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EMA/CVMP/382140/2013
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Triptorelin acetate (all food producing species)

On 3 March 2014 the European Commission adopted a Regulation[1] establishing maximum residue limits for triptorelin acetate in all food producing species valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Triptorelin acetate is intended for synchronisation of time of insemination and is administered by the intravaginal route.

Eli Lilly and Company Limited submitted the application for the establishment of maximum residue limits to the European Medicines Agency on 29 January 2013.

Based on the data in the dossier the Committee for Medicinal Products for Veterinary Use recommended, on 18 July 2013, the establishment of maximum residue limits for triptorelin acetate in all food producing species.

Subsequently the Commission recommended, on 14 January 2014, that maximum residue limits are established. This recommendation was confirmed on 4 February 2014 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 3 March 2014.

[1] Commission Implementing Regulation (EU) No 200/2014, O.J. L 62/8, of 04 March 2014

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Triptorelin acetate
Therapeutic class:	Agents acting on the reproductive system
Procedure number:	EMEA/V/MRL/003721/FULL/0001
Applicant:	Eli Lilly and Company Limited
Target species:	Porcine
Intended therapeutic indication:	Synchronisation of time of insemination
Route(s) of administration:	Intravaginal

1. Introduction

Triptorelin is a synthetic analogue of gonadotropin releasing hormone (GnRH). Triptorelin contains a single amino acid substitution, D-tryptophan[6] instead of glycine[6], compared to the endogenous GnRH.

Triptorelin acetate is intended for use in sows for the synchronisation of time of insemination in order to facilitate a single fixed time artificial insemination. The intended product is to be administered as an intravaginal gel as a single dose of 2 ml per sow, corresponding to 200 µg triptorelin as the acetate.

Triptorelin acetate is one of the most potent synthetic analogues of endogenous GnRH available and is approved for use in humans.

2. Scientific risk assessment

The amino acid sequence of GnRH and the analogues discussed are presented in Table 1.

Table 1. Amino acid sequence of GnRH agonists

	1	2	3	4	5	6	7	8	9	10
GnRH	pGlu	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly NH_2
Triptorelin	pGlu	His	Trp	Ser	Tyr	D-Trp	Leu	Arg	Pro	Gly NH_2
Nafarelin	pGlu	His	Trp	Ser	Tyr	D-Nal	Leu	Arg	Pro	Gly NH_2
Deslorelin	pGlu	His	Trp	Ser	Tyr	D-Trp	Leu	Arg	Pro	NHEt
Leuprolide	pGlu	His	Trp	Ser	Tyr	D-Leu	Leu	Arg	Pro	NHEt
Buserelin	pGlu	His	Trp	Ser	Tyr	D-ser(Tbu)	Leu	Arg	Pro	ethylamide
Peforelin	pGlu	His	Trp	Ser	His	Asp	Trp	Lys	Pro	Gly NH_2

2.1. Safety assessment

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.

2.1.1. Overview of pharmacological properties

Pharmacodynamics

Triptorelin is a synthetic decapeptide analogue of GnRH with significantly greater biological activity than the natural peptide, which at least in part is due to a decreased rate of degradation. In a two-week oestrus suppression assay in rats, triptorelin was found to be 100 times more potent than natural GnRH. The primary pharmacodynamic effects of GnRH and GnRH analogues, i.e. stimulated release of follicle stimulating hormone (FSH) and luteinising hormone (LH), and a resulting increase in circulating sex hormones, are well known.

In the preclinical dose range finding studies, intravaginal single dose administration of 100 µg triptorelin to pigs resulted in increased LH levels that peaked 3 hours after administration. At 24 hours after administration, the blood LH levels were considerably decreased and from 30 to 35 hours after administration they had returned to pre-dose levels in all animals. Similar results were observed in the target animal safety study, which showed increased LH levels at 2 and 5 hours following intravaginal administration of 1 times (200 µg) and 7 times (1400 µg) the recommended triptorelin acetate dose, that dropped to pre-dose levels the day after administration.

The expected secondary pharmacodynamic effects following repeated parenteral administration as a result to pituitary desensitisation and resulting gonadal suppression with reduction of serum sex steroids, was confirmed by the use in human medicine.

Pharmacokinetics

Based on the similarity with GnRH, the pharmacokinetics of triptorelin in humans are, in many aspects, expected to be comparable to that for GnRH. This was supported by data which showed that the pharmacokinetics of triptorelin in humans are characterised by a triphasic decline in plasma and a large volume of distribution indicating wide distribution to the tissues, degradation into biologically inactive fragments by peptidases, mainly in the kidney and the liver, but also in other tissues such as the pituitary, and a rapid clearance, predominantly by the kidney. The patterns of distribution and metabolism were overall similar for all GnRH analogues.

The differences in the pharmacokinetics between triptorelin and GnRH, i.e. longer terminal half-life (50 minutes to 2.8 hours for triptorelin and 13 to 60 minutes for GnRH in humans) and a substantial part of a parenteral triptorelin dose being excreted in urine as unchanged peptide, are explained by the amino acid substitution at position 6 (D-tryptophan instead of L-glycine), which due to conformational changes results in protection from cleavage by peptidases. This may also explain the higher affinity for pituitary receptors, which together with the prolonged elimination half-life, result in about 100 times higher potency for triptorelin as compared to GnRH. Plasma protein binding of the natural GnRH is reported to be negligible, which is expected to be true also for triptorelin.

The pharmacokinetic profile of triptorelin is in line with those for other GnRH analogues which also have a longer terminal half-life than GnRH due to higher stability against proteolytic degradation.

Due to the susceptibility to inactivation via gastrointestinal peptidase degradation, the oral bioavailability of this class of peptides in laboratory species and in humans is generally very low, e.g.,

estimated to be less than 1% in humans. A low oral bioavailability was indicated also for triptorelin in a repeat-dose toxicity study in rats where no effects were seen following oral administration up to the highest tested dose of 4 µg/kg bw.

2.1.2. Calculation of pharmacological ADI, if relevant

Human exposure to triptorelin via the oral route is expected to be negligible and therefore it is not considered necessary to establish a pharmacological ADI. This is consistent with the CVMP Guideline on the approach to establish a pharmacological ADI (EMA/CVMP/SWP/355689/2006).

2.1.3. Overview of toxicology

Except for a repeat-dose toxicity study in rats, none of the basic tests for establishment of MRLs were provided. For information on the acute safety of triptorelin and effects of triptorelin on reproduction in sows, a target animal safety study and 5 efficacy and safety studies (and 4 related reports of results and statistical analyses) were submitted. References of supporting toxicological data of other GnRH analogues were also provided.

The presented target animal safety study demonstrated the acute safety of triptorelin acetate in sows following intravaginal administration at 1 times and 7 times the recommended dose.

No biologically or toxicologically significant effects, e.g., effects on LH levels and oestrus cycling or any microscopic changes, were observed following oral administration of doses up to 4 µg/kg bw in a 45-day repeat dose toxicity study in rats. Whereas no increases in LH were observed on day 1 and at the end of the dosing period in the oral treatment and control groups, 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. The subcutaneous dose was given in order to induce a clear LH peak in rats that had not been desensitised by continuous systemic exposure to triptorelin.

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. In both sexes there was a dose dependent decrease in LH levels on day 14, as a result of desensitisation of the GnRH receptors. In males this resulted in a decrease in testosterone levels, atrophy of the reproduction organs and loss of spermatogenesis. In females, the decrease in LH levels resulted in a decrease in progesterone and ultimately cessation of the oestrus cycle as well as adrenal cortical hypertrophy, ovarian and vaginal atrophy. Furthermore, decreased bone marrow cellularity and mammary gland atrophy were observed in both sexes whereas a consistently increased body weight was only observed in females.

Due to their pharmacological effect, continuous or long term exposure to GnRH and GnRH analogues via parenteral route can be expected to induce effects toxic to reproduction.

While the results of the efficacy and safety studies supported the intended primary pharmacodynamic effects of triptorelin, e.g., in terms of increased pregnancy rate, there were no indications of any reproductive toxicity, e.g., in terms of pregnancy failure rate or total pigs per litter, following a single intravaginal administration of 200 µg triptorelin acetate.

Due to the low oral availability, triptorelin is however not expected to affect the reproduction following oral administration.

No data was provided for genotoxicity or carcinogenicity, which is acceptable for this kind of substance where human exposure via the oral route is expected to be negligible.

Overall, while the standard toxicology studies normally performed for establishment of MRLs were not provided in this case, the toxicology data package can be considered adequate as it is considered that residues in food will be inactivated in the human gastrointestinal tract. This is in line with the VICH guideline on studies to evaluate the safety of residues of veterinary drugs in human food: general approach to testing (EMEA/CVMP/VICH/486/02-Rev.2), which allows for the provisions of "scientifically based reasons as to why data may not need to be provided".

2.1.4. Calculation of the toxicological ADI or alternative limit

It is not considered necessary to establish a toxicological ADI for triptorelin acetate since the human systemic exposure via the oral route will be negligible.

2.1.5. Overview of microbiological properties of residues

Due to the chemical nature of the compound, i.e. a decapeptide, microbiological effects are not expected.

2.1.6. Calculation of microbiological ADI

As no microbiological effects are expected the establishment of a microbiological ADI is not considered necessary.

2.1.7. Observations in humans

Parenterally administered triptorelin is used in human medicine and is reported to be well tolerated. Observed side-effects included reversible, relatively minor effects which were all related to the secondary pharmacological action, i.e. loss of bone and sex drive in men and women, cessation of menses in women as well as hot flushes, vaginal dryness, transient headache, mild insomnia, emotional lability and slight weight gain in women.

2.1.8. Findings of EU or international scientific bodies

No information on evaluations by other scientific bodies was available.

2.1.9. Overall conclusions on the ADI

Neither a pharmacological nor a toxicological ADI is considered necessary as systemic exposure to residues will be negligible. A microbiological ADI is not considered necessary as, due to the chemical nature of the substance, microbiological effects are not expected.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

The preclinical dose range findings studies of intravaginal administration of triptorelin in pigs showed that 100 µg triptorelin in 1.2% methylcellulose was the most effective treatment in terms of LH release with 100% response rate, the shortest time to maximum blood levels of LH (3 hours) and the highest

and most uniform AUC. At 24 hours after administration blood LH levels were considerably decreased and at 30 to 35 hours after administration they had returned to pre-dose levels in all animals. Similar results were obtained in the target animal safety study, which showed increased LH levels at 2 and 5 hours following intravaginal administration of 1 times (200 µg) and 7 times (1400 µg) the recommended triptorelin acetate dose, which had dropped to pre-dose levels the day after administration.

The provided data support a similar pharmacokinetic behaviour of triptorelin and GnRH (and other GnRH analogues) in laboratory animals and humans, which due to the chemical nature of the compounds is expected to be applicable also for pigs. These decapeptides and nonapeptides were shown to be widely distributed to various organ tissues, with the highest levels of the residue observed in the pituitary gland, degradation into biologically inactive fragments by peptidases mainly in the kidney and the liver, and a rapid and predominant clearance by the kidney. The patterns of distribution and metabolism were similar overall for all GnRH analogues. Although the terminal half-lives of GnRH and GnRH analogues determined following the parenteral route are different as a result of, in general rather small, changes in the peptide structure (e.g. L-glycine replaced by D-tryptophan at position 6 in triptorelin), the reported values of 4.3 hours or less in humans are considered as relatively short.

2.2.2. Residue depletion studies

No residue depletion studies performed with triptorelin acetate were provided. Based on the provided data, the pharmacokinetic behaviour of triptorelin residues following intravaginal administration to pigs is expected to be characterised by a rapid absorption and extensive distribution to various organs, including pituitary, kidney and liver, followed by degradation into biologically inactive fragments by peptidases mainly in the kidney and the liver, and a rapid and predominant clearance by the kidney. Due to the intended frequency of use, i.e. single dose administration to sows once per oestrus cycle and at most 2 to 3 times per year, accumulation of residues in pig tissues is not expected.

The omission of a residue depletion study is 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, residues remaining in food will be inactivated in the human gastrointestinal tract.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than those described elsewhere in this report were available.

2.2.4. Analytical method for monitoring of residues

No analytical method for residue monitoring purposes was proposed. The absence of an analytical method can be considered acceptable for a “no MRL required” recommendation.

2.2.5. Findings of EU or international scientific bodies

No information on evaluations by other scientific bodies was available.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

No relevant data were provided but due to the chemical nature of the compound, i.e. a decapeptide, microbiological effects are not expected.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

No such considerations were identified.

3.3. Elaboration of MRLs

Based on the chemical nature and poor oral bioavailability of triptorelin it was concluded that it was not necessary to establish an ADI for triptorelin acetate.

While no studies were performed to specifically demonstrate the absorption, distribution, metabolism and excretion profile of the substance, the chemical similarity of triptorelin to known GnRH analogues combined with the supporting evidence from studies performed with triptorelin render such data unnecessary in this case. A “No MRL required” classification is recommended for triptorelin acetate based on the following:

- As other GNRH analogues, triptorelin will be rapidly absorbed and eliminated or deactivated in the target species,
- A repeat dose toxicity study in rats demonstrated that there were no effects seen at the highest oral dose administered. Triptorelin is used regularly in adult humans and is also indicated for use in children,
- Due to the chemical nature, the oral bioavailability of GnRH and its analogues in humans is low (estimated to less than 1%). A low oral bioavailability for triptorelin was supported by the repeat dose toxicity study in rats which demonstrated that there were no biological or toxicological effects following the highest oral dose tested,
- Due to the intended use, i.e. to synchronise insemination, sows will at most be treated 2 to 3 times a year, and it is unlikely that they will be slaughtered during the period 20 to 30 days between insemination and confirmation of pregnancy.

It is noted that Volume 8 of The rules governing medicinal products in the European Union highlights a number of factors that may be considered in relation to the appropriateness of establishing a “No MRL required” classification for a substance. These include the degree of absorption from the site of application (e.g., absorption from the gastro-intestinal tract), the extent with which the substance is likely to be used (e.g., use in individual animals versus use in entire herds, and infrequent versus frequent use) and whether an animal is likely to be slaughtered soon after treatment.

A recommendation for a “No MRL required” classification is further supported by previous assessments made by the CVMP for GnRH (gonadorelin) and other GnRH analogues which are structurally very

similar to triptorelin and have a “No MRL required” classification table 1 of the Annex to Regulation 37/2010.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the recommended maximum residue limits for triptorelin acetate (“No MRL required”) in porcine species to other food producing species and food commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal species/ food commodities	Extrapolation possible (YES/NO)	Justification
All food producing species	Yes	The recommendation for porcine species is based on low oral bioavailability in humans. As low oral bioavailability in humans is independent of the pharmacokinetic/residue depletion profile in the target species the conclusion for porcine species can be extrapolated to all other food producing species.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the establishment of an ADI is not considered necessary for triptorelin acetate;
- oral bioavailbility of residues of triptorelin acetate in humans is considered negligible;
- triptorelin acetate is a peptidic substance closely related to the natural occurring GnRH, which has been previously assessed and included in table 1 of the Annex to Regulation 37/2010 with a “No MRL required” classification for all food producing species;
- triptorelin acetate, like other GnRH analogues, will be rapidly absorbed and eliminated/degraded in the target species;
- a consumer’s systemic exposure to residues of triptorelin acetate will not be affected by the target species treated;

the Committee concludes that the establishment of maximum residue limits for triptorelin acetate for porcine species is not necessary for the protection of human health, and that this conclusion can be extrapolated all food producing species, and therefore recommends the inclusion of triptorelin acetate in table 1 of the Annex to Regulation (EU) No 37/2010 in accordance with the following table:

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

4. Background information on the procedure

Submission of the dossier 29 January 2013

Steps taken for assessment of the substance

Application validated: 13 February 2013

Clock started: 14 February 2013

CVMP opinion adopted: 18 July 2013