ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
MUTUAL RECOGNITION
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Ovuplant 2.1 mg Implantation Tablets for Horses (Mares)

PuAR correct as of 01/08/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0259/001/MR
Name, strength and pharmaceutical form	Ovuplant 2.1 mg Implantation Tablets for Horses (Mares)
Applicant	Arnolds Veterinary Products Ltd, Cartmel Drive Harlescott Shrewsbury Shropshire SY1 3TB
Active substance	Deslorelin (as deslorelin acetate)
ATC Vetcode	QH01CA
Target species	Horses
Indication for use	In mares: zootechnical treatment for the induction of ovulation within 48 hours, during oestrus in normally cycling mares (in sexual season), with an ovarian follicle greater than 30 mm diameter.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	04 December 2007
Date product first authorised in the Reference Member State (MRP only)	14 January 2005
Concerned Member States for original procedure	France Germany Ireland Italy The Netherlands Spain

I. SCIENTIFIC OVERVIEW

Ovuplant is indicated for use in oestrus mares with an ovarian follicle greater than 30 mm diameter to induce ovulation within 48 hours. Ovuplant is a cylindrical shaped implant, 2.3 mm diameter and 3.6 mm long, containing the active substance deslorelin, as deslorelin acetate. The total weight of the implant is about 25 mg and each implant is supplied pre-loaded in a polypropylene syringe with a stainless steel 11 gauge needle, packaged in a foil pouch. The product is administered by subcutaneous implantation in the lateral neck midway between the head and shoulder.

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 the active substance deslorelin (as deslorelin acetate) and excipients calcium hydrogen phosphate dihydrate and hydrogenated vegetable oil.

The implant is supplied preloaded in a polypropylene syringe with an attached stainless steel needle. Each preloaded implanter is supplied in a sealed foil pouch. Five of these are packaged in a cardboard carton. The particulars of the containers and controls performed are provided and conform to current guidelines.

The choice of the formulation is justified.

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.

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

C. Control of Starting Materials

The active substance is deslorelin (as deslorelin acetate). Supporting data have been provided in the form of an Active Substance Master File (ASMF). It is

considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

The excipients are the subjects of monographs in the European Pharmacopoeia. Compliance with the requirements of the pharmacopoeia is therefore applied as the specification for each of these substances.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Satisfactory specifications based on European Pharmacopoeia monographs are also supplied for materials used during manufacture.

F. 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.

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 intermediate product have been provided in accordance with applicable European guidelines, demonstrating the stability of the intermediate product 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

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years

Special precautions for storage
Store in a refrigerator (2°C-8°C)

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show the mechanism of action of deslorelin compounds and reports of intended effects in the target species. These effects are broadly similar to those reported in the literature for other GnRH agonists. The references presented are sufficient data to confirm the pharmacodynamics activity of this class of active compounds.

The applicant has also provided bibliographical data which demonstrate that, following subcutaneous administration, deslorelin is rapidly absorbed and cleared from plasma. It can be deduced from a study of the structure of deslorelin and buserelin, that metabolism of the two substances would also be similar. These data are considered sufficient to address this aspect of the dossier.

Toxicological Studies

No toxicological studies have been conducted with deslorelin, however the applicant has provided some bibliographical data on the related substance buserelin. These data are considered sufficient and it was concluded that any adverse effects are directly related to the mode of action of deslorelin.

Observations in Humans

The applicant has submitted six published references describing the use of deslorelin in the treatment of various disorders in humans (central precocious puberty, familial precocious puberty and premature ovarian failure). Some of the references submitted in other parts of the dossier also describe clinical use of deslorelin.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which refers to the relatively low chance of contact with Ovuplant and the expected lack of adverse effects following contact with the product. The applicant has identified the possible routes of exposure as skin contact or accidental self-injection. The applicant postulates that effects on the female reproductive tract are possible and the proposed warnings address the potential exposure of the operator to Ovuplant. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

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 environmental safety is considered to be satisfactory and no further information was 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.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because although deslorelin has been entered into Annex II of Regulation 2377/90 (no MRLs required), a 7 day meat withdrawal period is considered appropriate to allow for the 3 day release of active from the implant and any residues persisting beyond this time. The product is also contraindicated in animals producing milk for human consumption.

MRLs

Deslorelin is listed in Annex II of Council Regulation 2377/90

Withdrawal Periods

Based on the data provided above, a withdrawal period of 7 days for meat in horses and contraindication for mares producing milk for human consumption are justified.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has included a number of references that demonstrate the mechanism of action of deslorelin. It stimulates pituitary gonadotrophin release when administered as a single dose. However, after multiple doses, the synthesis and secretion of LH and FSH is inhibited in a dose-dependent manner. Pulsatile administration of GnRH has been proven to initiate the pre-ovulatory LH surge. This stimulation of LH release is the basis of its desired action in mares – to hasten ovulation.

Blood concentrations of FSH and LH appear to peak at around 12 hours after implantation and decrease towards baseline values at around 30 to 48 hours after implantation. This reflects the deslorelin release from the implant, which results in an LH peak within a narrow time frame, therefore stimulating ovulation of a pre-ovulatory follicle. The information contained in the SPC is satisfactory.

No pharmacokinetic studies have been presented measuring deslorelin levels *in-vivo*. The data presented indicate that there is poor oral bioavailability but rapid subcutaneous absorption of deslorelin. The stability tests presented do not mimic *in-vivo* conditions. The applicant has stated that there are no published references regarding the absorption, metabolism and excretion of deslorelin in horses and that safety and efficacy has been well established in the satisfactory clinical use of the product for over 7 years. Some references have been included to support the pharmacokinetics in other species. The information contained in the SPC is satisfactory.

Tolerance in the Target Species of Animals

A target animal tolerance study was conducted using multiples of the recommended dose in the target species. A placebo was used as a control. All doses were administered as indicated on three consecutive cycles. It was noted that follicles were significantly smaller before ovulation for deslorelin treated mares compared with placebo treated mares. However, treatment had no effect on the percentage of mares pregnant at days 18 or 50. A statement is included in the SPC highlighting this effect of the implant.

The study demonstrated that the product was well tolerated. Local reactions to implantation were seen but were of short duration; the incidence increased with multiple implantations and with higher dosages.

IV.B Clinical Studies

Dose determination studies demonstrated that an implant containing 2.2 mg deslorelin was the most effective regime; a greater number of mares ovulated within 48 hours of implantation compared to other dosages. The SPC reflects that mares should be implanted when the dominant follicle reaches a diameter of 30 mm or greater, therefore the follicle should always be mature enough to respond. However, there is a natural variation of mares' reproductive systems such that some will not respond within 48 hours of implantation.

Conception and pregnancy rates were recorded in several of the trials. There was no overall difference seen between deslorelin and placebo treated mares by the end of the studies. It was noted that in several trials, the follicle that ovulated was of a smaller diameter in deslorelin treated mares compared to placebo treated mares. An appropriate statement highlighting this fact is included in the SPC.

There were no systemic adverse effects reported in any trial. Swelling was the most common implantation site reaction. There was variability in the severity and incidence reported by investigators at different sites, which may have been due to different implantation techniques causing soft tissue trauma, introduction of infection and differences in assessment. All reactions only lasted up to 5 days and all resolved without treatment.

The efficacy and safety of deslorelin implantation during four successive cycles was satisfactorily investigated in the target species tolerance study. The clinical trials clearly established that deslorelin administered as a short-term implant advances ovulation in oestrus mares with a follicle greater than 30 mm diameter.

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.

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)