IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Equip Rotavirus emulsion for injection for horses

PRODUCT SUMMARY

EU Procedure number	IE/V/0574/001 (formerly UK/V/0241/001)
Name, strength and pharmaceutical form	Equip Rotavirus emulsion for injection for horses
Active substances(s)	Equine rotavirus H2 strain
Applicant	Zoetis Belgium S.A. 2nd Floor, Building 10 Cherrywood Business Park, Loughlinstown Co Dublin Ireland
Legal basis of application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target species	Horses
Indication for use	For vaccination of pregnant mares to provide passive transfer of antibodies to foals to reduce the risk of diarrhoea caused by Equine Rotavirus H2 serotype.
ATCvet code	QI05AA09
Date of completion of the original decentralised procedure	26 March 2008 (UK) 13 February 2009 (IE)
Date product first authorised in the Reference Member State (MRP only)	n/a
Concerned Member States	DE, FR, UK(NI)

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

Equip Rotavirus emulsion for injection for horses is an inactivated, adjuvanted vaccine which is intended for administration to pregnant mares with a view to protecting their foals against disease caused by equine rotavirus (ERoV) by means of passively transferred antibodies. The recommended vaccination schedule is 3 doses, a month apart, at the 8th, 9th and 10th month of gestation with the vaccine given by the intramuscular route. The three doses have to be given at the same stages in each pregnancy. Use of this vaccine in a mare can only aid the control of diarrhoea associated with rotavirus in its foal when the foal receives an adequate quantity of colostrum, shortly after birth. Both the mare's ability to respond by the production of antibodies in colostrum and the ability of the foal to ingest and absorb that colostrum is required for the vaccine to have an effect.
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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains inactivated equine rotavirus H2 strain. Excipients include Eagle's Earle's MEM growth medium, HEPES acid, sodium hydrogen carbonate, water for injection, hydrochloric acid and sodium hydroxide.
The container/closure system comprises sterile single-dose type 1 glass syringes containing one dose each, and closed with rubber tips. Syringes are supplied in packs of 3, 10, 20 and 40 units. The particulars of the containers and controls performed are provided and conform to the regulation.
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. The applicant provided details of the different stages of the method of preparation. This included a description of the expansion of the cell line, inoculation and incubation of the virus, harvesting, inactivating and neutralising the virus. A description of the preparation of the final bulk vaccine and filling were also provided.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

The product is manufactured in accordance with the European Pharmacopoeia (Ph. Eur.) and relevant European guidelines.

C. Control of Starting Materials

The active substance is equine rotavirus is of biological origin and is not described in a Pharmacopoeia. The development of the master seed was described and appropriately screened for the absence of extraneous agents. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Most starting materials of non-biological origin are in compliance with the relevant Ph. Eur. Those starting materials not described in a pharmacopeia comply with in-house specifications and certificates of analysis were provided.

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 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; any deviation from these requirements is justified. The tests include in particular appearance, identifications and assay of the active substance, the adjuvants and the excipient constituents, safety tests, sterility and purity tests and inactivation.
The demonstration of the batch to batch consistency is based on the results of 3 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.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life

24 months.

Special precautions for storage
Store and transport refrigerated (2°C - 8°C).
Protect from light.
Do not freeze.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Laboratory trials
The Applicant provided reports of laboratory safety studies carried out using Duvaxyn R. In one of the studies the safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal were addressed. Groups of pregnant mares at the stage of pregnancy recommended for vaccination (8 months pregnant) were administered either a 1.0 ml or 2.0 ml dose intramuscularly. Another group of horses were the control group. The groups receiving either 1.0 ml or 2.0 ml dose received two further 1.0 ml doses some days later at 9 and 10 months pregnant. A number of observations were made, serum samples were collected and tested for equine rotavirus antibodies and rectal temperatures were monitored at different time points. The vaccinated mares responded to the vaccination course by producing much higher antibody titres than the control group.

The vaccine was well tolerated and only transient and minor reactions were observed following either a single or double dose. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Another study was also provided although it was not carried out according to the recommended vaccine schedule.

Effects on reproductive performance were considered in the laboratory study described since the vaccine is intended for administration to pregnant animals during the 8th, 9th and 10th months of pregnancy. Safety was therefore confirmed for pregnant mares at the 8, 9 and 10th month of pregnancy as per the proposed recommendations for use (as well as at the 4th month).

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.

Polysorbate and Pluronic L121 are listed in Annex II of Regulation 2377/90 and no MRL is therefore applicable. All other ingredients are outside the scope of this regulation. No residues studies were considered necessary and a withdrawal period of zero days was justified. This is reflected on the SPC.
No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Precautions to be taken by the person administering the veterinary medicinal product.
In case of accidental self-injection/ingestion/spillage onto skin, seek medical advice immediately and show the package insert or label to the physician.

Field studies
The applicant provided details of three safety field studies.

One study investigated groups of pregnant mares in the last trimester of gestation on a farm with a history of rotavirus outbreaks. They were administered either the vaccine or a placebo intramuscularly during the 8th, 9th or 10th month of gestation. Any adverse reactions following vaccination were recorded. No adverse reactions were reported following immunisation of any of the mares that received the vaccine or the placebo. The vaccine is safe when administered to pregnant mares during the third trimester of gestation.

Another study also investigated the vaccination groups of pregnant mares vaccinated with equine rotavirus in the last trimester of gestation. One group of mares had been previously vaccinated with 3 doses of vaccine and received a single dose of vaccine between the 9th and 10th month of pregnancy. Another group that had not been previously vaccinated with equine rotavirus received 3 doses of the vaccine at 8, 9 and 10 months of gestation. Another group received a placebo. No adverse reactions attributable to vaccination were seen in any of the mares. No reproductive disorders that could be attributed to vaccination

were observed. The vaccine was concluded to be safe when administered either as a regular three-dose regime or as a single dose booster to pregnant mares in the last trimester of gestation.

Some details of a further field study were also provided but observations were limited.

The SPC carries suitable warnings with regard to use of the product in the target animal.

Ecotoxicity
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. 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

Laboratory Trials
A study was conducted in mares that were vaccinated 3 times, as per recommended vaccination schedule in the 8th, 9th and 10th months of gestation. Their foals were challenged at or after 14 days of age with a virulent strain of rotavirus and observed for 14 days for clinical signs of disease, abnormal body temperature, effect on weight and viral excretion. A good humoral response was seen in the mares and this was transferred to the foals. The study provides evidence of the positive effect of vaccination on antibody levels to equine rotavirus in mares and foals.
No information is available from this study on the duration of this effect in the foals.

Field Trials
A field trial was conducted in pregnant mares on at least 3 sets of premises. Groups were either given all 3 planned vaccinations at the 8th, 9th and 10th month of gestation, or were given 2 vaccinations, or 1 dose or were left unvaccinated as controls Blood samples were collected at the time of first vaccination, 2 weeks after the third dose and 2 days after foaling. Colostrum, then milk samples were collected 18-36 hours and 21 days after foaling. Serum samples were obtained from foals at 1-2 and 60 days of age. The first sample was used to assess the level of passive transfer. Control animals were not given any injections. The mares were observed after each vaccination. Foals were observed for clinical signs for 60 days. There were no cases of rotavirus diarrhoea in any of the foals in the study. No local reactions were observed. The administration of the vaccine resulted in a significant increase in antibody titre in mares and an increase in the titres in colostrum, milk and the serum of foals. The data suggest that, when the majority of the mares are vaccinated, the vaccine is effective at providing herd immunity and reducing the incidence of disease to almost zero. The study adds further evidence that the vaccine will aid in the prevention of diarrhoea due to equine rotavirus in foals born to vaccinated dams.

Another study investigated groups of pregnant mares in the last trimester of gestation on a farm with a history of rotavirus outbreaks. They were administered either the vaccine or a placebo intramuscularly during the 8th, 9th or 10th month of gestation. Vaccine efficacy was monitored by evaluating the serological response of mares to immunization and the level of passive immunity passed to foals. Vaccine efficacy was also monitored by determining the incidence and severity of equine rotavirus diarrhoea in foals. Faecal samples from foals with diarrhoea were tested for the presence of rotavirus. Available faecal samples were also tested for the presence of viable rotavirus by tissue culture isolation. The incidence of equine rotavirus diarrhoea was low in this study with a confirmed disease rate of only 14% in control foals compared with historical rates greater than 30%. Nearly half of the farms were free from rotavirus disease. The study provided supporting evidence of the beneficial effect on levels of antibody titres transferred to foals from vaccinated dams. It also provided some evidence of duration of these raised antibodies in the foal for 60 days. There was also an indication that the raised antibody levels have a beneficial effect on the incidence of rotaviral diarrhoea, particularly in the first 40 days of life.

A further field trial was provided. One group of mares that had been previously vaccinated received a single dose of vaccine between the 9th and 10th month of pregnancy. Another group that had not been previously vaccinated with equine rotavirus received either 3 doses of the vaccine at 8, 9 and 10 months gestation, or a placebo. The mares were monitored for adverse reactions to the vaccines.

Serum samples were tested for the presence of virus neutralizing antibodies specific for equine rotavirus using a constant virus, varying serum assay. Vaccine efficacy was also monitored by determining the incidence and severity of equine rotavirus diarrhoea in foals. Faecal samples from foals with diarrhoea were tested for the presence of rotavirus. There were no adverse reactions to the vaccinations. Foals born to vaccinated mares had significantly higher ERoV antibody titres within 24 hours of birth compared with foals from control mares. Foals from mares which received a single booster dose had even higher titres. Antibody titres in foals from both vaccinated groups remained significantly higher than control foals at 60 days. The incidence

of equine rotavirus diarrhoea was unexpectedly low in this study with a confirmed disease rate of only 2.2% in control foals compared with historical rates greater than 30%. Over half of the farms were free from rotavirus disease.

The claims in the SPC are justified:

For vaccination of pregnant mares to provide passive transfer of antibodies to foals to reduce the risk of diarrhoea caused by Equine Rotavirus H2 serotype. Mares are able to transfer the passive immunity to the foals 4 weeks after the third vaccination. Foals of the vaccinated mares show an increase in antibodies against Equine Rotavirus for approximately sixty days.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.