Dublin Ireland
Legal basis of application	DCP application in accordance with Article 12(3)of Directive 2001/82/EC as amended.
Date of completion of procedure	22/01/15
Target species	Cattle (pregnant cows and heifers)
Indication for use	For the active immunisation of pregnant cows and heifers to provide passive immunity to calves via colostrum/milk to reduce the severity of diarrhoea caused by bovine rotavirus, bovine coronavirus and enteropathogenic *E. coli* F5 (K99) and to reduce the shedding of virus by calves infected with bovine rotavirus or bovine coronavirus. Onset of immunity: Passive immunity commences with colostrum feeding and is dependent on calves receiving sufficient colostrum after birth.
ATCvet code	QI02AL01
Concerned Member States	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HR, IT, LT, LU, LV, MT, NL, NO, PT, RO, SE, SI, 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

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.Qualitative and Quantitative Particulars

The product contains the following active substances per 3 ml vaccine dose:

Bovine rotavirus strain TM-91, serotype G6P1 (inactivated)≥ 6.0 log2 (VNT)*
Bovine coronavirus strain C-197 (inactivated)≥ 5.0 log2 (HIT)**
E. coli strain EC/17 (inactivated) expressing F5 (K99) Adhesin ≥ 44.8 % of inhibition (ELISA)***

* VNT – virus neutralisation test (rabbit serology induced by 2/3 dose of vaccine)
** HIT – haemagglutination inhibition test (rabbit serology induced by 2/3 dose of vaccine)
***ELISA – Enzyme-linked immunosorbent assay (rabbit serology induced by 2/3 dose of vaccine)

Montanide ISA 206 VG (1.6ml / 3ml dose) is used as adjuvant.

Thiomersal is included in the vaccine as a preservative. Disodium phosphate dodecahydrate, sodium chloride; potassium chloride, potassium dihydrogen phosphate and water for injection are used as excipeints
Eagles Minimum Essential Medium (MEM) and formaldehyde used during production of the active substances are also present in the vaccine.

The container/closure system consists of 20 ml, 100 ml and 500 ml Type I glass vials for the 15 ml, 90 ml and 450 ml vaccine presentations respectively.
The 450 ml vaccine presentation is also available in a 500 ml LDPE bottle.
Chlorobutyl rubber stoppers are used as closures for the 20 ml and 100 ml glass vial and 500 ml LDPE bottle presentations and bromobutyl rubber stoppers are used for the 500 ml glass vial presentation.

The choice of the adjuvant, vaccine strains, inactivating agent, formulation 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 at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C.Control of Starting Materials

Starting materials of non-biological origin used in production comply with Ph. Eur. monographs or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and have been appropriately screened for the absence of extraneous agents according to the relevant Ph. Eur. monographs and EU guidelines - any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

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

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.

D.Control Tests During Production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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 general characteristics of the finished product e.g. appearance, viscosity and pH, identification of active substances including identity testing and appropriate extraneous agents testing, sterility testing in line with the relevant Ph. Eur. monograph, identification and assay of adjuvant and batch potency.

The demonstration of the batch to batch consistency is based on the results of 3 consecutive batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

F.Stability

The active substances are fully tested to ensure compliance with specifications prior to their use in manufacture of the product.

Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (2 years) when stored under the approved conditions.

The 10 hour in-use shelf-life of the vaccine is supported by the data provided.

G.Other Information

Not applicable.

III. SAFETY ASSESSMENT

The batches used in the laboratory safety studies were representative of the production process except that the content of the active substances was higher than for production batches. In addition, the formaldehyde content of the batches was higher than the maximum limit of 0.5g/L permitted for use in routine production batches.
The batches used in the safety studies were considered to represent a worst case situation for the safety investigations.

Laboratory Trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose was demonstrated in a number of studies in the target species (pregnant cows and heifers in the third trimester of gestation) including a GLP/GCP compliant study conducted in accordance with the relevant Ph. Eur. monographs for each of the active substances of the vaccine.

As the investigation of the safety of an overdose administration of inactivated vaccines is no longer a requirement of Directive 2001/82/EC as amended, it can be considered that the overdose studies also represent a worst case scenario for the safety investigations.

Adverse reactions following vaccination were limited to mild local reactions which resolved within 15 days of vaccination, and very slight transient increases in temperature. No other local reactions, systemic reactions, or adverse effects on reproductive performance of vaccinated cows or the progeny were observed following vaccination.
The adverse events are adequately described in the SPC.
No additional reactions were observed after an overdose compared to a single dose administration – this is also reflected 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 and excipients used are included in Annex 1 of Commission Regulation (EU) 37/2010 as allowed substances and where relevant are within the permitted limits.
The level of formaldehyde in the vaccine is within the 0.5 g/L Ph. Eur. limit. Based
on this, no withdrawal period is required following use.

No specific assessment of the interaction of this product with any other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Field Studies

One GCP-standard field study involving three commercial dairy farms was performed in one EU member state in accordance with the field study requirements specified in the Ph. Eur. monograph for neonatal ruminant colibacillosis vaccine (inactivated). In total, 60 pregnant animals (20 per farm) were vaccinated according to the route and schedule recommended for the vaccine while 30 animals (10 per farm) were included as non-vaccinated controls.
The results of the field study reflected those obtained in the laboratory studies: mild injection site reactions and slight temperature increases post vaccination were observed with no adverse effects on the course of pregnancy, parturition or on the progeny of vaccinated dams.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.
The main risk to the user is the potential for accidental self-injection. Although the inactivated active substances and excipients do not pose a risk to the user, the vaccine contains mineral oil as an adjuvant which has potential adverse effects should accidental self-injection occur. Appropriate risk mitigation measures are included in the SPC and package leaflet in accordance with established precautionary statements for mineral oil-containing vaccines to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required.
The assessment concluded that there is no risk for the environment associated with the use of Bovigen Scour as recommended.
The standard disposal statement for inactivated immunologicals is included in the SPC.

IV. CLINICAL ASSESSMENT

Laboratory Trials

The efficacy of the product has been demonstrated in 3 laboratory challenge studies in which animals were vaccinated according to the recommended basic vaccination scheme.
The same vaccine batch was used in each study. The batch was representative of the production process except that the content of the active substances was lower than for routine batches and the formaldehyde content of the batches was higher than the maximum limit of 0.5g/L permitted for use in routine production batches.
As formaldehyde is not considered to have an effect on the efficacy of the vaccine, the batch used was considered acceptable.

Each study involved a challenge infection for one of the active substances of the vaccine in accordance with the immunogenicity requirements of the relevant Ph. Eur. monograph for that active substance.
The studies supported the claim that vaccination leads to passive protection of calves born to vaccinated dams via colostrum/milk to:
-reduce the severity of diarrhoea caused by bovine rotavirus, bovine coronavirus and enteropathogenic *E. coli* F5 (K99) and -reduce the shedding of virus by calves infected with bovine rotavirus or bovine coronavirus.

Field Trials

One field study involving 30 animals (20 vaccinates and 10 controls) was performed in one EU member state.
This study was designed to confirm the efficacy of the re-vaccination scheme and as such, animals which had been vaccinated according to the Bovigen Scour basic vaccination regimen in a previous pregnancy were re-vaccinated during the subsequent pregnancy in the 12 – 3 week period before calving.
Efficacy was based on serology as a surrogate marker of protection which is considered an acceptable approach given that the efficacy of the vaccine is based on the generation of antibodies in pregnant animals and the subsequent protection of progeny via the passive transfer of antibodies via colostrum.
The study demonstrated that revaccination with one dose of the vaccine in the 12 – 3 week period before calving induces a similar serological response as achieved following basic vaccination with two doses.

Efficacy under field conditions was investigated in a small number of animals (30). However Directive 2001/82/EC as amended states that 'both safety and efficacy may be investigated in the same field trials', and considering that the field safety studies were conducted in 3 x farms without any evidence of vaccine breakdown, it is considered that the field data provided is adequate to support the claims requested for the vaccine.

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.

VI. 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 HPRA website.

This section 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.

Changes:

None.

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."