I. INTRODUCTION

This was an application for an extension to the Marketing Authorisation for Receptal 0.004 mg/ml Solution for Injection, which has been marketed in the UK since 1993, to include pigs as an additional target species. The application was made in accordance with Article 13 of Directive 2001/82/EC as amended. Receptal 0.004 mg/ml Solution for Injection contains the active substance Buserelin at 0.004 mg/ml. The product has the following indications: for the treatment of infertility of ovarian origin and improvement of pregnancy rate in cows, for the synchronisation of oestrus in dairy cattle and for reducing the calving to conception intervals in these animals when used in conjunction with a PGF[1] 2α analogue with luteolytic activity, to induce ovulation of a mature follicle in mares, to induce ovulation in pigs (gilts) after oestrus, for the improvement of conception rate and induction of ovulation in rabbits and to facilitate stripping and reduce mortality due to egg binding in rainbow trout.

The product is administered by intramuscular, intravenous or subcutaneous injection, depending on species. In cattle, horses and rabbits, the preferred route of administration is by intramuscular injection (i.m), but the product may also be injected intravenously (i.v.) or subcutaneously (s.c.). In pigs, the preferred route of administration is i.m, but the product may also be injected i.v.Trout are injected i.m, above the lateral line, posterior to the dorsal fin.

Cattle (For full details, refer to the SPC)[2]

The dose for the treatment of follicular cysts and acyclia is 5.0 ml. The dose for delayed ovulation and the improvement of pregnancy rate is 2.5 ml. For the synchronisation of oestrus in dairy cattle, the product may be used as part of a 10-day GnRH[3]/prostaglandin/GnRH oestrus synchronisation and insemination regime.

Horses (For the treatment of mares, for full details, refer to the SPC)

The dose to induce ovulation of a mature follicle and thereby synchronise ovulation more closely with mating is 10 ml.

Pigs (For the treatment of gilts, for full details, refer to the SPC)

The dose for the induction of ovulation after oestrus synchronisation, in order to facilitate a single fixed time artificial insemination programme is 10 µg (2.5 ml/animal).

Rabbits (For full details, refer to the SPC)

For the induction of ovulation for post-partum insemination and for the improvement of conception rate, the dose is 0.2 ml.

Rainbow trout (For full details, refer to the SPC)

The dose is 0.75 – 1.0 ml per kg bodyweight (3-4 µg/ Buserelin/kg bodyweight).

[1] Placental growth factor.
[2] SPC – Summary of Product Characteristics.
[3] GnRH - gonadotrophin-releasing hormone.

II. QUALITY ASPECTS

Product Development and Composition

As this was an extension application to add a species to an existing product, and Receptal 0.004% mg/ml Solution for Injection has been authorised since 1993, no further data were required in this section.

Active Substance

Active substance 1

A certificate of suitability was provided showing that Buserelin is cited in the European Pharmacopoeia is used in the product.

Other Substances

Excipients are:-
Benzyl alcohol, sodium chloride, sodium dihydrogen phosphate monohydrate, sodium hydroxide (pH adjustment), hydrochloric acid (pH adjustment) and water for injections.

Packaging Materials

10 ml and 5 x 10 ml clear Type I multidose glass bottles closed with bromobutyl rubber stoppers with an aluminium overseal.

Finished Product Quality Control

Current tests performed on the finished product are considered satisfactory.

Stability of the Product

Finished Product

The shelf life remains at three years for product stored at a temperature not exceeding 25^{o}C and protected from light.

In-Use

Following withdrawal of the first dose, the product should be stored in a refrigerator and used within 24 hours.

CONCLUSIONS ON QUALITY

The Quality aspects of the application were considered satisfactory.

III. SAFETY ASPECTS

Introduction

This was an application for an extension to the Marketing Authorisation for Receptal 0.004 mg/ml Solution for Injection to add pigs as a target species. Use of the product in the other species cited on the SPC is already established.

Pharmacology

Pharmacodynamics

Buserelin is a synthetic analogue of GnRH. GnRH plays a role in the control of reproduction by modulating the secretion of pituitary gonadotrophins: luteinising hormone (LH), and follicle stimulating hormone (FSH). The active substance is used in humans to treat conditions related to infertility and other sex hormone dependant pathologies. A reference was provided relating to the use of Buserelin in healthy men and non-pregnant women, (Brogden *et al* 1990). Three trials were performed to investigate the use of Buserelin in pigs

Administered as a single dose, Buserelin stimulates pituitary gonadotrophin release. Prolonged exposure results in pituitary desenstization and reduced LH concentrations... In men, Buserelin causes luteinising hormone and follicle stimulating hormone release, increasing circulating testosterone concentrations. It does not affect growth hormone, prolactin, cortisol or thyroid stimulating hormone concentrations. Prolonged exposure causes pituitary desensitisation, lowered testosterone and impaired testicular function.

Pharmacokinetics

A series of references were provided. One indicated that in women with endometriosis who were administered Buserelin, the main serum metabolite (also found in urine), was Buserelin (5-9) pentapeptide. Another reference confirmed that the main metabolite in human urine is not an active substance. A third reference highlighted the rapid absorption and elimination of Buserelin in women, with complete elimination occurring within 8 hours.

Toxicology

As this was an application for an extension to an existing Marketing Authorisation, no data were required in this section.

Residues

No new residues data were required for this application. Absorption and elimination of Buserelin from all animals, including pigs and humans has been shown to be rapid. The withdrawal period for meat from cattle, horses, pigs and rabbits for this product is zero days. The withdrawal period for milk from cattle is zero hours. The product is not to be used in trout intended for human consumption.

Environmental Safety

The product carries the disposal advice 'dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority.' Residues may enter the environment via slurry from housed animals which are then applied to the land. A Phase I risk assessment was provided by the applicant, in addition to an acceptable PEC_{soil} [4] calculation. The assessment ends at Phase I, with data showing favourable results with regard to relevant VICH[5] parameters.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

The end user of the product is the veterinarian. The most likely routes of exposure are accidental self-injection and dermal absorption. With the aid of supporting data supplied in the form of reference material, the applicant has stated that there is no likelihood of dermal absorption. The maximum amount of Buserelin that could be absorbed by a 60 kg adult is 0.7µg/kg. The maximum therapeutic dose for a human is 100 µg/kg/day; therefore, the margin of safety for the product with regard to accidental self-injection is large.

Conclusions on Consumer Safety

The withdrawal period for meat from cattle, horses, pigs and rabbits is zero days. The withdrawal period for milk from cattle is zero hours. The product is not to be used in trout intended for human consumption.

Conclusions on Environmental Safety

Acceptable data were provided in relation to environmental safety.

IV. CLINICAL ASPECTS

Introduction

This was an application for an extension to include a new species, pigs, in accordance with Article 13 of Directive 2001/82/EC as amended, 'to induce ovulation in pigs'. Use of the product in the other species cited on the SPC is already established.

Clinical Pharmacology

Pharmacodynamics

Reference was made to two studies in which a number of animals were treated with synthetic GnRH, in order to investigate ovulation and pregnancy rates. The studies provided evidence of the efficacy of Buserelin in inducing ovulation, that ovulation was synchronised, and that Buserelin acts by causing a luteinising hormone surge. The studies supported the dose rate established for use of the product in gilts.

[4] PEC_{soil} – Figure provided after calculation of the predicted concentration of active substance in the upper 5 cm of soil.
[5] VICH – International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

Pharmacokinetics

Data were provided of a study in which luteinising hormone concentration in male pigs was measured following i.v. and i.m. injection with 10 µg of Buserelin, in order to examine the pharmacodynamic effect of Buserelin on plasma luteinising hormone. Results showed that the bioavailability of Buserelin following administration was very high.

Tolerance in the Target Species

A report was included which examined the safety of Receptal 0.004 mg/ml Solution for Injection for the breeding sow. A suitable number of animals were injected with 1000IU PMSG[6] prior to i.m. injection of 3.5 ml of product once, for one day, or 3.5 ml of product once for three days, or 10.5 ml of product once, for one day. Physiological analyses were performed as appropriate, and no abnormal findings were reported 7 days post-injection. The safety of the product, as used in the novel target species was supported.

Resistance

Not applicable for this type of product.

Clinical Efficacy

Data from 3 references were provided by the applicant. In the first reference, a GCP (Good Clinical Practice) field trial was conducted on a suitable number of animals, in order to investigate the induction and synchronisation of ovulations in nulliparous sows in which oestrus was synchronised. All animals were pre-synchronised with Regumate Porcine 0.4% w/v Oral Solution, (synchronises oestrus, improves farrowing rate and litter size), before random division into 4 groups. One group then received only saline, two groups received 10 µg of Receptal 0.004 mg/ml Solution for Injection at 104 or 120 hours after a final feed of Regumate Porcine 0.4% w/v Oral Solution, and the last group received 800IU PMSG 24 hours after the end of the Regumate injections, followed by Receptal (10 µg) 104 hours after the end of the Regumate therapy. Study end-points were: the time of ovulation, synchronisation of ovulation and fertility and prolificacy following 2 inseminations at oestrus.

Ovulation occurred significantly earlier when Receptal 0.004 mg/ml Solution for Injection was injected at 104 hours compared to 120 hours, or not used. In addition, synchronisation was closer when Receptal was injected at 104 hours. Fertility was high and similar in all groups. It was numerically higher when Receptal was injected at 120 (92%) compared to 104 hours (81.2). The combination of Receptal after the final Regumate treatment was shown to efficiently control ovulation. Finally, inclusion of PMSG in the treatment scheme fails to improve all parameters studied. No adverse effects were seen.

A second report examined a clinical test of the effectiveness of Buserelin for inducing ovulation in mature sows and gilts. The field trial involved a large number of suitable animals, and compared the recommended 10 µg dose with two positive controls using either 500IU hCG[7] or 50 µg alternative GnRH agonist. Gilts were pre-synchronised with Regumate Porcine 0.4% w/v Oral Solution; followed by an injection of 800IU PMSG 24 hours after the last treated feed.

[6] PMSG – Pregnant mare's serum gonadotrophin.
[7] hCG – Human chorionic gonadotrophin.

Random groups organised form the original number then received either 10 µg Receptal 0.004% mg/ml Solution for Injection, or 50 µg D-Phe 6 GnRH.
All ovulation inducing treatments were performed 104 hours after the final Regumate feed, after which, all gilts were artificially inseminated twice. The safe and effective use of 10 µg of Receptal 0.004% mg/ml Solution for Injection in pigs was assured.

The third report investigated whether the use of PMSG after the end of Regumate treatment and induction of ovulation permitted a single fixed time artificial insemination. A suitable number of animals were divided into groups following treatment with Regumate Porcine 0.4% w/v Oral Solution. Controls received no further treatment prior to insemination, two groups received PMSG 600IU 24 hours after the Regumate/Receptal treatment, at either 72 hours or 96 hours after the end of the Regumate. A further group received Receptal 96 hours after the end of Regumate, and final group, Receptal after 120 hours after the end of the Regumate. All artificial insemination was performed 36 hours post treatment. End points measured were fertility and prolificacy, and ovulation induction assessment at a variety of time points. Results showed that Receptal 0.004% mg/ml Solution for Injection gave good results with regard to fertility and prolificacy. In addition, the importance of the correct timing of administration demonstrated how cystic follicles could be avoided. (A warning is cited in the SPC).

A study report was provided which analysed the safety and efficacy of Receptal 0.004% mg/ml Solution for Injection for allowing a systematic insemination of gilts. A suitable number of animals were divided into groups for a multicentre, non-blinded, randomised, negatively controlled field study. All animals received 18 days of treatment with 20 mg (5ml) Regumate Porcine 0.4% w/v Oral Solution. 115 -120 hours later, a proportion of gilts were injected with 2.5 ml of Receptal 0.004% mg/ml Solution for Injection, and 30-33 hours later artificial insemination was performed. It was concluded that the clinical safety and efficacy of Buserelin at a dose of 10 µg, for the induction and synchronisation of ovulation in pigs, in addition to the maintenance of high levels of fertility and profligacy following single fixed time artificial insemination was demonstrated.

CONCLUSIONS ON CLINICAL ASPECTS

Buserelin induces and synchronises ovulation in gilts by triggering a luteinising hormone surge. In gilts the dose rate should be 10µg via i.m administration. High bioavailability of the product was demonstrated via the i.m. route. It is important to time the dose of Buserelin carefully in order to optimise the release of mature oocytes, thus maximising fertility and profligacy. Dosing in this way results in high levels of fertility and profligacy after a single fixed time insemination.

PART V. OVERALL CONCLUSION ON THE PRODUCT

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.

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)