IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

ReproCyc PRRS EU lyophilisate and solvent for suspension for injection for pigs

PRODUCT SUMMARY

EU Procedure Number	IE/V/444/001 (formerly UK/V/0536/001/DC)
Name, Strength, Pharmaceutical Form	ReproCyc PRRS EU lyophilisate and solvent for suspension for injection for pigs
Active Substances(s)	Live attenuated prrs 94881 virus
Applicant	Boehringer Ingelheim Vetmedica GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany
Legal Basis of Application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target Species	Pigs
Indication For Use	For active immunisation of breeding females from farms affected with European (genotype 1) Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) to reduce the duration of viraemia, the proportion of viraemic gilts/sows and viral loads in blood after exposure to PRRSV as shown under experimental conditions. Onset of immunity: 4 weeks Duration of immunity: 17 weeks Vaccination of breeding females according to the recommended schedule described in section 4.9 reduces the negative reproductive disorders associated with PRRSV. Under experimental challenge conditions a reduction in transplacental virus transmission after challenge was additionally demonstrated. In piglets from vaccinated sows, a reduction in the negative impact of PRRS virus infection (mortality, clinical signs and weight gain) was also demonstrated during the first 20 days of life.
ATC Code	QI09AD03
Date of completion of the original decentralised procedure	22 January 2015 (UK) 02 April 2015 (IE)
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain. UK added via RMS change

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

ReproCyc PRRS EU Lyophilisate and Solvent for Suspension for Pigs is a live veterinary vaccine. It is indicated for the active immunisation of breeding females from farms affected with European (genotype 1) Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), to reduce the duration of viraemia, the proportion of viraemic gilts / sows and viral loads in blood after exposure to PRRSV as shown under experimental conditions. The product is a lyophilised powder formulation containing $10^{3.9}$ – $10^{7.0}TCID_{50}$ strain 94881 (genotype 1) per dose following reconstitution. The vaccine is administered by intramuscular injection.

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.[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. The efficacy[2] 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.
[1] SPC – Summary of Product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITY ASPECTS

II.A. Composition
The lyophilised powder fraction contains live attenuated porcine reproductive and respiratory syndrome virus (PRRSV), strain 94881 ($10^{3.9}$ – $10^{7.0}$ $TCID_{50}$ per 2 ml dose) as the active ingredient and the excipients sucrose, gelatin, potassium hydroxide, glutamic acid, potassium dihydrogen phosphate, dipotassium phosphate and sodium chloride.

The solvent supplied for reconstitution of the lyophilised powder fraction contains phosphate buffered saline (PBS) and carbomer (adjuvant).

The container/closure system for the lyophilisate consists of a Type I glass vial with bromobutyl rubber stopper and aluminium seal. The container / closure for the solvent consist of high density polyethylene (HDPE) vials with a bromo- or chlorobutyl rubber stopper and aluminium seal. The lyophilisate fraction is presented in 20 ml (10 doses), 100 ml (50 doses) or 200 ml (100 doses) vials and are packaged in cartons with 1, 12 or 25 vials. The particulars of the containers and controls performed are provided and conform to the regulation.

The vaccine strain originates from a European PRRSV field strain. Attenuation of this strain was performed by serial passaging in cell cultures to produce the vaccine strain. The choice of the vaccine strain is satisfactorily justified.

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 product is manufactured by inoculation of cells with the Working Seed Virus (WSV). Following inoculation and propagation steps the antigen is harvested, stabilised and frozen. For the formulation of the final blend, virus suspensions are thawed and mixed with stabiliser and diluent to adjust concentrations as required and then filled into sterilised vials before lyophilisation is performed. Stoppers are inserted and the vials are sealed with aluminium caps.Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is Porcine Respiratory and Reproductive Syndrome Virus. Starting materials used in product comply with the relevant Ph. Eur. 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 relevant Ph. Eur. monographs and guidelines; any deviation has been adequately justified.

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

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

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.E. Control Tests on the Intermediate Product

The tests performed during production of the antigen are described and the results of a sufficient number of consecutive runs, conforming to the specifications, are provided.

II.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 final product is tested for appearance, pH, identification, potency, sterility, residual moisture, extraneous agents and mycoplasma.

The demonstration of the batch to batch consistency is based on the results of data provided for a sufficient number of lyophilised powder batches and solvent batches including production scale batches. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on batches of the lyophilised powder and solvent batches have been provided in accordance with applicable European guidelines, demonstrating the stability of the lyophilised fraction over 2 years shelf life and over 3 years for the solvent, when stored at 2-8°C.

The in-use shelf-life of the reconstituted vaccine, 8 hours, is supported by the data provided.

H. Genetically Modified Organisms

None.

J. Other Information

Shelf life of the vaccine lyophilisate as package for sale: 2 years
Shelf life of the solvent as packaged for sale: 3 years
Shelf life after reconstitution according to directions: 8 hours

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

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

All batches used in the safety studies were representative of the production process. The dose used in the studies was as per the recommended dose and contained the maximum finished product antigen content. Studies were performed in accordance with the requirements of Directive 2001/82/EC, as amended, and the relevant guidelines.

Laboratory trials

The safety of a single dose, an overdose and the repeated administration of one dose of the product in the target animals, and the special requirements for live vaccines, were investigated in nine GLP-compliant laboratory studies. In each safety study a suitable number of animals were used and were in compliance with the general safety Ph. Eur. monographs.

In one study, for a single and repeated dose, a suitable number of pregnant gilts were given a dose above the maximum release titre of the vaccine per gilt at approximately 90 days of gestation. A control group was included. The gilts were injected intramuscularly with the vaccine and observed for 14 days after vaccination. On day 14 post vaccination the repeated dose group gilts were vaccinated again and observed for a further 14 days. The administration of a single dose, followed by a repeated administration of the product to PRRS-naïve pregnant gilts was supported in the study.

Further supportive studies were carried out to examine the safety of the administration of a 10x overdose compared to negative controls. In the studies pregnant, pre-breeding and lactating gilts received a 10x overdose of the vaccine via intramuscular injection and clinical signs such as examination of reproductive performance, body temperature and injection site reactions were observed. Following administration of an overdose (10x), no additional adverse reactions were observed further to those seen after administration of a single dose.

While vaccination of naïve animals during pregnancy under the recommended conditions of use has been shown to be safe under laboratory conditions, there is a standard warning stating that PRRSV naïve gilts should not be vaccinated during pregnancy. This is a standard precautionary measure given the nature of PRRSV attenuated vaccines. Also, the vaccination schedule indicates that for protection against PRRSV during pregnancy, vaccination of naïve gilts is recommended before integration into the sow herd between 5 and 2 weeks prior to breeding.

Examination of the reproductive performance was evaluated in different laboratory studies. The vaccine is contraindicated boars used for breeding and this is stated in the SPC Do not use in boars used for breeding.

Spread and dissemination of the vaccine strain

The spread and dissemination of the vaccine strain was investigated in one study in which twenty pregnant gilts were divided into two groups; one group received a dose at the maximum release titre intramuscularly; the other group were the control group. Four groups of seronegative sentinel animals were sequentially commingled with vaccinated gilts in order to evaluate horizontal transmission to in-contact animals. Gilts were observed for 44 days for clinical signs. Blood samples and swab samples were collected at different time points as well as tissue samples at necropsy for the detection and/or isolation of the vaccine strain.

It was concluded that vaccinated animals may excrete the vaccine strain in their faeces. The potential excretion of the vaccine strain in the urine was not investigated. The vaccine strain may spread up to 5 weeks after vaccination to unvaccinated cohabitating animals (horizontal transmission) without any clinical consequence.

In a different study, the vaccine strain was detected in new-born piglets (blood and lung samples) after vaccination of naïve gilts during the last third trimester of gestation with no clinical consequence.

Reversion of virulence of the vaccine strain

Serial passage studies were performed with PRRS master seed virus at the maximum release titre. Piglets wereinoculated with the master seed via the intramuscular route. Virus was recovered from blood / lung lavage fluid samples and four consecutive passages were performed in piglets using the intranasal route. Piglets were observed for 14 days after each passage. The last passage (5^{th}) was collected and inoculated intranasally into PRRSV seronegative pregnant sows. Clinical signs were observed and serology, viraemia, temperature and weight gain (piglets) were noted.

The studies concluded that there is no reversion of virulence of the vaccine strain under laboratory conditions. The recombination of the vaccine strain with field strains would not be expected to result in any worse consequence than what may occur following natural recombination of field strains.

Study of residues

The adjuvant Carbomer is outside the scope of Regulation (EC) No. 470/2009. All the other excipients present in the vaccine are either listed in Commission Regulation (EU) No. 37/2010 in Annex I (not being necessary for the protection of public health to establish MRLs) or are non-pharmacologically active substances for which no MRL is required. Consequently, there is no need to perform residue studies for the vaccine and no withdrawal period is required.

User Safety

The main risk concerning user safety is accidental self-injection. However, although the vaccine is live, PRRSv is not known to infect humans, and no other components are present in the vaccine that would present a risk to the user. It is accepted that use of the vaccine does not pose an unacceptable risk to the user. Advice is included in the SPC to seek medical advice in the event that an adverse reaction was to occur following accidental self-injection.

Interactions

The compatibility of ReproCyc PRRS EU for use with another veterinary medicinal product has not been established. Therefore, the standard warning when no information is available concerning the use of this product with any other veterinary medicinal product is included in the SPC.

Field studies

Three field studies were carried out to demonstrate the safety of the vaccine under field conditions in farms with a recent history of PRRSV outbreaks. Each of the studies was performed in a different European country covering a representative spectrum of the current European pig husbandry practices. All the studies were carried out following the principles of Good Clinical Practice (GCP).

In total more than 1,500 female pigs at different stages of reproduction were vaccinated with ReproCyc PRRS EU. In two of the studies, the safety profile of the vaccine was compared to a positive control (a commercially available live-attenuated PRRSV vaccine).

The results obtained reflected those observed in the laboratory safety studies (i.e. transient increases in body temperature and mild injection site reactions – swelling, redness - were observed). The reproductive parameters of animals vaccinated with ReproCyc PRRS EU were not inferior to the reproductive parameters of the animals administered with the positive control.

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 is a very low risk to the environment associated with use of the vaccine. 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

The applicant justified that the vaccine strain included in ReproCyc PRRS EU is relevant to the current epidemiological situation in the EU. The challenge strain used in the laboratory efficacy trials as well as the field challenge strains isolated in two of the farms where the field trials were carried out were confirmed as heterologous to the vaccine strain and are considered to represent a substantial genetic diversity across type 1 PRRSV in Europe.

Clinical Studies

Laboratory Trials

The claimed indications for ReproCyc PRRS EU are supported by different laboratory efficacy (vaccination-challenge) studies in naïve pregnant gilts and non-pregnant gilts vaccinated according to the recommended vaccination schedule. In all studies, parameters such as viraemia, clinical assessments, serology and viral detection were measured.

The claimed onset of immunity was based in the results of a randomised, blinded, GCP-compliant study in which two groups of a sufficient number of PRRSV naïve non-pregnant gilts were administered one dose or two doses (administered 8 weeks apart) of vaccine at the minimum efficacious titre. A control group of gilts which were given two doses of placebo 8 weeks apart was also included. All the gilts were challenged 5 weeks after the last administration with a heterologous PRRSV isolate. Vaccination with either a single dose or a repeated dose significantly reduced viraemia and virus load after challenge in this study.

The duration of immunity was established based on the results of a controlled, randomised, blinded trial in which 28 PRRSV seronegative pregnant gilts were vaccinated at the minimum efficacious titre following the recommended vaccination schedule. A group of gilts was included as challenge control group and were administered the placebo following the same schedule. A negative control group was also included. All gilts were challenged 17 weeks later, approximately at day 90 of gestation, with an heterologous PRRSV challenge strain. The results of the study demonstrated that vaccination reduced the incidence, level and duration of viraemia after challenge. A reduction in transplacental virus transmission during pregnancy was also observed. In piglets born to vaccinated sows, a reduction in the negative impact of PRRSV infection (mortality, clinical signs and weight gain) was demonstrated during the first 20 days of life.

The efficacy of the product has been demonstrated in the laboratory studies in accordance with the relevant requirements which show the efficacy of the vaccine with regards to the following claims:

Reduction in duration of viraemia and reduction in the proportion of viraemic animals and viral loads in blood after exposure to PRRSV under experimental conditions. The onset of immunity is 5 weeks and the duration of immunity is 17 weeks.

Vaccination of breeding females according to the recommended schedule reduces the negative reproductive disorders associated with PRRSV.

Under experimental challenge conditions, a reduction in transplacental virus transmission after challenge was also demonstrated. In piglets born to vaccinated sows, a reduction in the negative impact of PRRSV infection (mortality, clinical signs and weight gain) was also demonstrated during the first 20 days of life.

Field Trials

Three field studies were carried out in order to demonstrate the safety and efficacy of the vaccine under field conditions, in farms with recent history of PRRSV outbreaks. Each of the studies was performed in a different European country covering a representative spectrum of the current European pig husbandry practices. In general, all the studies were carried out following the principles of Good Clinical Practice (GCP).

Circulation of field PRRSV was confirmed in two of the studies. The field strains were characterised and confirmed to be heterologous to the vaccine strain. In general and despite of the limitations due to the design, these two field studies can be considered as supportive of the efficacy claims demonstrated under laboratory conditions, particularly in relation to the reduction of negative reproductive disorders associated with PRRSV infection.

Study title	Field safety and efficacy study in pregnant sows / gilts via vaccination with a PRRS vaccine.
Objectives	To demonstrate combined safety and efficacy of an intramuscular administration of ReproCyc PRRS EU in pregnant sows / gilts formulated to contain an intermediate titre (historical comparison).
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	ReproCyc PRRS EU (intermediate titre).
Control product/placebo	Competitor PRRS vaccine
Animals	611 Commercial Cross Breed sows and gilts at the beginning of the study, which reduced to 503 at the end of the study.
Randomisation	Not disclosed.
Blinding	Unblinded
Method	Sows and gilts were in a closed farm. Farm has a history of periodical recurring PRRSV outbreaks despite sow vaccine. At the start of the study the whole herd was vaccinated with a competitor PRRS vaccine regardless of the pregnancy status and stage of breeding cycle. Four months after the study start date, the test vaccine was administered. Approximately five months later a further dose of the test vaccine was administered. The safety and efficacy of the product was determined by clinical observations, injection site reactions, rectal temperatures, PRRS serology and viraemia, reproductive performance, abortion / return to service, weaning rate, average daily weight gain (ADWG) and detection of PRRSV in lungs of the litters.
Statistical method	Statistical analyses were performed using SAS 8.2 software. All tests on difference between treatment group cycles (initial vaccination, vaccination at four months, followed by final vaccination) were two-sided tests. Statistical significance was demonstrated at $p \leq 0.05$. Rectal temperatures, injection site observations, clinical observations and viraemia were analysed with Fisher's exact test and/or ANOVA, as appropriate. Safety parameters were also assessed.

RESULTS	Clinical observations for respiration, digestion and other observations were not different between the control and vaccinated groups; however behaviour was significantly higher in the control group compared to the vaccine groups. Rectal temperatures in all groups were not above the physiological range of 38-39°C, however significant differences between the control and vaccinated groups was noted in the two weeks following vaccination. Local reactions were significantly higher in the control group. No differences were detected between groups for reproductive performance or total number of piglets per litter at weaning. However a significant difference was noted in AWDG from birth to weaning. One positive blood sample from one piglet from the vaccinated group was detected at weaning. With the exception of one sample, all sows and gilt blood sample were negative for PRRSV.
Duration of follow-up	None
Adverse events	No relevant systemic reactions were observed following vaccination.
DISCUSSION	The field study was accepted as providing positive information with regard to the safety of the product, and only supportive information on the efficacy of the vaccine in pregnant gilts and sows due to the limitations derived from the study design (historical comparison). Additional safety and efficacy data was subsequently provided in order to fully support the stated indication.

Study title	Field safety and efficacy study in breeding sows / gilts for vaccination with PRRS vaccine.
Objectives	To demonstrate combined safety and efficacy of an intramuscular administration of ReproCyc PRRS EU in pregnant sows / gilts formulated to contain an intermediate titre (side by side comparison).
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	ReproCyc PRRS EU (intermediate titre)
Control product/placebo	Competitor PRRS vaccine
Animals	505 Commercial Cross Breed sows and gilts at the beginning of the study.
Randomisation	Randomised
Blinding	Blinded
Method	Sows and gilts were located on a farrowing farm. Farm previously had a PRRS outbreak and animals presented with typical clinical signs. At the start of the study the herd was divided into two groups, with an evenly distributed reproductive status. On Day 0 one group was vaccinated with the test vaccine and the second group (positive control) were vaccinated with a competitor PRRS vaccine, regardless of the pregnancy status. The safety and efficacy of the vaccine was determined by clinical observations, rectal temperatures, PRRS serology and viraemia, reproductive performance, abortion / return to service, weaning rate, average daily weight gain (ADWG) and detection of PRRSV in lungs of the litters.

Statistical method	Statistical analyses were performed using SAS 8.2 software. All tests on difference between treatment groups were designed as two-sided tests. Rectal temperatures were analysed using Fischer's exact test and ANOVA. Injection site observations, clinical observations were analysed with Fisher's exact test.
RESULTS	The main clinical observation post-vaccination in both groups was a reduction in appetite. No difference was observed in rectal temperatures between the groups. The number of gilts / sows displaying injection site reactions between Day 0 and Day 14 was significantly lower in the test vaccine group in comparison to the positive control group (p=0.0299). Serology demonstrated that the majority of sows / gilts in both groups were seropositive to PRRSV. All sow and gilt blood samples at scheduled time points were negative for PRRSV. One sample taken outside the scheduled time points was tested positive and was taken from a sow which delivered a litter with mummified offspring. The number of live piglets per litter at weaning were similar in both groups and the proportion of live piglets at weaning was significantly higher (p=0.0047) in the test vaccine group. No significant difference was observed in both groups in return to service. Four abortions occurred during the study, two in each group. No difference was detected between groups for any of the reproductive parameters monitored. The mean total number of piglets that died during the suckling period and the mean percentage of mortality per litter until weaning were significantly lower in the test vaccine group compared to the positive control, p=0.0077 and 0.0047 respectively. The mean body weight at birth did not differ between groups. The body weights at day of weaning and the AWDG from birth to weaning were significantly higher in the test vaccine group, p=0.0259 and p=0.0369 respectively. The mean proportion of viraemic piglets in both groups was not significantly different.
Duration of follow-up	None
Adverse events	No relevant systemic reactions or abnormal clinical signs were observed following vaccination.
DISCUSSION	The field study was accepted as providing positive information with regard to the safety of the product, and supportive information on the efficacy of the vaccine in pregnant gilts and sows. Additional safety and efficacy data was subsequently provided in order to fully support the stated indication.

Study title	Field safety and efficacy study in breeding sows / gilts for vaccination with PRRS vaccine.
Objectives	To demonstrate combined safety and efficacy of an intramuscular administration of ReproCyc PRRS EU in pregnant sows / gilts formulated to contain an intermediate relative potency (side by side comparison).
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	ReproCyc PRRS EU (intermediate titre)
Control product/placebo	Negative control (PBS)
Animals	498 Commercial Cross Breed sows and gilts at the beginning of the study.
Randomisation	Randomised
Blinding	Non - Blinded

Method	History of EU PRRS infection confirmed on farm through screening. Based on evidence farm was considered PRRSV positive. At the start of the study the herd was divided into two groups. On Day 0 one group was vaccinated with the test vaccine and the second group were vaccinated with a negative control. The safety and efficacy of the vaccine was determined by clinical observations, rectal temperatures, PRRS serology and viraemia, reproductive performance, abortion / return to service, weaning rate, average daily weight gain (ADWG) and detection of PRRSV in lungs of the litters. The study ended 4 months post vaccination for sows and gilts and for piglets it ended at weaning.
Statistical method	Statistical analyses were performed using SAS 8.2 software. All tests on difference between treatment groups were designed as two-sided tests. Rectal temperatures were analysed using Fischer's exact test and ANOVA. Injection site observations, clinical observations were analysed with Fisher's exact test.
RESULTS	During the study, 2 sows / gilts exhibited lameness in the control group and a further sow aborted. It was agreed by the investigator and monitor this was unlikely related to treatment. No difference was observed in rectal temperatures between the groups. No injection site reactions were noted in any sows / gilts during the study. All sows and gilts were PRRSV negative at all blood collection time points throughout the study. No significant difference was noted between groups in the total number of piglets per litter at weaning or return to service. Six abortions occurred in the study, three cases in each group. No difference between groups was noted in reproductive performance, piglet mortality or piglet growth performance over the suckling period. One piglet was tested viraemic at weaning from all sample animals and the majority of all piglet serum samples were PRRS serological positive at weaning.
Duration of follow-up	None
Adverse events	No relevant systemic reactions or abnormal clinical signs were observed following vaccination.
DISCUSSION	Due to a lack of field PRRSV exposure in the study animals, the field efficacy of the test vaccine could not be evaluated in this study, and further evaluation of relevant data were required to substantiate the claims of the product. However, safety data was considered suitably supportive of the claims of the product.

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.

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:

Quality Changes

Summary of change (Application number)	**Approval date**
Change to the shelf life of the veterinary medicinal product (IE/V/0444/001/IB/002)	11/12/2018
Change to the shelf life of the veterinary medicinal product (IE/V/0444/001/IB/004)	21/12/2018