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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for OvuGel (EMEA/V/C/005219/0000)

INN: triptorelin acetate

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant VETOQUINOL submitted on 21 May 2019 an application for a marketing authorisation to the European Medicines Agency (The Agency) for OvuGel, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 8 November 2018 as OvuGel contains a new active substance (triptorelin acetate), which was not authorised as a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004.

The applicant applied for the following indication: "For the synchronisation of ovulation in weaned sows to enable a single fixed-time artificial insemination."

The active substance of OvuGel (triptorelin acetate), is a synthetic analogue of gonadotropin releasing hormones (GnRH), which stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which then further stimulate the production of sex steroids and ovulation. The target species is pigs (sow for reproduction). OvuGel is presented as a vaginal gel containing 0.1 mg triptorelin acetate/ml, and is presented in one vial of 50 ml. The product is to be administered intravaginally using a suitable intravaginal administration tool.

The rapporteur appointed is Bruno Urbain and the co-rapporteur is Anna Wachnik-Święcicka.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

Scientific advice

The applicant received scientific advice from the CVMP. The scientific advice pertained to safety and clinical development of the dossier. This advice was followed by the applicant.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated September 2017) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse event occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The active substance is manufactured within the EEA. A valid GMP certificate and QP declaration were provided.

The finished product manufacturer is based outside the EEA. This site has been inspected by the French Agency in December 2019 and a valid EU GMP certificate dated 3 February 2020 has been granted.

The manufacturer responsible for batch release is VETOQUINOL, Magny Vernois, 70200 Lure, France. A valid GMP certificate issued by ANSES dated 03 April 2018 has been provided.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as vaginal gel containing 100 micrograms triptorelin (corresponding to 104.6 micrograms triptorelin acetate) per ml as active substance.

Other ingredients are sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, sodium chloride, L-Methionine, sodium citrate, citric acid anhydrous, methylcellulose and purified water.

The product is available in a multidose 50 ml type I amber glass vial closed with a bromobutyl rubber stopper and an aluminium seal as described in section 6.5 of the SPC.

Containers

The primary packaging is a multidose 50 ml type I amber glass vial closed with a silicone coated bromobutyl rubber stopper and an aluminium seal. The glass vials and rubber stoppers comply with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The secondary packaging is a carton box containing a unique vial containing 50 ml vaginal gel. The specified fill volume assures that at least 50 ml can be withdrawn from each bottle.

Development pharmaceutics

OvuGel is a viscous hydrogel allowing for optimum delivery of the active substance across the vaginal epithelia. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

The formulation used during the pivotal clinical studies is the same as that intended for marketing.

Pharmaceutical development of the finished product contains Quality by design elements. The quality target product profile (QTPP) was defined as a vaginal gel, which should be administered using commercially available multidose automatic injectors on which an infusion tube is plugged. The aim was to develop a drug product that should be stable over minimum 24 months (at 2-8°C) with an in-use shelf life after first broaching of 28 days, that meets compendial and other relevant quality standards, and is packaged protected from light.

Drug product development:

The aim of the formulation development was good solubilization of triptorelin, suitable viscosity for ensuring high transport rate across cell membranes, long-term stability of the drug product over at least 24 months under refrigerated conditions, and microbial preservative efficacy of the formula allowing for an in-use shelf life of 28 days.

Formulations containing different preservatives were tested for their impact on product stability, leading to the choice of a combination of methylparaben sodium salt and propylparaben sodium salt, whose content is supported by preservative efficacy studies.

Sodium chloride was added to the formulation at the common approximate concentration of 0.9% to produce an isotonic solution.

Manufacturing process development:

The manufacturing process development has been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. The risk identification was based on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

Development studies were performed at laboratory scale in order to define process steps, identification of critical process parameters and critical materials attributes. Process optimization studies were performed at pilot scale to define tentative operating parameters and IPC acceptance limits and establish the risk-based strategy for scale-up to commercial size batches and for Process Performance Qualification. Finally, three consecutive batches at full scale on the industrial equipment have been manufactured.

The experience gained at pilot and commercial scale did not identify any particular sensitivity of parameters to scale-up. For the final process risk analysis and process control strategy, potential hazards for each manufacturing operation were assessed with regard to probability and detectability, and the required level of supervision of the manufacturing process was determined for routine production and product life cycle management. Established Conditions (ECs) were defined considering the criticality of the manufacturing steps. Any changes to the ECs would trigger a regulatory variation.

Container closure system:

The primary packaging of triptorelin solution was selected with regard to volume (yielding at least 50.0 ml extractable volume), protection from light, tightness, compatibility with the product and safety (leachables).

Dosing accuracy studies performed in the field with several commercially available devices showed that all devices were suited to deliver accurate doses of 2.0 mL. However, there were considerable differences in product loss when emptying one single bottle, ranging from 2.3 mL to 5.8 mL with an average of 3.7 ml. The most suitable type of device has been limited to a bottle mount automatic self-filling syringe, as pistol grip devices show higher product waste. In the Quality Target Product Profile (QTPP) the extractable volume has been stated as ≥ 50.0 ml and the target for excess filling volume was adjusted accordingly to ensure that 50.0 ml gel can be withdrawn from one bottle.

Microbiological attributes:

The solution is non-sterile. It complies with Ph. Eur. limits for vaginal products.

Method of manufacture

The manufacturing process consists of three main steps - manufacture of the bulk, filling and packaging.

The manufacturing process is considered to be a standard manufacturing process consisting of two separate dissolutions, mixing and then progressive addition and dispersion of ingredients to obtain a uniform gel; pH adjustment is then carried out (if needed) before filling and labelling. The critical steps of the manufacturing process and associated critical process parameters (CPPs) that were identified during process development. These steps are adequately controlled.

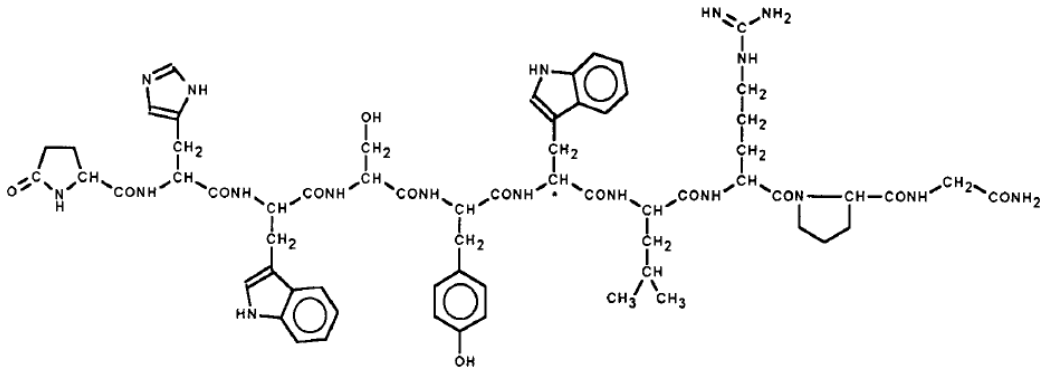
Process validation was performed on a on three consecutive commercial scale GMP batches manufactured on the industrial equipment. All results comply with the finished product specifications and are comparable for all three batches.
From the process validation studies it can be concluded that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Control of starting materials

Active substance

Triptorelin acetate is a linear decapeptide in mostly L-conformation. Only the tryptophan building block on position 6 from the amino end is in D-conformation.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Triptorelin acetates chemical name is L-Pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolyl- glycinamide, acetate salt. It has the following structure:



The active substance is an amorphous, white or off white, highly hygroscopic powder that is freely soluble in acetic acid; soluble in water, 0.1M hydrochloric acid, 0.1M sodium hydroxide, DMF and practically insoluble in acetone and chloroform.

Triptorelin acetate exhibits stereoisomerism due to the presence of 9 chiral centres (glycine does not possess a side chain and is thus not chiral). Enantiomeric purity is controlled routinely by HPLC which has been shown in spiking experiments to be discriminatory to enantiomeric impurities.

Polymorphism has not been observed for triptorelin acetate.

Triptorelin acetate is not described in a pharmacopeia of an EU member state or the Ph. Eur. The active substance specifications proposed by the applicant include tests for appearance, appearance of solution, water content, specific optical rotation, amino acid analysis, identification, assay, acetic acid content and impurities. The ASMF holder additionally specifies heavy metals and residual solvent content as well as microbial burden and endotoxin level. Thus, triptorelin acetate is considered to be comprehensibly controlled by the complete set of parameters.

Analytical methods for the determination of release specification parameters have been described in detail and validation data for the non-Ph. Eur. methods is included in the dossier. Information on the reference standards is provided.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed and characterised with regards to their origin. A special focus was set on the origin and fate of enantiomeric impurities that put the highest demand on the whole active substance manufacturing process.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Triptorelin acetate is synthesised using commercially available, well defined starting materials with acceptable specifications.

Detailed information on the manufacture of the active substance has been provided in the restricted part of the ASMF.

Batch analysis data for 3 batches of commercial batch size of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability data on 3 batches of the active substance from the proposed manufacturer stored in the intended commercial package for 60 months under long term conditions at -20°C and 5°C, for up to 24 months under accelerated conditions at 25°C/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines were provided.

During long-term stability testing at -20°C and 5°C all tested parameters were within the specification. Degradation products increased slightly under accelerated conditions at 25°C/60% RH with triptorelin free acid being the main degradation product.

Photostability testing showed that triptorelin acetate is prone to UV irradiation and should be stored protected from light. Results on stress testing were also provided on one batch. According to the stress testing results, triptorelin acetate is unstable at higher temperatures, acidic and basic conditions. But it is stable in water and under oxidative conditions.

The following parameters were tested for long-term and accelerated stability testing:

- Appearance
- Appearance of solution
- Assay
- Related substances: individual related substances, total related substances

The analytical methods used were the same as for the active substance specification and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable when stored refrigerated. The stability results justify the proposed retest period of 36 months at +2°C to +8°C in the proposed container.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. and USP standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The product does not contain any materials derived from human or animal origin.

Control tests on the finished product

The proposed specifications of the finished product at release and during shelf life include tests for appearance of solution, pH, viscosity, filled volume, identification of triptorelin (retention time, UV spectrum) and preservatives, assay of triptorelin and preservatives, unspecified and total triptorelin degradation products, and microbiological quality. Acceptance criteria for release and shelf life are identical except for triptorelin assay and total degradation products.

For the determination of pH and microbiological quality, the Ph. Eur. methods are used; identification and assay of triptorelin, preservatives and degradation products are performed using in-house methods. The same methods are used for testing both at release and during shelf life.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines. Information on the reference standards used for assay and preservatives testing is provided.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Due to the history of the finished product, testing results for several batches from different manufacturers are available and the following stability data for OvuGel according to the VICH guideline GL3 were provided:

- Three batches of 500 kg from a first manufacturer (former manufacturer) stored under long term conditions for 36 months at 5 ºC ± 3 °C. One additional batch was stored for 6 months at 30 °C.
- Three batches of 250 l, from a second manufacturer (former manufacturer), were stored under long term conditions for 36 months at 5 ºC± 3 °C and for 12 months under accelerated conditions at 25 ºC/60% RH. These batches were also used for photostability and in-use stability testing.
- Three batches of 500 kg from a third manufacturer (current proposed manufacturer), were stored under long term conditions for 36 months at 5 ºC± 3 °C and for 6 months under accelerated conditions at 25 ºC/60% RH.

The batches of product are identical to those proposed for marketing and were packed in the same type of primary packaging proposed for marketing. The primary packaging proposed for marketing only differs for the rubber stopper which was recently changed for a siliconized rubber stopper. This change is supported by one batch put on stability for 6 months under accelerated conditions and 36 months under long-term conditions, with bottles in horizontal position. At present, stability data through 6 months at 25 °C / 60 % RH and at 2 °C - 8 °C are available. They do not show any significant changes and are comparable to data generated with the previous rubber stoppers.

Samples were tested for appearance, pH, viscosity, triptorelin assay and degradation products, preservatives contents and microbial quality. The analytical procedures used are stability indicating. No significant changes have been observed under the proposed storage conditions.

In addition, one batch was exposed to light as defined in the VICH guideline GL5 on photostability testing of new veterinary drug substances and medicinal products.

In-use stability studies over 28 days were carried out on a fresh batch, a batch aged about 24 months and a batch at the end of the proposed shelf life of 36 months. From the in-use stability results it can be concluded that triptorelin gel can be used over 28 days when stored at the recommended storage condition of 2°C - 8°C. However, studies show that in-use storage at 25°C does not raise any stability concern.

Based on the available stability data, the proposed shelf-life of 3 years and the storage conditions as stated in the SPC (2 °C – 8 °C) are acceptable. An in-use shelf life of 28 days is acceptable when stored in a refrigerator (2°C – 8°C) or at temperatures not above 25°C.

Overall conclusions on quality

The development pharmaceutics of the formulation has been suitably explained. The manufacturing process and in-process controls have been described in sufficient detail.

The information on the active substance is provided in an Active Substance Master File (ASMF) and is satisfactory.

The excipients and packaging materials comply with compendial requirement.

The finished product specification includes all relevant quality attributes and is sufficient to assure consistent quality. The control methods are described and appropriately validated.

Stability studies on the finished product are performed under VICH conditions. The proposed shelf life of 3 years when stored at 2 – 8 °C is acceptable. In-use stability of 28 days has been demonstrated on a fresh batch of the product and on a batch at the end of its shelf-life.

Based on the review of the data on quality, the manufacture and control of the drug product are considered acceptable and conform to current EU guidelines.

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied retrospective Quality by Design principles to support the development of the finished product. However, no design spaces were claimed for the manufacturing process of the drug product.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

Part 3 – Safety

Safety documentation

The active substance of OvuGel, triptorelin acetate, is a new active substance not authorised for a veterinary medicinal product in the EU before. A full safety file in accordance with Article 12(3)(j) has been provided.

The application makes reference to the studies submitted, literature and previous assessment of the CVMP in the context of the establishment of maximum residues limits for triptorelin acetate (European public MRL assessment report EMA/CVMP/382140/2013), which states that "Triptorelin is a decapeptide and potential residues in food products obtained from treated animals will be broken down into naturally occurring amino acids in the human gastro-intestinal tract and so will not be absorbed". In light of this, a full safety data package was not submitted.

Pharmacodynamics

See Part 4.

Pharmacokinetics

In humans and rats, triptorelin is poorly bioavailable when administered via oral or rectal routes, in the region of 0.1%, due to proteolysis activity in the body, favoured by the non-binding of GnRH to plasma proteins.

The target animal pharmacokinetics study demonstrated that intravaginal administration of 200 µg triptorelin/sow had a considerably lower bioavailability compared to intravenous administration (less than 7.45 %). Plasma levels of triptorelin were quantifiable at 6 hours after intravaginal administration (12 hours following intravenous administration), and harmonic mean half-life values after intravaginal administration (3.92 hours) were in the same order as for intravenous administration (4.47 hours).

The intravenous administration indicated that triptorelin in pigs is widely distributed, has a relatively short half-life (and residence time) and is rapidly cleared from the system, as would be expected for a GnRH analogue.

Toxicological studies

The active substance triptorelin acetate was previously assessed by the CVMP in the context of the establishment of MRLs and the key findings of the toxicity studies evaluated (EMA/CVMP/382140/2013) are summarised below.

In addition, a number of safety studies in the target species, discussed in part 4 supports the toxicological profile of triptorelin.

Single dose toxicity

Two toxicity studies after acute exposure to triptorelin were conducted in rats. The first one was conducted after single administration in female and male rats of 0 µg/kg body weight (bw) (control), 4 µg/kg bw by the oral route and 4 µg/kg bw by the subcutaneous route (group 3). Animals were observed for 24 hours and samples for serum LH analysis. The second study was conducted after single oral administration in female rats of 300 mg/kg bw and 2000 mg/kg bw. Each dose level was administered with 3 to 4 days between administrations. Animals were observed for 14 days then necropsied. In the first study, no clinical sign and no mortality was observed. Serum luteinising hormone (LH) concentrations were increased between 1 hour and 4 hours post-dosing in both males and females receiving the subcutaneous injection but not in those receiving the oral administration of triptorelin or the placebo. In the second study, no treatment-related effects (on clinical observations, body weight, and necropsy) were observed. It is agreed that triptorelin was considered as a category 5 chemical, by the Globally Harmonized System of Classification and Labelling of Chemicals, with LD50 for oral and dermal route between 2000 and 5000 mg/kg bw.

In a pilot laboratory study in the target species and the target species pharmacokinetics study, 200 µg triptorelin acetate/sow was administered intravenously. The 200 µg dose used in the pharmacokinetics study represents at least 13x the likely exposure following intravaginal administration. There were no adverse events during dosing or observed during the 72 hours following administration in the pilot study or in the pharmacokinetics study.

The single dose safety following intravaginal administration was demonstrated at 1x and 7x times the recommended treatment dose and also following administration of an overdose of 3x the recommended treatment dose in the reproduction study.

The single dose safety is adequately demonstrated. No treatment related signs of acute clinical toxicity were noted in any of the studies.

Repeat dose toxicity

In the MRL summary report (EMEA/CVMP/382140/2013) it was considered that in a 45 day repeat dose rat toxicity study no biologically or toxicologically significant effects, e.g. effects on Luteinizing Hormone (LH) levels and oestrus cycle or any microscopic changes, were observed following oral administration of doses up to 4 µg/kg bw. No increases in LH were observed on day 1 or at the end of the dosing period in the oral treatment and control groups; however, the LH levels were increased in response to a single subcutaneous dose of 400 µg triptorelin acetate/kg bw given on day 14 prior to the oral dose.

All of the effects observed following subcutaneous administrations of 4 and 400 µg/kg bw in rats were consistent with the known pharmacological effects of triptorelin and other GnRH analogues following long term treatment.

A target animal safety study included repeated intravaginal administration of the target dose over three consecutive days and also three times the target dose over three consecutive days. No deviations in blood biochemistry, haematology, urinalysis or necropsy were recorded. The only histopathological finding was the presence of luteal cysts. These were considered to be a consequence of the pharmacological activity of the test compound, and to be expected in animals receiving hormonal treatment.

It has been adequately demonstrated that repeated dosing of triptorelin in rats and the target species does not induce systemic or local toxicity.

Tolerance in the target species of animal

See part 4.

Overall, no other triptorelin associated adverse events or systemic or local signs of toxicity were recorded in pigs, other than those related to the pharmacological activity of triptorelin.

Reproductive toxicity

No OECD Guideline 421 compliant rat study was submitted to study reproductive/developmental toxicity. This is acceptable since the action and toxicology of triptorelin is relatively well known and no major adverse events on development are expected in the target species.

In a GLP-compliant target animal reproductive safety study, conducted in line with VICH GL43 target animal safety, it was confirmed that 3x the recommended dose (600 µg triptorelin acetate/sow; single administration at 96 hr ± 2 hr after weaning) followed by insemination did not provoke significant differences in reproductive performance parameters or piglet viability. The weight of stillborn piglets was greater following triptorelin treatment than in the control animals. However, this finding was attributed to a large number of stillborn piglets to a single triptorelin-treated sow, which had a protracted farrowing.

In conclusion, the use of triptorelin gel in this study had no adverse effects on sow reproduction or the viability of the offspring.

It is accepted that assessment following administration during gestation and lactation was not included for the following reasons: OvuGel should not be used in pregnant or lactating sows; due to the route of administration it is unlikely that accidental administration would occur during gestation or lactation; the group housing requirements for sows eliminates the chance of accidental administration; lactating sows are housed separately from those intended for breeding. The SPC carries an appropriate warning.

For reproductive toxicity in the light of user safety and consumer safety, it is referred to the respective sections.

Genotoxicity and carcinogenicity

Triptorelin is a decapeptide and will be broken down into naturally occurring amino acids in the human gastro-intestinal tract and so will not be absorbed. Human exposure via the oral route is considered to be negligible and hence it is considered that genotoxicity studies are not required. This approach was accepted by CVMP during the review of the MRL application (EMEA/CVMP/382140/2013). No MRL is required for any food producing species. Regarding oral exposure, there is no concern about the genotoxic and carcinogenic potential of triptorelin. However, when considering user safety and target animal safety, direct exposure and carcinogenicity should be considered. Given the low skin absorption of triptorelin in humans, the review of the toxicological data obtained for the development of triptorelin medicinal products for humans and the mutagenicity profile of molecules of the same class as triptorelin, and the safety precautions listed in the SPC, it is unlikely that carcinogenic effects will be observed in the user after handling OvuGel.

Considering the available safety data after repeated exposure to triptorelin in rats and mice, and that in sows repeated use consists of non-consecutive administrations, there is no concern over carcinogenicity for the target species.

Studies of other effects

Triptorelin is a decapeptide with a low oral bioavailability due to natural breakdown to amino acids in the intestinal tract. No additional studies for metabolites were provided and none are considered necessary.

From the GLP and OECD compliant skin irritation tests, it follows that triptorelin has no skin irritating properties.

From the GLP and OECD compliant eye irritating test, it was concluded that triptorelin has no eye irritating properties. Conjunctival reactions may be possible.

Excipients

All excipients are routinely used in both human and veterinary medicinal products within the EU and no additional studies are provided. All of the excipients are listed in the Excipient Handbook and are considered safe, and therefore are of no toxicological concern in the present formulation.

User safety

A user safety risk assessment was submitted in accordance with the Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1).

All possible risks associated with triptorelin during the exposure scenarios were described. Dermal, ocular and oral exposure were considered. All of the excipients are routinely used in both human and veterinary medicinal products currently available within the EU. However, hypersensitivity reactions to parabens (such as sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate) are mentioned in published literature.

Mitigation of this risk of hypersensitivity by dermal contact has been appropriately addressed by the applicant in the product information with special precautions for the user. However, despite the somewhat equivocal nature of the data in the public literature on the potential for parabens to elicit hypersensitivity reactions (generally of the delayed type and appearing as contact dermatitis), including the 'parabens paradox' (pertaining to the increased propensity of parabens to elicit reactions in sensitised individuals with broken skin and incidents of patients who have reacted previously to a parabens-containing topical medicine but have not reacted when the medicine has been applied to another, unaffected, site),

considering the long history of these concerns and similar warnings on other products containing parabens, the first paragraph of the user safety warnings was amended to read as follows: *'The product can cause eye irritation. People with known hypersensitivity to GnRH analogues or any of the excipients (including parabens) should avoid contact with the veterinary medicinal product."*

No risk quantification with MOE value calculation is performed. This is acceptable since it was concluded that the risk associated with dermal exposure is minimal, given that the penetration of triptorelin through human skin is almost zero. In addition, from the GLP and OECD compliant skin irritation tests, it followed that triptorelin has no skin irritating properties. Nevertheless, the warning "*Personal protective equipment consisting of overalls and gloves should be worn when handling the veterinary medicinal product*" mitigates any possible risk associated with dermal exposure.

Ocular exposure was considered as relevant. However, from the GLP and OECD compliant eye irritating test, it was concluded that triptorelin has no eye irritating properties. Conjunctival reactions may be possible. This risk is entirely covered by following risk mitigation measures: "*Avoid direct contact with skin or eyes, wash hands after handling the product. In case of accidental contact with the eyes, rinse thoroughly and seek medical advice immediately.*"

Given the nature of the product and the mode of administration, it was considered as unlikely that ocular absorption of triptorelin poses an unreasonable risk. In any case, this risk would be mitigated by the aforementioned risk mitigation measures. It is accepted that no risk associated with oral exposure is likely, given that triptorelin is a decapeptide that will be immediately digested in the digestive tract. In the EPMAR (EMA/CVMP/382140/2013) it is stated indeed: *"Neither a pharmacological nor a toxicological ADI is considered necessary as systemic exposure to residues will be negligible."*

The margin of exposure (MOE) is not estimated for pregnant women and women of child-bearing age. Therefore, the following precautions are included in the SPC: "*Triptorelin can affect reproductive cycles in women and therefore, it is recommended that pregnant women should not handle the veterinary medicinal product, and that women of child-bearing age should handle the veterinary medicinal product with caution"*.

Environmental risk assessment

The Environmental Risk Assessment has been conducted in accordance with the VICH guideline (VICH GL6 (Ecotoxicity) Phase I, June 2000 Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products (VMPs) – Phase I), with reference to the CVMP guideline on environmental impact assessment for veterinary medicinal products, (Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in Support of the VICH Guidelines GL6 and GL38 EMEA/CVMP/ERA/418282/2005-Rev.1).

According to the VICH GL6 guideline and based on the intended dose and use pattern, it is considered that there is no risk to the environment from the administration of OvuGel (triptorelin) to sows for reproduction.

The maximum predicted environmental concentration in soil was 0.0052 µg/kg, i.e. lower than the threshold of 100 µg/kg - assuming total excretion of the active as parent compound, and the environmental risk assessment can stop at Phase I. This predicted level assumes that all animals will receive 3 treatments per year. There are further additional safeguards for the environment due to the fact that the active ingredient triptorelin would be metabolised in the animal, in the same manner as endogenous or nutritional proteins.

Based on the data provided, OvuGel is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

MRLs

The active substance in OvuGel, triptorelin acetate, is an allowed substance for which no MRLs are required as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Triptorelin acetate	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	Agents acting on the reproductive system

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Residue studies

No residue studies were submitted. The omission of a residue depletion study was considered justified as no constituent of the product is subject to numerical MRLs. In addition, this is supported by the following arguments:

Pharmacokinetic data from a range of species indicate that GnRH analogues are rapidly eliminated, and this is consistent with data on observed LH levels in sows following administration of triptorelin.

In a pharmacokinetic study, it was shown that the bioavailability of triptorelin acetate following intravaginal administration of OvuGel was low and that circulating levels of triptorelin were no longer detectable 6 hours after administration. Additionally, the $T_{1/2}$ was identified as 3.92 hours following intravaginal administration supporting the expectation that residues of triptorelin are not expected to be present in any tissues at the time of slaughter.

In addition, triptorelin is a decapeptide and potential residues in food products obtained from treated animals will be broken down into naturally occurring amino acids in the human gastro-intestinal tract and so will not be absorbed (EMEA/CVMP/382140/2013).

In the absence of bioavailability and with no requirement for an MRL, no further residues data are required.

Withdrawal periods

A withdrawal period of zero days for meat is proposed. This is acceptable since according to the EPMAR for triptorelin acetate (EMEA/CVMP/382140/2013) the establishment of an ADI is not considered necessary and no MRL is required on the basis that: the oral bioavailability of residues of triptorelin acetate in humans is considered negligible; triptorelin acetate, like other GnRH analogues, will be rapidly absorbed and eliminated/degraded in the target species, and a consumer's systemic exposure to residues of triptorelin acetate will not be affected by the target species treated.

Overall conclusions on the safety and residues documentation

The pharmacokinetic profile of triptorelin was exhaustively described in laboratory animals and humans based on literature data. In addition, the pharmacokinetics of OvuGel were elucidated by means of the

target animal study. From this study, it can be concluded that the bioavailability of triptorelin from OvuGel administered intravaginally to sows is less than 7.4% of the 200 µg triptorelin dose entering systemic circulation when compared to intravenous administration. It can also be concluded that although intravaginal administration of triptorelin had a low bioavailability, plasma levels of triptorelin were quantifiable and harmonic mean $T_{1/2}$ life values were in the same order as for intravenous administration. The submitted data is considered as adequate in order to characterize the pharmacokinetics of triptorelin.

The pharmacodynamic profile of triptorelin is described in part 4. Two single-dose toxicity studies after acute exposure to triptorelin were conducted in rats. Triptorelin acetate administered subcutaneously in a single dose at 4 µg/kg bw resulted in increased serum luteinizing hormone (LH) concentrations in both male and female rats between 1 and 4 hours post dose, whereas administration of the same dose orally did not affect LH concentrations in either sex. In one, no deaths occurred at 300 mg/kg bw and 1 of 6 rats at 2000 mg/kg bw died following a single oral dose of triptorelin acetate. The cause of death was not possible to be determined. The oral and dermal LD50 of triptorelin was determined to fall between 2000 –5000 mg/kg bw.

In the repeated dose toxicity study, triptorelin acetate was well-tolerated when administered orally to rats at doses up to 4 µg/kg bw/day for 45 days, with no effects on the oestrous cycle. When administered subcutaneously to rats at both 4 and 400 µg/kg bw/day, the oestrous cycle ceased by 32 and 17 days, respectively, of dosing. Body weight increased and progesterone levels were decreased in females, and testosterone levels were markedly decreased in males given triptorelin acetate SC at both 4 and 400 µg/kg bw/day. There were dose-responsive decreases in LH in animals of both sexes receiving 4 and 400 µg/kg BW/day SC relative to controls and animals receiving oral dosing. Triptorelin acetate-related microscopic findings were observed in the reproductive organs, bone marrow and mammary glands of males and females.

No OECD Guideline 421 compliant rat study was submitted to study reproductive/developmental toxicity. This is acceptable in the light of target animal safety and user safety since the action and toxicology of triptorelin is relatively well known and no major adverse events on development are expected in the target species.

Given that triptorelin is a decapeptide, it is concluded that it has no genotoxic or carcinogenic potential after oral or direct dermal exposure. In addition, considering the available safety data after repeated exposure to triptorelin in rats and mice, and that in sows repeated use consists of non-consecutive administrations, there is no concern on carcinogenicity for the target species.

Reproductive safety was been satisfactorily confirmed in sows in a study. It was concluded that 600 µg triptorelin gel/sow had no adverse effects on sow reproduction, including number of piglets born (total born, born dead, born alive, mummified) per litter, or live piglet weights. Assessment following administration during gestation and lactation was not included for the following reasons: OvuGel will not be labelled for use in pregnant or lactating sows; due to the route of administration it is unlikely that accidental administration would occur during gestation or lactation; the group housing requirements for sows eliminates the chance of accidental administration; lactating sows are housed separately from those intended for breeding.

A user safety risk assessment was submitted in accordance with the Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1). The dermal, ocular and oral exposure were considered. All of the excipients are routinely used in both human and veterinary medicinal products currently available within the EU. A warning on the presence of parabens is included in the product information.

According to VICH GL6 guideline and based on the intended dose and use pattern, it is considered that there is no risk to the environment from the administration of OvuGel (triptorelin) to sows for

reproduction. The maximum predicted environmental concentration in soil was 0.0052 µg/kg assuming total excretion of the active as parent compound, assuming that all animals will receive 3 treatments per year. In addition, the active ingredient triptorelin would be metabolised in the animal, in the same manner as endogenous or nutritional proteins. The Environmental risk assessment stops at Phase I.

In conclusion, the safety profile of OvuGel has been supported and seems acceptable. The data presented are considered adequate to characterise the toxicity profile of triptorelin.

Triptorelin acetate is included in Table I of the Annex to Commission Regulation (EU) No 37/2010 with no requirement for an MRL within the European Union for all food producing species.

The omission of a residue depletion study was considered justified as pharmacokinetic data from a range of species indicate that GnRH analogues are rapidly eliminated, and this is consistent with data on observed LH levels in sows following administration of triptorelin. In addition, triptorelin is a decapeptide and potential residues in food products obtained from treated animals will be broken down into naturally occurring amino acids in the human gastro-intestinal tract and so will not be absorbed (EMEA/CVMP/3821/2013).

In the absence of bioavailability and no requirement for an MRL, no further residues data are required and a zero day withdrawal period for meat is acceptable.

Part 4 – Efficacy

Pharmacodynamics

Physiologically, a sow remains anoestrus during lactation; following weaning prolactin levels gradually decrease, and blood levels of luteinizing hormone (LH) and estradiol increase, resulting in a stimulation of oestrus. Triptorelin is a new hormonal product for sows, acting as a (synthetic) analogue of gonadotropin releasing hormone (GnRH). It stimulates the release of LH and follicle stimulating hormone (FSH). These in turn stimulate the production of sex steroids and gametogenesis (ovulation).

The pharmacodynamics of triptorelin was supported by literature data and by preclinical dose finding studies. From these studies, it was concluded that increased LH levels in sows peaked between 3 (100 µg triptorelin/sow) and 16 hours (untreated control) after intravaginal administration. At 24 hours after administration, the blood LH levels had considerably decreased, and 30 to 35 hours after administration they had returned to pre-dose levels in all animals. Similar results were observed in a swine safety study which showed increased LH levels at 2 and 5 hours following intravaginal administration of 200 µg and 1400 µg triptorelin acetate, which dropped to pre-dose levels the day after administration.

In the dose justification study, ovulation rates were determined following intravaginal administration of 1, 25, 100 or 200 µg triptorelin 96 hours after weaning. Total ovulation rates by 48 hours post treatment increased with increasing doses of triptorelin (1-200 µg/sow).

A dose-determination study confirmed that neither the formulation vehicle for triptorelin gel nor the intravaginal administration influences the synchrony of ovulation, and that the effect on ovulation was solely due to triptorelin.

Secondary pharmacodynamics effects following chronic parental administration are pituitary desensitisation followed by gonadal suppression resulting in reduction of serum sex steroids. This has been observed following use in human medicine.

Pharmacokinetics

In a GLP-compliant pharmacokinetics study, it was demonstrated that bioavailability after intravaginal administration of 200 µg triptorelin/sow was 13-fold lower (<7.45%) than after intravenous administration. See also part 3.

Dose determination / finding studies

The dose finding studies investigated the optimal gel viscosity in order to maximize absorption of triptorelin, and the optimal concentration of triptorelin in the final formulation to achieve a consistent and timely LH response. In addition, the optimum period for the time of treatment post-weaning, and the optimum time for post-treatment insemination were investigated.

All studies were non-GLP compliant but well designed and included sows (parity 1-7) from breeds commonly used in European sow husbandry.

Role of viscosity

Since viscosity of the formulation is important for the effectiveness of triptorelin, three non-GLP studies were conducted in the USA:

In two proof-of-concept dose-finding non GLP studies, 32 ovariectomised, oestrogen treated commercial gilts (+/- 200 days of age and +/- 100 kg body weight) were administered 100 µg triptorelin, intravaginally, in a gel containing 1.2, 1.5 or 1.8% methylcellulose. In terms of the time range over which ovulation occurred, the duration for ovulation in the 1.2% and 1.5% gel (+ triptorelin) groups was shorter, compared to the controls and to the 0.6% and 0.9% methylcellulose. This was also confirmed in a third, similar study performed in 71 sows.

The CVMP agreed with the applicant's conclusions that the best LH response was achieved with a viscosity of 1.2 % methylcellulose.

Dose determination

Five dose finding studies were conducted in the USA. In four of them, the optimal dose for ovulation synchronization in sows was determined.

In two non-GCP compliant studies, the efficacy of fixed time insemination at 8 and 32 hours following administration of 100 µg triptorelin/sow at 96 h post weaning was tested. Farrowing rates and litter sizes were equal to or lower compared with the negative controls (sows inseminated according to normal farm practices, i.e. 2 inseminations at 24 h intervals based on oestrus detection). It was satisfactorily shown that treatment with triptorelin gel, administered intravaginally 96 h after weaning, reduced the duration of oestrus, synchronised ovulation and facilitated fixed-time inseminations.
However, insemination at both time points, 8 and 32 hours after treatment with a dose of 100 µg triptorelin/sow, was considered to be suboptimal as smaller litter sizes were seen compared to the control group.

In two further studies, 66 weaned sows were inseminated between 24-30 hours after treatment with 100 µg triptorelin/sow administered 96 h post weaning or at oestrus detection. However, pregnancy and farrowing rate in the triptorelin treated group was lower compared with the control group. The applicant concluded that the dose of 100 µg triptorelin/sow, which appeared to be effective in gilts (as determined in the two proof-of-concept studies, see above), should be further optimized in sows.

Therefore, a dose range of 0, 25, 100 and 200 µg triptorelin/sow was tested in two non-GCP compliant dose justification studies, involving in total 256 and 226, respectively, commercial, weaned sows (parity 1 - ≥3). Sows were blocked by length of lactation, parity and genotype and randomly assigned to one of

four treatments.
Pregnancy rate, farrowing rate, total number of piglets born, or number of piglets born alive were comparable in all groups. Significantly more sows treated with 200 µg triptorelin/sow had ovulated at 48 h post treatment (81%) compared to the controls (42%), while the 25 µg and 100 µg treatment groups did not differ (63 and 64%) significantly from the controls. The CVMP supported the applicant's conclusion that from these data, the administration of 200 µg triptorelin per sows can be considered as the most suitable dose to allow synchronizing ovulation to 48 hours after treatment at 96 hours post weaning.

In another, controlled randomized non-GCP study, including 113 weaned sows (parity 1-7), the potential of a placebo effect of the gel alone was examined. Three groups of sows received either 200 µg triptorelin in formulated gel, placebo gel or no treatment. Treatments were administered 96 hours (± 2 hours) post-weaning and sows were inseminated according to the farms normal breeding procedure. The applicant concluded that 200 µg triptorelin gel/sow administered at 96 hours post-weaning synchronizes ovulation in postpartum sows, and that neither the formulation vehicle for triptorelin gel nor the intravaginal administration influence the synchrony of ovulation. Therefore, the oestrus synchronisation observed with OvuGel is due solely to the active ingredient triptorelin. This study also confirms conclusions from the dose justification study that 200 µg triptorelin/sow advances ovulation, as significantly improved synchronisation of ovulation was observed at 48 and 56 hours post-treatment. Also, in agreement with data from the dose justification study, synchronising the time of ovulation did not adversely affect pregnancy or farrowing rates or litter size, and the means are representative of reported average industry performance parameters for the last several years.

In the study protocol of the above-mentioned study which included 113 weaned sows, it was indicated that blinding was not possible; however, the CVMP did not agree with the applicant that partial blinding could not be achieved. Partial blinding is possible if the personnel who administer the pharmaceutical product and the inseminators are not involved in the assessment of the sows, this was also confirmed during a Scientific Advice (EMA/CVMP/SAWP/189733/2013). Nevertheless, as this was not a pivotal study and the primary and secondary endpoints were all objective parameters, the lack of blinding in this study was not further questioned.

None of the dose determination studies were conducted in line with VICH GL 9 on Good Clinical Practices. However, since all these studies were well-conducted and well-documented, and results confirmed by the field trials, this was considered acceptable.

In conclusion, the CVMP accepted that a dose of 200 µg of triptorelin/sow was the most effective dose level to achieve synchronisation of ovulation at 48 hours compared to other doses of triptorelin. Furthermore, doses of 25 µg to 200 µg of triptorelin per sow did not adversely affect reproductive parameters.

Timing of treatment and insemination

In order to confirm the optimal timing of treatment and insemination, ten supportive well designed non-GCP controlled randomized studies conducted in the USA, and two pivotal well designed GCP-compliant multicentre studies (one conducted in the USA and one in the EU) were submitted.

Time of administration

In a non-GCP study in 128 postpartum sows (parity 1-7) investigating the effect of treatment with 200 µg triptorelin/sow at 72, 84 or 96 hours post weaning, 96 hours provided the best results in synchronisation of ovulation, and following a fixed time single insemination resulted in farrowing rates (91.1%), pregnancy rates (89.9%) and litter parameters (1.0 stillborn, 8.6 born live per litter) that are not different from control sows. The majority of sows ovulated during an 8 hour period, at 40 to 48 hours after treatment.

In another non-GCP study, different combinations of treatment and insemination times were examined. Sows (252 commercial, weaned) were treated 96, 100 or 104 hours post-weaning, and inseminated once at 15, 18 or 21 hours post-treatment, respectively. Control sows were inseminated every 24 hours while in oestrus.
Farrowing rates were not different between groups. Litter size was significantly higher in sows treated at 96 hours compared to those treated at 104 hours but did not differ from the other groups. The results suggest that the optimal time for treatment is 96 hours post-weaning.

Time of insemination

The optimal frequency of insemination following treatment with OvuGel was studied in a non-GCP study in 403 uni- and multiparous, weaned sows. Sows were inseminated at 24 hours, 30 hours, or 24 and 30 hours after treatment with 200 µg triptorelin 96 h post-weaning or daily while in oestrus (untreated control animals). Pregnancy rates did not differ among these four insemination protocols: 84.3% for controls, 90.0% for sows inseminated at 24 hours, 81.2% for sows inseminated at 30 hours, and 89.0% for sows inseminated at 24 hours and at 30 hours.

In another non-GCP study in 120 sows, fixed time inseminations at 18, 24 or 30 hours following treatment with either 200 µg triptorelin gel or insemination after 24 hours following placebo gel treatment were compared. There were more foetuses in triptorelin-treated sows inseminated at 18 and 24 hours post-treatment than in sows inseminated at 30 hours post-treatment or in the control sows. The applicant therefore concluded that a single fixed time insemination 18 or 24 hours following treatment at 96 hours post-weaning provides an ovulation rate, pregnancy rate and number of viable foetuses comparable to insemination according normal farm practices but without the need for oestrus detection or multiple inseminations.

This conclusion was also supported by the results from three further non-GCP compliant, non-pivotal studies.

In another non-GCP compliant study, sows were inseminated at 15, 18, 21 or 27 hours after triptorelin administered 103 hours after weaning. It was demonstrated in this study that the optimal time of insemination relative to time of treatment is dependent on the time of treatment relative to weaning, or the total time since weaning.

None of the studies was conducted in line with VICH GL 9 on Good Clinical Practices. However, since all these studies were well-conducted and well-documented and results confirmed by the field trials, this is acceptable.

In conclusion, OvuGel (200 µg triptorelin/sow as the acetate/2 ml intra vaginal dose) administered 96 ±2 hours after weaning is effective to synchronize the time of ovulation; thereby facilitating a single fixed-time insemination in weaned sows at 22 ±2 hours after treatment in farms representing the diversity of husbandry practices across the European pig production.

Target animal tolerance

In support of the target animal safety, the applicant submitted the pivotal target animal safety study and two supportive GLP-compliant safety studies:

A GLP-compliant swine safety study showed that OvuGel (triptorelin gel) was safe to administer to 24 commercial sows at the recommended treatment dose (RTD) of 0.2 mg triptorelin/sow and at a significant overdose (7xRTD). There were no abnormal general health observations. Food consumption remained consistent. There were no abnormal necropsy findings or changes in organ weight that could be dose related. There were no significant abnormalities in the serum chemistry, haematology, urinalysis or serum endocrine function results.

In a GLP-compliant reproductive safety study, using 600 µg triptorelin acetate/sow (3xRTD; single administration at 96 hr ± 2 hr after weaning), no adverse effects on sow reproduction or the viability of the offspring could be identified in 20 Landrace/Landroc sows (parity 1-6). There were no significant treatment differences in conception rate (all sows conceived), sow weight, body condition scores, gestation length, farrowing rate (all sows farrowed), number of piglets born (total born, born dead, born alive, mummified) per litter, or live piglet weights.

The pivotal target animal safety study was GLP-compliant and conducted in line with VICH GL43 (target animal safety) in 32 Landroc/Whiteroc sows (uni- and pluriparous). Sows (n=8 per group) were either treated with the single recommended treatment dose of 200 µg / animal (1xRTD) or placebo, or at overdoses, i.e. repeatedly over 3 days with either the recommended dose (3 days x 1xRTD), or with an overdose (3 days 3xRTD).

No adverse effects of the triptorelin gel administration were found, based on clinical observations, blood haematology, chemistry and hormone, urinalysis, gross pathology and histopathology of different organs.

These preclinical studies demonstrated the safety of the product.

In addition to the preclinical studies, the clinical studies also assessed safety parameters at the recommended dose of 200 µg / animal.

In the dose confirmation field study, live litter birth weight was higher for triptorelin gel treated sows than for control (vehicle gel treated) sows, likely because of the numerically larger litter size in treated sows. No differences among other reproductive safety variables were observed e.g. number of stillborn or mummified piglets, pre-wean mortality, number of pigs weaned or weaning weight. Pregnancy rate (84.2%), conception rate (84.2%) and farrowing rate (81.4%) in the triptorelin gel treated sows were comparable ($p>0.05$) to contemporary (=control sows) (respectively 76.2%, 76.2% and 73.0%).

In the pivotal clinical EU field study, no differences were found in reproductive safety parameters between untreated controls and triptorelin treated sows e.g. pregnancy failure, fate of repeating and non-pregnant sows, gestation length, piglets born (total, live, dead and mummified), live born litter weight and weaned litter weight, wean to oestrus interval, piglet mortality and all adverse events.

In conclusion, the safety of the recommended dose for OvuGel has been satisfactorily confirmed in the target species. No issues have been identified in target animal safety studies.

However, the safety of treatment in sows in subsequent reproductive cycles has not been investigated and potential long-term effects of cyst occurrence cannot be excluded.

OvuGel should not be used in sows with reproductive tract abnormalities, infertility or general health disorders, since animals with such conditions were not investigated.

Clinical studies

Dose confirmation

A pivotal GCP compliant 5-centre study was conducted with 2145 uni- and multiparous sows in the USA to demonstrate the effectiveness of triptorelin gel (OvuGel) to synchronise the time of insemination in post-partum sows. The animals were sorted first by lactation length and then parity, and paired within each parity group based on lactation length. Sows received 200 µg triptorelin/sow (OvuGel), or placebo gel 96 +/- 4 hours post weaning and were inseminated 22 +/- 2.5 hours later. A third group was untreated and was inseminated based on oestrus detection.

For efficacy and safety evaluation, a margin of inferiority was established for each parameter. The CVMP noted that a margin of inferiority of 10% for farrowing rate might economically not be acceptable. But

since farrowing rates in the treated group were higher than in the control groups, no further questions were raised.

Pregnancy and farrowing rates were higher for the triptorelin treated sows (82.0 % and 79.0 %) than for the control sows (78.9 % and 76.6 %). Also, piglet index (total number of piglets born alive per sow), one of the best indicators of herd performance, was greater for the triptorelin treated sows (894) than for the control sows (745).

Conception rates were higher in untreated control sows relative to treated sows. However, the CVMP agreed with the applicant that conception rate is not a valid or useful parameter when comparing placebo- or triptorelin-treated sows inseminated at a single fixed time, with control sows, which were inseminated twice at oestrus. Indeed, all the placebo- and triptorelin–treated sows were inseminated, whereas only those control sows detected in oestrus were inseminated.

The study demonstrates that reproductive performance is substantially lower in uniparous sows than in multiparous sows when measured by farrowing rate and litter size.

In addition, fertility levels differed significantly between the farms. However, it is deduced that triptorelin gel was effective at all sites, regardless of the fertility level at that site.

It is concluded that the study demonstrated convincingly the effectiveness of triptorelin gel administered intravaginally at 200 µg/animal to weaned sows, approximately 96 hours after weaning, to induce ovulation at approximately 20 hours ± 4 hours after treatment. As a consequence, this will facilitate a single, fixed-time insemination on the day following treatment.

Field studies

Two field studies were conducted in Europe: the pivotal one in sows and an exploratory one in gilts.

Pivotal field study in sows

The pivotal field study was conducted in compliance with VICH GL9 Good Clinical Practice (CVMP/VICH/595/98 FINAL) and the CVMP guideline on veterinary medicinal products for zootechnical purposes (7AE7a), and the study report includes all relevant data including tabulated individual data, statistical analysis and study protocol and amendments.

The study design, especially deviations from these guidelines such as the absence of a placebo control group and the partial blinding, had been previously discussed and agreed by the CVMP in a scientific advice (EMA/CVMP/SAWP/189733/2013), and the applicant followed this advice. Based on the consistent results of the pre-clinical studies (dose determination, dose justification and the dose confirmation field study conducted in the USA), the absence of a placebo group was accepted. A full blinding of the study was not possible for practical reasons; however, the personnel aware of the treatment allocation and subsequent artificial insemination (AI) procedures were bound not to unveil the treatment to other personnel responsible for clinical or fertility observations. In addition, the efficacy criteria were objective data. The partial blinding was confirmed in a scientific advice (EMA/CVMP/SAWP/717529/2015) and accepted by the CVMP for this study.

The study was conducted in two countries (Spain and France), on 3 farms in each country, reflecting the variety of management practices in the EU in two different climates. The study report included all necessary information about each study site and management practices. Depending on the site, semen was obtained from certified artificial insemination (AI) centres, or fresh semen was produced on farm. The semen source (same boar or same batch of mixed boars and collection date) was balanced across control and treated groups.

The justification of the sample size was appropriately made in the study protocol.

In this study, 703 commercial weaned postpartum sows (parity 1-7) with a lactation length of at least 21 days were included, all sows were from the same breed or genetic cross, each study site consisted of another genetic line. Sows (n=353 in the intent-to-treat (ITT) population; n=349 in the per-protocol (PP) population) were treated with OvuGel as recommended and inseminated once, 22 ± 2 hours after treatment and within 118 ± 2 hours after weaning, using a commercially available vaginal applicator, sows in the control group (n=350, ITT; 332 in the PP population) were inseminated according to the normal farm practices.

Non inferiority (non-inferiority margin = 10%) was demonstrated for pregnancy rate between treatment and the controls in the ITT population (89.24% and 92.57%) and the PP analysis (89.40% and 92.77%).

No significant differences in pregnancy rates between parities were recorded.

Non inferiority (non-inferiority margin = 10%) was demonstrated for farrowing rate between treatment (86.3%) and control (91.0%) group.

Pregnancy failures, return to oestrus, pregnancy rate after second insemination, the total number of piglets, the number of piglets born alive, the number of piglets stillborn or mummified, born and weaned litter weight, the wean to oestrus interval and piglet mortality were not significantly different in the treated compared to the control group.

Gestation length was significantly shorter in the treated group, but this was due to a single sow with a gestation length of 106 days.

Fifteen (10 serious and 5 non serious) adverse events were noted in the control group, no adverse events were recorded in the treatment group.

In summary, the CVMP agreed with the applicant that the results of this study show that the use of OvuGel under the recommended conditions of use post-weaning in sows, associated with a single, fixed time artificial insemination at 22 ± 2 h post treatment results in similar fertility and reproduction performance as the standard insemination practice of 2 inseminations at 24 h intervals based on oestrus detection. The safety of use of OvuGel was also demonstrated as no product-related adverse effects or trends to an increase in abnormal conditions were detected during the study.

Field study in gilts

In addition, another GCP-compliant field study conducted in the EU was conducted to investigate the treatment and insemination schedule with OvuGel in gilts.

The results were not fully conclusive and did not support the efficacy of the treatment regimen in gilts. However, the results confirmed the safe use of OvuGel in gilts. As the efficacy has not been demonstrated in gilts, the use of OvuGel is not recommended in these animals.

Other studies

Directions how to use

From three supportive non-GCP studies using different commercially available applicators, it was concluded that, when provided with the proper instructions for use, farm staff with no prior experience in administering OvuGel could obtain at least 24 doses of OvuGel from a vial containing a minimum of 52 ml with product wastage of less than two doses.

Overall conclusion on efficacy

Pharmacology:
The pharmacodynamics of triptorelin was convincingly supported by literature data and by preclinical

dose range finding studies. It was concluded that increased LH levels peaked between 2 (200 µg triptorelin), 3 (100 µg triptorelin), or 5 (1400 µg triptorelin) hours after administration. At 30 to 35 hours after administration, blood levels had returned to pre-dose levels.

In the pharmacokinetics study in sows, it was demonstrated that the bioavailability after intravaginal administration was 13-fold lower (less than 7.45%) than after intravenous administration.

Dose:
The dose determination and confirmation studies as well as the field studies demonstrated satisfactorily the safety and effectiveness of a single intravaginal dose of 2 ml OvuGel (200 µg triptorelin as the acetate) administered 96 ± 2 hours after weaning, to synchronize the time of ovulation, which will facilitate a single fixed-time insemination in weaned sows 22 ± 2 hours after treatment in sow farms with varying husbandry practices.

Target animal safety:
One pivotal target animal safety study and two further preclinical studies demonstrate that the product was well-tolerated without systemic or local adverse effects, and without any negative effects on sow reproductive performance. This was confirmed by the results of the clinical studies.

Efficacy:
The results from the pivotal GCP-compliant European clinical field trial demonstrated that a single dose of 2 ml OvuGel (equivalent to 0.2 mg triptorelin) administered intravaginally at 96 hours ± 2 hours after weaning and followed by a single artificial insemination at a fixed time point (22 ± 2 h post treatment) resulted in similar fertility and reproduction performance as the standard insemination practice (two inseminations at 24 h intervals based on oestrus detection). This was also supported by the results of other, supportive clinical and preclinical studies, conducted in Europe and the USA. However, whilst the product was safe to use in gilts, efficacy has not been demonstrated in this target population, and the use of OvuGel is therefore not recommended in gilts.

In conclusion, the safety and efficacy of the product have been satisfactorily demonstrated in weaned sows, when used at the recommended dose and posology.

Part 5 – Benefit-risk assessment

Introduction

OvuGel (active substance: triptorelin acetate) is a synthetic analogue of gonadotropin releasing hormone (GnRH), which stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which then further stimulate the production of sex steroids and ovulation. OvuGel is intended to be used for the synchronisation of ovulation in weaned sows to enable a single fixed-time artificial insemination.

OvuGel is presented as a vaginal gel containing 0.1 mg triptorelin acetate/ml, and is presented in one vial of 50 ml. The product is to be administered intravaginally at 96 hours ± 2 hours after weaning at a single dose of 0.2 mg triptorelin acetate per animal, using a suitable intravaginal administration tool.

The proposed withdrawal period for meat and offal is 0 days.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The benefit of OvuGel is its efficacy in the synchronisation of ovulation in weaned sows to enable a single fixed-time artificial insemination.

Well-designed clinical and preclinical studies, conducted in Europe and the USA, including different sow breeds and representing the diversity of pig husbandry practices across Europe, demonstrated the safety and effectiveness of triptorelin gel (200 µg triptorelin as the acetate/animal, i.e. 2 ml intravaginal dose) administered 96 ± 2 hours after weaning to synchronize the time of ovulation. This facilitates a single fixed-time insemination (22 ± 2 hours after treatment) in weaned sows. Effective treatment in gilts was not supported by adequate data, and the product is therefore not recommended in this target animal population.

The clinical and preclinical studies demonstrate that the product was well-tolerated without general or local adverse effects, and without any negative effects on sow reproductive performance.

Additional benefits

OvuGel is easy to administer and facilitates the management of sows post-weaning.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety:

Risks for the target animal:
The safety has been confirmed in the target species. No treatment related risks are identified in the target animal when used as recommended in the SPC. A warning indicating that safety of treatment in sows in subsequent reproductive cycles has not been demonstrated and that potential long-term effects of cyst occurrence cannot be excluded is included in section 4.5 of the SPC.

Risk for the user:
OvuGel can provoke conjunctival irritation and skin hypersensitivity, but not skin irritation. Specific measures are necessary to mitigate any risk such as worn personal protective equipment consisting of overalls and gloves when handling the veterinary medicinal product. Also, a warning regarding hypersensitivity to GnRH analogues or any of the excipients (including parabens) is introduced in the SPC.

Risk for the environment:
Based on the data provided the ERA can stop at Phase I, as none of the Phase I criteria are met. OvuGel is not expected to pose a risk for the environment.

Risk for the consumer:
Triptorelin acetate has been evaluated previously in respect to the safety of residues and is included in table I of the Annex to Regulation (EU) No 37/2010 with a "no MRL required" classification for all food producing species. OvuGel is not expected to pose a risk to the consumer of meat derived from treated

animals. The residue studies available did not show residues of concern in the target tissues following treatment, and the withdrawal period for meat is set at 0 days.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, the user, the environment, and the consumer; and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The applicant applied for the following indication: For the synchronisation of ovulation in weaned sows to enable a single fixed-time artificial insemination.

The product has been shown to be efficacious to synchronize the time of ovulation and facilitate a single fixed-time insemination in weaned sows 22 ± 2 hours after treatment in sow farms with varying husbandry practices.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including withdrawal period, have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for OvuGel is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.