Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

MUTUAL RECOGNITION PROCEDURE
DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Maprelin 75 µg/ml solution for injection for pigs

Date: 4 August 2009

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0129/001/MR /
Name, strength and pharmaceutical form	Maprelin 75 µg/ml solution for injection for pigs
Applicant	Veyx-Pharma GmbH Söhreweg 6 34639 Schwarzenborn Germany
Active substance(s)	Peforelin
ATC Vetcode	ATCvet-Code: QH01CA
Target species	Pig
Indication for use	For biotechnical use and intended for group or herd treatment. • Induction of the oestrous cycle in sows after weaning • Induction of oestrus in sexually mature gilts following therapy to inhibit the oestrus cycle with progestagens

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original Mutual recognition procedure Decentralised procedure	25 February 2009
Date product first authorised in the Reference Member State	8 July 2008
Concerned Member States for original procedure	AT, BE, BG, CZ, EE, FR, HU, IE, IT, LV, LT, LU, NL, PL, PT, RO, SK, SI, ES, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

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The product contains 75 µg peforelin per ml and the excipients chlorocresol, acetic acid, sodium hydroxide, and water for injections.

The container/closure system consists of colourless type I glass vials with fluorinated bromobutyl rubber stoppers and aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation.

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

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

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

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

C. Control of Starting Materials

The active substance is peforelin, a novel active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

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

Detailed information on peforelin are provided in an Active Substance Master File (ASMF).

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

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

E. Control on intermediate products (pharmaceuticals)

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There are no intermediate products.

F. Control Tests on the Finished Product

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

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The claim of a 28 days stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at +5°C±3°C.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL) (*for pharmaceuticals only)*

III.A Safety Testing

Pharmacological Studies

See IV.A. Pre-clinical studies.

Toxicological Studies

Peforelin is a decapeptide analogue of the natural gonadotropin releasing hormone (GnRH) which was originally detected in the hypothalamus of the lamprey. Compared to the natural gonadorelin it has chemical modifications in the amino acid composition at positions 5 to 8 which probably cause the high efficacy of peforelin. The substance does not possess any unusual amino acid modifications or other chemical structural alerts.

All information on bioavailability and pharmacokinetics of peforelin in pigs were fully consistent with what is known from literature about other GnRH analogues. Oral bioavailability was practically absent in pigs. It seemed to be pointless to explore oral toxic effects of the substance by requesting oral toxicity studies and it was accepted, that the applicant did not perform any toxicity studies with peforelin in laboratory animal species, but referred to data on D-Phe-6-LHRH, that is closely related to peforelin. It was concluded, that there is no safety concern for peforelin.

Observations in Humans

Maprelin 75 µg is not intended for use in humans.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which showed that the likelihood of exposure to Maprelin 75 µg is generally considered to be low. The main routes of accidental exposure may be from dermal or ocular contact or parenterally by accidental self-injection. The risk of dermal absorption is unlikely but can generally not be excluded.
The data indicated that the potential effects on users of the product would relate to the pharmacological action of perforelin that may cause effects on the reproductive

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system via influencing the secretion of sex steroids. Concern would arise in the case of accidental exposure of pregnant women, since GnRH analogues have been shown to be foetoxic in laboratory animals and for women in child bearing age. The sensitisation potential of Maprelin 75 µg was regarded.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that the ERA stops in Phase I and no further risk assessment according to phase II is required.

Peforelin, a hormone similar to GnRH, as polypeptide is subject to rapid cleavage in the digestive tract. In the animal organism Peforelin undergoes rapid decomposition into oligopeptides and individual amino acids, which are further metabolized or become a discretionary output of the amino acid pool. Due to the very short half-life of Peforelin in animal organism it is very likely, that residues of this hormone will not enter the environment.

Therefore it is to be concluded that there is no environmental impact when Maprelin 75 µg/ml Injektionslösung für Schweine is used as prescribed. No special warnings regarding the environment are required.

III.B Residues documentation

Residue Studies

Residue studies with Peforelin in the target species pig have not been provided. The behaviour of Peforelin as a decapeptide analogue of the natural gonadrotropin releasing hormone (GnRH) was demonstrated by different literature.

In view of Annex II entry for Peforelin in CR (EEC) 2377/90 there is no need for a routine analytical method.

MRLs

Based on the toxicological evaluation Peforelin was included in Annex II of Council Regulation (EEC) No 2377/90 for pigs by CR (EEC) No 1838/97 at 24 September 1997 changed by CR (EEC) No 1451/06 at 29 September 2006. There was no need

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to establish an ADI (Acceptable Daily Intake = an estimate of the amount that can be ingested daily over a lifetime without appreciable health risk) for Peforelin.

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues
Peforelin	-	Porcine	-	-

The preservative excipient chlorocresol was included in Annex II of CR (EEC) No. 2377/90 by CR (EEC) No 1742/96 in 1996 for all food producing species and no ADI was established. Chlorocresol is rapidly metabolised and excreted. Clorocresol has no potential to accumulate in tissues and is of low toxicity.

Withdrawal Periods

The applied withdrawal period of zero days for edible tissues of pigs is justified and in compliance with the depletion profile in plasma. Peforelin is expected to be rapidly metabolised, degraded and eliminated in the target animal.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has conducted studies and provided bibliographical data. Data show that peforelin is a decapeptide analogue of the natural gonadotropine releasing hormone (GnRH, synonyme: gonadorelin) with chemical modifications in the amino acid composition at positions 5 to 8 (5-His-6-Asp-7-Trp-8-Lys). Originally peforelin was detected in the hypothalamus of the sea lamprey (Petromyzon marinus). In the sea lamprey peforelin induces oestrogen release from the gonads presumably via hypophysis. Data obtained in rats and cattle yielded in inconsistent conclusions on the action of peforelin on the release of LH and FSH. In pigs, it was demonstrated that a single intramuscular administration of recommended doses of peforelin to male castrated pigs released FSH. Concurrently there was no relevant LH-response seen, thus giving evidence for the desired effect. In weaned sows a single intramuscular administration of peforelin induces the oestrous cycle, indicating that the pharmacological effects proven in animal models do result in the desired biotechnical effect in the target animals.

The pharmacokinetic results for peforelin appear to be fully consistent with literature information on other GnRH analogues. Following intramuscular administration

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peforelin is subject to rapid absorption with a short plasma half-life of probably a few minutes. Immediately after administration, all GnRH analogues undergo rapid enzymatic degradation. Biotransformation mainly occurs in plasma, but also in several organs and tissues, respectively. The newly formed oligopeptides are devoid of any biological action. Their elimination takes place either via the kidneys or by further decomposition in the liver to amino acids that enter the metabolic pathway. An accumulation of the decapeptide or its degradation products does not occur in the animal body.

Tolerance in the Target Species of Animals

The applicant has conducted a controlled target animal tolerance study using Maprelin 75 µg at the maximum recommended dose and the 3fold thereof in the target species. Isotonic NaCl solution served as control treatment. All doses were administered by intramuscular route on one occasion. The study lasted 36 days and incorporated a 21 day cycle.

There were no clinical, haematological or clinical chemical findings deviating from normal. Under the conditions of the study, cycle activities were within the norm. The injection sites were clinically inconspicuous. Post mortem examinations including injection sites revealed no treatment related findings.

The favourable tolerance of Maprelin 75 µg documented in the target animal safety study is confirmed in the clinical studies.

Post marketing information has also been provided. It reports on suspected lack of efficacy. It relates to induction of oestrus in sexually mature gilts following therapy to inhibit the oestrus cycle with altrenogest. The incidence of that suspected lack of efficacy was 0.036%. Another type of suspected adverse reactions was not reported.

These data provided is in line with the safety profile indicated by the product literature.

IV.B Clinical Studies

Field Trials

Dose determination studies

1. Indication for use: Induction of the oestrous cycle in sows after weaning

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Several investigations have shown primi- and pluriparous sows differ in their responsiveness towards exogenously administered endocrinologically active substances including GnRH. Thus, due consideration was given to this indication in terms of the dose of peforelin needed in primi- and pluriparous sows.

1.1

The efficacious dose of peforelin (XP10) was determined in a blinded controlled field study in healthy sows in breeding condition, in various parities weaned off from their litters after a period of 4 weeks. Following an interval of 24 hours after weaning sows were treated by injecting intramuscularly peforelin at doses between 50 and 200 µg per sow. Prolosan, i.e. PMSG (eCG) served as positive control. Oestrus rate was the main efficacy parameter. The information coming from literature concerning the oestrus rate after PMSG (eCG)-stimulation was confirmed. Peforelin doses of 50 µg and 100 µg per sow were not able to induce oestrus satisfactorily. Doses of 150 µg and 200 µg per sow resulted in oestrus rates comparable to that achieved with PMSG (eCG). The dose of 200 µg peforelin per sow did not increase the oestrus rate compared to the dose of 150 µg per sow. Therefore, it is concluded that a peforelin dose of 150 µg per sow appears suitable for oestrus induction in weaned sows. Clinical examinations reveal neither general nor local adverse reactions.

1.2

The efficacious dose of peforelin (Maprelin 75 µg) was determined in a blinded field study in healthy pluriparous sows in breeding condition, with a previous suckling period of 25 – 31 days. Following intervals of 0 - 48 hours after weaning sows were treated by injecting intramuscularly peforelin doses between 100 and 225 µg. Oestrus rate was the main efficacy parameter. Secondary parameters were weaning to oestrus interval and pregnancy rate. Maprelin 75 µg at the dose of 150 µg peforelin (2 ml Maprelin 75 µg) per sow, injected at an interval of 24 hours post weaning, proved superior to other treatment posologies. Thus, in terms of dose and injection time point, these were considered suitable. Clinical examinations revealed neither general nor local adverse reactions.

1.3

The efficacious dose of peforelin (Maprelin 75 µg) was determined in a blinded field study in healthy primiparous sows in breeding condition, which had weaned off from their litter after a suckling period of 4 weeks. Following an interval of 24 hours after weaning sows were treated by injecting intramuscularly peforelin at doses of 37.5 and 75 µg per sow. Efficacy parameters were oestrus events, returns to oestrus and pregnancy, and farrowing results. The results demonstrate that the dose of 0.5 ml Maprelin 75 µg (37.5 µg peforelin) per sow was more suitable for the induction of oestrus in primiparous sows than the higher dose tested (1 ml Maprelin 75 µg= 75.0 µg peforelin per sow). The oestrus events were significantly better in the group treated with 0.5 ml Maprelin 75 µg than in the group treated with 1 ml Maprelin 75

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µg. The results for the remaining parameters were similar in both groups. Clinical examinations revealed neither general nor local adverse reactions.

2. Indication for use: Induction of oestrus in sexually mature gilts following therapy to inhibit the oestrus cycle with progestagens

As regards this indication the optimum time interval between the last treatment for blocking the cycle and the administration of peforelin had to be elicited, since investigations demonstrated that the time interval between the final administration of the cyclus blocking product and the hormonal stimulation of the cycle is crucially important in gilts.

2.1

In a pilot study in healthy pre-pubertal gilts the influence of the timing of the injection of Maprelin 75 µg on the reaction of the ovary was examined. Puberty was induced by simultaneous intramuscular injection of 500 IU PMSG (eCG) + 250 IU hCG. Nine days later altrenogest (Regumate) treatment commenced. Three groups of gilts were created for oestrus induction with Maprelin 75 µg (2 ml = 150 µg peforelin/gilt), which was administered intramuscularly 24 hours (group 1), 36 hours (group 2) and 48 hours (group 3) after termination of treatment for cyclus blockade with Regumate. The animals were slaughtered 30 days after the last administration of Regumate. The functional status of the ovaries, in particular, the number of corpora albicantia was evaluated as efficacy parameter. The mean number of corpora albicantia in animals with detectable stimulation effects indicated that the injection of Maprelin 75 µg 48 hours after cessation of Regumate treatment (cycle blockade) had the most favourable outcome.

2.2

In another study, healthy crossbred pubertal gilts in breeding condition, which were pre-treated with 20 mg altrenogest per gilt (5 ml Regumate) over an 18 day period, were used. 36 hours (group 1) and 48 hours (group 2) after last administration of Regumate gilts were injected intramuscularly with 2 ml Maprelin 75 µg per gilt (150 µg peforelin/gilt). Gilts diagnosed as being on-heat were inseminated twice. Oestrus rate, interval between last treatment with Regumate and commencement of oestrus, pregnancy rate were used as efficacy parameters. It was found that the injection of Maprelin 75 µg 48 hours after cessation of Regumate treatment (cycle blockade) had the most favourable outcome.

According to the above study results the injection of 2 ml Maprelin 75 µg per gilt (150 µg peforelin/gilt) 48 hours after cessation of treatment for cyclus blockade is favourable.

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Dose-confirmation studies

1. Indication for use: Induction of the oestrous cycle in sows after weaning

1.1
The dose determined efficacious in pluriparous sows was confirmed in a blinded controlled field study in healthy pluriparous sows in breeding condition, with a previous suckling period of 25 – 31 days. Following an interval of 24 hours post weaning sows were treated intramuscularly with 2 ml Maprelin 75 µg IM = 150 µg peforelin, or intramuscularly with 2 ml isotonic NaCl solution [placebo control], or subcutaneously with 16 ml Prolosan = 800 IE PMSG (eCG) [positive control]. The oestrus rate induced with Maprelin 75 µg was equal to that induced with Prolosan and significantly superior to the placebo treatment. The weaning to oestrus interval was reduced. Maprelin 75 µg and Prolosan were equally effective. There were also no differences in terms of insemination results between both products, whilst they were significantly superior to placebo. Factors that were related to parameters of the fertility performance were evaluated. However, no parameter could be detected to significantly influence the fertility performance. Neither general nor local adverse reactions were detected.

1.2
The dose determined efficacious in pluriparous sows was confirmed in a blinded controlled field study in healthy, primi- and pluriparous sows in breeding condition, with a previous suckling period of 21 – 28 days. 2 ml Maprelin 75 µg = 150 µg peforelin were injected intramuscularly 24 hours after weaning. A control group received no treatment. Compared to untreated controls, treatment with Maprelin 75 µg achieved a significant effect in bringing forward the onset of oestrus. This resulted in a concentrated clustering of 1st insemination times. The insemination results maintained at a high level without a statistically significant difference between untreated and Maprelin 75 µg treated sows. Neither general nor local adverse reactions were detected.

1.3

The dose determined efficacious in pluriparous sows was examined in a blinded controlled field study in healthy primiparous sows in breeding condition, which had weaned off from their litter after a suckling period of 4 weeks. Sows received 2 ml Maprelin 75 µg = 150 µg peforelin intramuscularly 24 hours after weaning. Untreated sows served as control. Efficacy parameters were oestrus events, returns to oestrus and pregnancy rate, and farrowing results. There were no significant differences between treated and untreated sows. Thus, the dose of 2 ml Maprelin 75 µg (150 µg peforelin) per sow was not suitable for the induction of oestrus in primiparous sows.

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As a result, this dose was no longer investigated. Neither general nor local adverse reactions were detected.

1.4
The dose determined efficacious in primiparous sows was confirmed in a blinded controlled field study in healthy primiparous sows in breeding condition, which had weaned off from their litter after a suckling period of 4 weeks. Sows were treated intramuscularly with 0.5 ml Maprelin 75 µg= 37.5 µg peforelin 24 hours after weaning. Control sows remained untreated. Results confirm efficacy of 0.5 ml Maprelin 75 µg= 37.5 µg peforelin in primiparous sows by demonstrating a significant increase in oestrus, pregnancy and farrowing rates compared to untreated controls. These results are comparable with the results from previous studies in pluriparous sows receiving 2 ml Maprelin 75 µg= 150 µg peforelin. Neither general nor local adverse events were reported.

2. Indication for use: Induction of oestrus in sexually mature gilts following therapy to inhibit the oestrus cycle with progestagens.

2.1

After having determined an interval of 48 hours between cessation of cycle blocking treatment and Maprelin 75 µg treatment being the most appropriate interval, the controlled and blinded study was conducted to prove efficacy by comparing pubertal gilts in breeding condition, which received i) Regumate (altrenogest) without subsequent gonadotropin stimulation, or ii) Regumate + Premagon (1000 IU PMSG (eCG)/gilt) subcutaneously 48 hours after last Regumate administration, or iii) Regumate + Maprelin 75 µg (150 µg peforelin) intramuscularly 48 hours after last Regumate administration. The study covered the time period of the medicated oestrus synchronization, insemination of the gilts, farrowing and subsequent weaning of the piglets. Efficacy parameters were oestrus events, pregnancy – and farrowing results. The study demonstrates that gilts which received Maprelin 75 µg or Premagon came in oestrus more frequently within the most relevant time frame, i.e. within the first 5 – 8 days than untreated gilts. Further biotechnical parameters monitored remained insignificantly changed by treatments except the piglet index indicating significantly more piglets per 100 first inseminations in gilts treated with Maprelin 75 µg. Neither general nor local adverse events were reported.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

Data obtained in rats and cattle yielded in inconsistent conclusions on the action of peforelin on the release of LH and FSH. It appears that in rat and cattle peforelin was a weak agonist for the pituitary GnRH receptor and stimulates both

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gonadotropins in a dose-dependent fashion. Data demonstrate peforelin to stimulate selectively the secretion of FSH in castrated male pigs at recommended doses, and to induce the oestrus cycle in weaned sows. Like other GnRH-analoga peforelin is rapidly metabolised and excreted. Peforelin formulated as Maprelin 75 µg was safe after single injection up to 3fold the recommended dose in the target species.

Maprelin 75 µgis designed for biotechnical use in healthy female pigs. The claimed efficacy was demonstrated by appropriate studies. According to target animal safety data derived from one tolerance study and the clinical studies there were no local or systemic adverse effects monitored after intramuscular administration of Maprelin 75 µg up to the threefold of the recommended dose. Therefore, the benefit risk balance is positive.

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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MODULE 4

POST-AUTHORISATION ASSESSMENTS

None.

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