Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CIDR OVIS 0.35 g Vaginal Delivery System for Sheep

Date Created: September 2017

Updated: April 2018

PuAR correct as of 17/04/2018 when RMS was transferred to ES. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0603/001/DC
Name, strength and pharmaceutical form	CIDR OVIS 0.35 g Vaginal Delivery System for Sheep
Applicant	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE
Active substance(s)	Progesterone
ATC Vetcode	QG03DA04
Target species	Sheep
Indication for use	For the induction and synchronisation of oestrus and ovulation in non-cycling ewes during seasonal anoestrus. For the induction and synchronisation of oestrus and ovulation in cycling and in non-cycling ewes for advancing the breeding season. To be used in combination with eCG.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	26/04/2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	First Use Cyprus, France, Greece, Italy, Portugal and Spain Repeat Use The Netherlands

I. SCIENTIFIC OVERVIEW

This application was submitted in accordance with Article 12 (3) of Directive 2001/81/EC, as amended by 2004/28/EC. CIDR OVIS 0.35 g Vaginal Delivery System for Sheep is an intravaginal insert device that contains 0.35 g of progesterone per device.

The vaginal delivery system comprises an internal nylon 'T' shaped spine and an outer layer of progesterone impregnated silicone rubber. The progesterone is distributed throughout the silicone matrix.

The product is indicated for the induction and synchronisation of oestrus and ovulation in non-cycling ewes during seasonal anoestrus and for the induction and synchronisation of oestrus and ovulation in cycling and in non-cycling ewes for advancing the breeding season in ewes.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any 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.

[1] SPC – Summary of product Characteristics.

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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 0.35 g progesterone and the excipients silicone elastomer and nylon spine.

The devices are packed in heat-sealed low-density polyethylene sachets in units of 20 per sachet. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a non-standard heating, mixing and moulding process.

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 progesterone an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Certificates of suitability were provided.

The excipients liquid silicone rubber and nylon spine are not described in a pharmacopoeia; certificates of analysis were provided.

CIDR Ovis inserts are packaged in heat-sealed, polyethylene sachets (20 inserts per sachet).

[2] Efficacy – The production of a desired or intended result.

II.C.4. Substances of Biological Origin

A declaration stating compliance with the Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products was provided.

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

Not applicable

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for: colour, wing flexibility, weight, degradation, drug release rate, microbial limits, identification and content of progesterone.

II.F. 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.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Do not store above 30°C.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that the vaginal delivery system delivers progesterone at a controlled rate across the vaginal mucosa into the blood stream. This suppresses the release of gonadotrophin releasing hormone and consequently luteinising hormone thus inhibiting follicle maturation

and so controlling the oestrous cycle. After removal of the device, circulating blood levels of progesterone fall sharply therefore allowing follicle maturation, behavioural oestrus and ovulation.

The applicant has also provided bibliographical data which show that the pharmacokinetic profile of progesterone when administered as a single device was characterised by a maximum concentration in plasma of up to 5.9 ng/ml. Peak concentrations were followed by a decline in systemic exposure to a steady state of approximately 2 ng/ml. After removing the device circulating blood levels of progesterone fall sharply reaching baseline levels by 12 hours.

Toxicological Studies

The applicant has provided bibliographical data which show:

- Single Dose Toxicity

The information provided indicates that single dose LD_{50} is species and age dependent and has been reported in the range of 26.5 mg/kg to 2700 mg/kg, varying between administration route and laboratory species.

- Repeated Dose Toxicity

In rats oral administration of progesterone led to virtually no observable effects (NOEL[3] of 160 mg/kg bodyweight/day). However, subcutaneous administration revealed effects only at the highest dose of 16 mg/kg bodyweight/day (NOEL of 4 mg/kg bodyweight/day): in females and male rats, the endocrine target organs (gonads, uterus and prostate) were atrophied and in males the pituitary weight was increased.

- Reproductive Toxicity, including Teratogenicity

An expert summary was provided which concluded the effect of progesterone at the hypothalamic-pituitary level causing suppression of the luteinising hormone surge and follicle stimulating hormone, lead to the suppression of menstrual cycles and ovulation in women and suppressed spermatogenesis in men. Similar observations have been made in rabbits, monkeys and rats. Other female reproductive endpoints identified in animals subsequent to progesterone exposure are prolonged gestation and impaired maternal behaviour. Male reproductive effects demonstrated in animal studies include impaired mating and paternal behaviour. Effects on the developing female reproductive system in mice exposed to progesterone as neonates are reflected in persistent vaginal oestrous and altered sexual behaviour. Effects on the developing male reproductive system from postnatal exposure in sheep and rats are reflected in delayed puberty and altered male mating behaviour.

[3] No observed effect limit

Progesterone is a natural hormone intimately associated with the reproductive mechanism in all mammals. For this reason, an extensive investigation of the reproductive toxicity, including foetal toxicity and fertility studies, of the hormone has not been performed.

The CVMP[4] MRL summary report indicates that from a study in rabbits an oral NOEL (based on reproductive effects) of 3.2 mg/kg bodyweight/day can be established, while the subcutaneous NOEL (based on reproductive effects) is 0.025 mg/kg bodyweight/day.

Data on teratogenicity/embryotoxicity reveal that no congenital disorders are found after treatment with natural progesterone.

- Mutagenicity

The data provided indicate that progesterone is not mutagenic.

- Carcinogenicity

The CVMP MRL summary report indicates steroid hormones are devoid of genotoxic activity in vivo and these compounds exert their carcinogenic action only after prolonged exposure and at levels considerably higher than those required for a physiological (hormonal) response.

Observations in Humans

Bibliographical information were provided which show that long term administration of high levels of progesterone are likely to elicit similar toxic effects in humans as described in animals. Progesterone is well documented for use in contraception and to treat the symptoms of menopause.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that there is potential for dermal, oral and hand to eye exposure. Exposure in all cases would be to the whole product.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- Progesterone is a potent steroid hormone and may cause adverse effects on the reproductive system in cases of high or prolonged exposure.
- Adverse effects on unborn children cannot be ruled out.
- The product may cause skin and eye irritation, as well as allergic skin rashes.

[4] Committee for Medicinal Products for Veterinary Use

- Those administering the product should avoid contact with the silicone section; pregnant women should avoid using the product completely.
- Wear gloves when administering and disposing of the product; insert the device using the applicator.
- Wash hands and exposed skin with soap and water after use.
- Do not smoke, eat or drink while handling the product.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH[5] and CVMP guidelines.

Phase I:

A Phase II Assessment is not required as the active ingredient is a natural substance (Question 2 of the VICH decision tree). Any use replaces the natural secretion and excretion of progesterone, but does not increase the natural levels, since ewes will not have an additional cycle.

The Phase I assessment ended at question 17 of the VICH decision tree as the initial predicted environmental concentration (PEC) in soil is less than 100 µg/kg.

III.B.2 Residues documentation

Residue Studies

The applicant has provided bibliographical data which show that treated animals do not have significantly higher physiological concentrations of progesterone than non-treated animals.

MRLs

Progesterone is listed in Table 1 of Regulation 37/2010 with No MRL Required.

Withdrawal Periods

Based on the data provided, a withdrawal period of zero days for meat and zero hours for milk are justified.

[5] Veterinary International Conference on Harmonisation

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Bibliographical data has been provided which show that the vaginal delivery system delivers progesterone at a controlled rate across the vaginal mucosa into the blood stream. This suppresses the release of gonadotrophin releasing hormone and consequently luteinising hormone thus inhibiting follicle maturation and so controlling the oestrous cycle. After removal of the device, circulating blood levels of progesterone fall sharply therefore allowing follicle maturation, behavioural oestrus and ovulation.

The applicant has also provided bibliographical data which show that the pharmacokinetic profile of progesterone when administered as a single device was characterised by a maximum concentration in plasma of up to 5.9 ng/ml within 2 hours post-dosing. Peak concentrations were followed by a decline in systemic exposure to a steady state of approximately 2 ng/ml. After removing the device, circulating blood levels of progesterone fall sharply reaching baseline levels by 12 hours.

Tolerance in the Target Species

Bibliographical data has been provided which shows that local irritation and discharge of cloudy/yellow mucus are common and discharge of dark red/brown mucus or mucus with fresh blood is uncommon. However, these signs typically resolve within 2 days of removal of the device without the need for treatment. Target animal safety assessments conducted during the field studies (see section IV.II.) are in line with these observations.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has provided bibliographical data, for dose determination and dose confirmation, which demonstrates that using a dose of 0.35 g for the proprietary efficacy studies was justified.

Field Trials

The test product in all studies was a US commercial product (EAZY-BREED™ CIDR® Sheep), this product is identical to the proposed product. Each batch passed the product specifications test.

Study title	Multi-location Study in the European Union to evaluate the Efficacy of CIDR in Sheep for Induction and Synchronisation of Oestrus during Seasonal Anoestrus. Zoetis Belgium SA Veterinary Medicine Research & Development
Objectives	To evaluate the efficacy and safety of CIDR Sheep (intravaginal device loaded with 0.35 g progesterone) for induction and synchronisation of oestrus in ewes during seasonal anoestrus when administered for 12 days followed by an injection of eCG (equine serum gonadotrophin) under EU field conditions.
Test site(s)	Multi-centre within the EU
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	CIDR Sheep (progesterone), Each insert contains 0.35 g of progesterone impregnated in a silicon elastomer skin moulded over a nylon spine.
Control Product/Placebo	No treatment
Animals	Ewes non-pregnant, primi- or multiparous, lactating or dry, aged 1 -10 years. Rams aged 3 - 5 years. **Inclusion criteria:** • Healthy, as determined by a veterinarian • Meets site specific criteria to be eligible for breeding. • Ewes must be a minimum of 45 days post-partum on study day 0. • Plasma progesterone concentration is ≤ 0.5 ng/mL on Day –7. • No contact with rams for a minimum of 60 days. **Exclusion criteria:** • Body condition score of <2 or >4 • Poor health or evidence of disease • Any prior reproductive problems
Outcomes/endpoints	Oestrus response rate, the proportion of the enrolled ewes which were marked or mounted.
Randomisation	Randomised. Using a random treatment allocation plan.
Blinding	Partially blinded. Clinical and oestrus observations were blinded.
Method	CIDR Sheep inserted and removed after 12 days. At the time of intravaginal insert removal, 500 IU of eCG was administered intramuscularly to each ewe in the Test Product group. Rams introduced.

	Ewes observed for colour marks every 12 hours for 3 days. Pregnancy diagnosis on Day 65 ±10 (43 to 63 days after removal of intravaginal inserts).
Statistical method	Oestrus response in the non-cycling ewes was analysed using a generalised linear mixed model with a binomial error distribution and a logit link function. The statistical model included fixed effect for treatment and random effects of site and site by treatment interaction. Back-transformed least squares means, standard errors and 95% confidence intervals were constructed.
RESULTS	
Participant flow	Two groups of ewes: Group 1 – 86 non-treated animals Group 2 – 76 treated animals.
Duration of follow-up	Ewes monitored until lambing.
Outcomes for endpoints	Oestrus response rate: Group 1: Lower 95% CI[6] 0.049 and Upper 95% CI 0.290 Group 2: Lower 95% CI 0.851 and Upper 95% CI 0.997 Oestrus response rate in negative control animals (12.7% - Group 1) was significantly lower than in CIDR Sheep treated animals (97.6% - Group 2); (P = 0.0009).
Adverse events	None that were considered related to the treatment.
DISCUSSION	This study demonstrates that the use of CIDR Sheep in non-cycling ewes, followed by an injection of eCG, resulted in an oestrus response rate of 97.6%.

Study title	Multi-location Study in the European Union to Evaluate the Efficacy of CIDR in Sheep for Induction and Synchronisation of Oestrus when Advancing the Breeding Season. Zoetis Belgium SA Veterinary Medicine Research & Development
Objectives	To evaluate the efficacy and safety of CIDR Sheep (intravaginal device loaded with 0.35 g progesterone) for induction and synchronisation of oestrus in cycling and non-cycling ewes for advancing the breeding season when administered for 12 days followed by an injection of eCG (equine serum gonadotrophin) under EU field conditions.
Test site(s)	Multi-centre within the EU
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	CIDR Sheep (progesterone), Each insert contains 0.35 g of progesterone impregnated in a silicon elastomer

[6] Confidence interval

	skin moulded over a nylon spine.
Control Product/Placebo	No treatment.
Animals	Ewes non-pregnant, primi- or multiparous, lactating or dry, aged 1 -8 years. Rams aged 1 - 4 years. **Inclusion criteria:** • Healthy, as determined by a veterinarian • Meets site specific criteria to be eligible for breeding. • Ewes must be a minimum of 45 days post-partum on study day 0. • No contact with rams for a minimum of 60 days. **Exclusion criteria:** • Body condition score of <2 or >4 • Poor health or evidence of disease • Any prior reproductive problems
Outcomes/endpoints	Oestrus response rate, the proportion of the enrolled ewes which were marked or mounted.
Randomisation	Randomised. Using a random treatment allocation plan.
Blinding	Partially blinded. Clinical and oestrus observations were blinded.
Method	CIDR Sheep inserted and removed after 12 days. At the time of intravaginal insert removal, 500 IU of eCG was administered intramuscularly to each ewe in the Test Product group. Rams introduced. Ewes observed for colour marks every 12 hours for 3 days. Pregnancy diagnosis (approximately 60 days after removal of intravaginal inserts).
Statistical method	Oestrus response was analysed using a generalised linear mixed model with a binomial error distribution and a logit link function. The statistical model included fixed effect for treatment and random effects of site and site by treatment interaction. Back-transformed least squares means, standard errors and 95% confidence intervals were constructed.
RESULTS	
Participant flow	Two groups of ewes: Group 1 – 167 non-treated animals Group 2 – 156 treated animals.
Duration of follow-up	Ewes monitored until lambing.
Outcomes for endpoints	Oestrus response rate: Group 1: Lower 95% CI 0.037 and Upper 95% CI 0.309 Group 2: Lower 95% CI 0.861 and Upper 95% CI 0.992 Oestrus response rate in CIDR Sheep treated animals (96.5% - Group 2) was significantly higher than in

	control animals (11.6% - Group 1); (P = 0.0003).
Adverse events	None that were considered related to the treatment.
DISCUSSION	This study demonstrates that the use of CIDR® Sheep in cycling and non-cycling ewes, followed by an injection of eCG, resulted in an oestrus response rate of 96.5%.

Study title	Time of Ovulation Post-CIDR Sheep removal in Ewes after Synchronisation of Oestrus with a 12-days CIDR® Sheep + eCG Synchronisation Protocol. Zoetis Belgium SA Veterinary Medicine Research & Development
Objectives	To evaluate the time of ovulation in ewes after treatment with a CIDR Sheep (intravaginal device loaded with 0.35 g progesterone) + eCG protocol.
Test site(s)	Single centre within the EU
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	CIDR Sheep (progesterone), Each insert contains 0.35 g of progesterone impregnated in a silicon elastomer skin moulded over a nylon spine.
Control	Uncontrolled.
Animals	Ewes primi- or multiparous, aged 2 – 4 years. **Inclusion criteria:** • Healthy, as determined by a veterinarian • Cycling **Exclusion criteria:** • Body condition score of <2 or >4 • Treatment with a prostaglandin, progesterone, or bovine somatotropin product by any route within 60 days prior to Study Day 0. • Poor health or evidence of disease • Any prior reproductive problems • Absence of corpus luteum
Outcomes/endpoints	Time of ovulation; the middle point between the last identification of a dominant follicle and its disappearance.
Randomisation	Randomised. Random animals were selected from a group of eligible ewes.
Blinding	Not blinded.
Method	CIDR Sheep inserted and removed after 12 days. At the time of intravaginal insert removal, 500 IU of eCG was administered intramuscularly. Ovaries scanned at time of removal until the first dominant follicle on either of the ovaries ovulated (disappearance of dominant follicle between two examinations).

Statistical method	Descriptive only
RESULTS	
Participant flow	One groups of 11 ewes.
Duration of follow-up	Ewes completed the study at the time when ovulation of a dominant follicle was confirmed by ultrasound.
Outcomes for endpoints	Time of ovulation was between 42 and 58 hours post administration of eCG, with the majority between 50 and 54 hours.
Adverse events	None.
DISCUSSION	Ovulation occurred between 42 and 58 hours following eCG injection, with the majority (73%) ovulating between 50 and 54 hours. In the case that artificial insemination and advanced breeding techniques (e.g. embryo transfer) are applied, the timing of ovulation should be taken into consideration for the selected technique for optimal results.

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 products is favourable.

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)