Maprelin®

Peforelin 75 µg/ml

- Synthetically produced GnRH analogue
- Reliable oestrus stimulation
- Very good fertility results

veyx

Delayed or complete absence of the onset of oestrus in female breeding animals considerably reduces the profitability of piglet production. Therefore, ensuring a timely and, if possible, a synchronised onset of oestrus become the focus of herd management when sows are kept in groups. With Maprelin® it is possible to initiate oestrus following an anoestrus period in sows of all age groups:

- in gilts after a preceding medicinal inhibition of cycle
- in primiparous sows (first litter born) after completion of lactation
- in pluriparous sows (more than one litter born) after completion of lactation

Maprelin® 75 µg/ml
injection solution for pigs
Peforelin

Active substance and other ingredients
Maprelin® is a clear, colourless aqueous solution for injection containing:
Active substance:

Peforelin	75.0 µg/ml
Excipients:	
Chlorocresol	1.0 mg/ml

Indications
For biotechnical use, for medicated treatment of groups or herd application.

- Inducing the oestrous cycle in sows after weaning
- Induction of oestrus in sexually mature gilts following therapy to inhibit the oestrous cycle with progestagens

Contraindications
Do not use in prepubertal gilts, in case of infertility or general health disorders.
Do not use in case of hypersensitivity to the active substance or to any of the excipients.

Adverse reactions
None known.
If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon or pharmacist.

Target species
Pig (sows and gilts)

Dosage for each species, routes and method of administration
Dosage in µg Peforelin and ml Maprelin® per animal. The dosage is dependent on the parity.

Primiparous sows	24 hours after weaning off the piglets:	37.5 µg = 0.5 ml
Pluriparous sows	24 hours after weaning off the piglets:	150 µg = 2.0 ml
Gilts	48 hours after the termination of the medication for the inhibition of the cycle:	150 µg = 2.0 ml

For intramuscular injection. For single administration.
Use automatic syringe equipment for the 10 ml and 50 ml vials.

Advice on correct administration
None.

Withdrawal period
Pig: Meat and offal Zero days

Special storage precautions
Keep out of the reach and sight of children.
Store in a refrigerator (2° C – 8° C).
Protect from light.
Keep the vial in the outer carton.
Do not use after the expiry date which is stated on the vial and carton.

Shelf life after first opening the container: 28 days.
When the container is broached (opened) for the first time, using the in-use shelf-life which is specified on this package insert, the date on which any product remaining in the vial should be discarded should be worked out. This discard date should be written in the space provided on the label.

Special warnings

Special warnings for each target species:
None.

Special precautions for use:
Special precautions for use in animals:
None.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
The product might induce irritation and sensitization. Persons with a known hypersensitivity to GnRH analogues or any of the excipients should not administer the veterinary medicinal product. Pregnant women should not administer the veterinary medicinal product, as an accidental self-injection by the user cannot be excluded and because GnRH analogues have been shown to be foetotoxic in laboratory animals. Women in childbearing age should administer the product with special caution.
In the case of accidental self-injection, seek medical advice and show the package leaflet to the doctor. In case of accidental contact with the skin, the corresponding area should be thoroughly cleaned with soap and water, as GnRH analogues may be absorbed through the intact skin. In case of contact with the eyes, they should be thoroughly rinsed with water.

Use during pregnancy, lactation or lay:
The safety of the product has not been established in sows and gilts during pregnancy and lactation. Laboratory studies in mice produced evidence of teratogenic effects. Do not use Maprelin® in animals during pregnancy and lactation.

Interaction with other medicinal products and other forms of interaction:
The simultaneous treatment of Maprelin® with PMSG or hCG can possibly lead to an overreaction of the ovaries.
No interactions were reported following administration of the product 48 hours after the end of a preceding Altrenogest therapy.

Overdose (symptoms, emergency procedures, antidotes), if necessary:
No adverse reactions were ascertained in pigs following treatment with up to three times the highest recommended dosage.

Incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

Special precautions for the disposal of unused product or waste materials, if any
Any unused veterinary medicinal product or waste materials derived from such vet-erinary medicinal product should be disposed of in accordance with local re-quirements. Ask your veterinary surgeon how to dispose of medicines no longer required.

To be supplied only on veterinary prescription.

Package sizes
10 ml and 50 ml vials

To be supplied only on veterinary prescription. The information given in this product brochure conforms to the state of knowledge upon completion. Please read the package leaflet prior to using the veterinary medicinal product.
The provisions of a national marketing authorisation, which may be different from the details given in this brochure, are binding.

General

As the preparations currently used for stimulating oestrus in the pig have consi-derable disadvantages due to the method of producing the active substance from biological materials (e.g. PMSG/eCG from the serum of pregnant mares), research activities of Veyx-Pharma were centred on the development of a product with a completely synthetically produced active substance. Veyx-Pharma has achieved this aim with the market approval registration of Maprelin® containing the syn-thetic active substance Peforelin. Peforelin is an analogue of the Gonadotropin Re-leasing Hormone (GnRH), which is also known as Lamprey (I)-GnRH-III because of its discovery in the hypothalamus of the lamprey. This GnRH-analogue stimulates FSH release selectively in the pig. FSH, the follicle stimulating hormone, initiates follicular growth and thus produces the basic prerequisite for the onset of oestrus. Following the product's use oestrus commences within a few days after wea-ning off the piglets, or the ending of a medication for the inhibition of the cycle, respectively. The achievable results are commensurate with the requirements of state-of-the-art optimum management. To this end Maprelin® increases the oes-trus rate as well as the farrowing results and improves the piglet index. Maprelin® is used 24 hours after weaning off the piglets or 48 hours following the ending of a medication for the inhibition of the cycle, respectively. Maprelin® can thus be integrated into the herd management routines without difficulty. As a result of the GnRH structure of the active substance Peforelin, the preparation is well tolerated both locally and in general. The active substance comprises solely of amino acids and is broken down very rapidly without any residue formation, resulting in no withdrawal period requirement.

Maprelin® is a ready to use injection solution (i.e. does not require time-consuming dissolving of the active substance). The preparation remains usable for 4 weeks after initial opening.

Chemistry

Peforelin is a GnRH analogue with the chemical name Gonadorelin[5-His, 6-Asp, 7-Trp, 8-Lys]. It is a decapeptide with the molecular formula $C_{59}H_{74}N_{18}O_{14}$ and a molar mass of 1259.4 g/mol. Compared to natural GnRH, it has the following amino acid sequence:

GnRH: pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2

Peforelin: pGlu-His-Trp-Ser-His-Asp-Trp-Lys-Pro-Gly-NH_2

Pharmacology

FSH is responsible for initiating follicular growth in the reproductive cycle of the sow and thereby it achieves the prerequisite for the onset of oestrus. The GnRH analogue Peforelin influences this control mechanism. In the pig it selectively stimulates the release of FSH, as was demonstrated in two studies initiated by Veyx-Pharma (see Figure 1) using an animal model based on castrated boars using different active substance dosages.

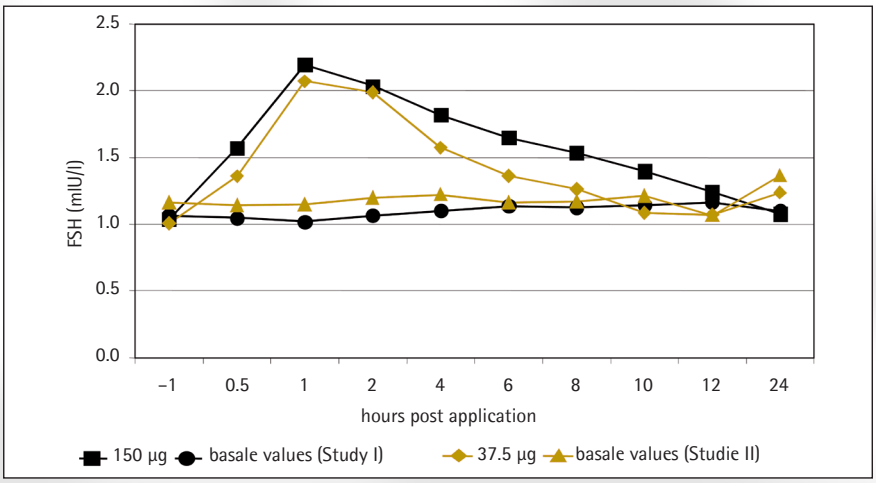


Figure 1: Blood plasma concentrations (mean values) of FSH in castrated boars, which were either given 150 µg or 37.5 µg Peforelin (i.m.) compared to the corresponding basal values
The application of Peforelin was carried out after the first blood sampling (-1).

Following an application of 37.5 µg and 150 µg Peforelin/animal, a treatment associated FSH peak occurred for both dosages, whilst the LH secretion was not influenced. The FSH concentration for the boars treated with 37.5 µg Peforelin attained the basal value 4 hours earlier than for those animals treated with the higher dosage. The FSH values were generally lower in the boars treated with the smaller dose. A dose dependent effect is evident for Peforelin.
On the basis of these results, because of its FSH selectivity, the mode of effect of the oestrus stimulating substance Peforelin differs from the mode of effect of conventional GnRH analogues. The latter primarily stimulate the release of LH and to a limited extent also the release of FSH. Thus, the conventional GnRH analogues are used to induce ovulation.

Peforelin is absorbed rapidly following intramuscular application. Elimination from the blood-stream occurs quickly whilst the hormonal effect is maintained over several hours.

GnRH analogues can only be detected for a short time in the liver, kidneys and the pituitary. There they are broken down by enzymes into inactive biological metabolites, which are then excreted via the renal pathways. No storage of the decapeptide or its degradation products occurs in the animal body. Thereby, the need for a withdrawal period following the application of Maprelin® can be dispensed with.

When administered orally, Peforelin as a polypeptide undergoes a prompt splitting by the digestive enzymes and thus loses its efficacy.

The investigations carried out under institutional experimental conditions on gilts, covered all of the usual clinical, clinical-chemical, pathological-anatomical, pathological-histological, as well as immunological parameters, to assess the tolerance in the target animal. The very good level of tolerance determined in this study is consistent with the pharmacological-toxicological research results of other GnRH analogues.

The target animals also tolerated the injection of Maprelin® under field conditions through to the desired effect, without reaction. There were absolutely no references to local or general intolerance reactions.

On the basis of the considerably lower molecular weight, the application of the GnRH analogue Peforelin provides the advantage over heterologous gonadotropins (e.g. PMSG) of reducing the possibility for sensitising and thus it lowers the risk of an immune reaction.

Pharmacotherapy

The clinical investigations were carried out in cooperation with the University of Leipzig (Prof. Dr. J. Kauffold, Prof. Dr. A. Sobiraj), the University of Gießen (Prof. Dr. A. Wehrend), the Anhalt University of Applied science (Prof. Dr. habil. M. Wähner) and veterinary practitioners from different regions in Germany.
In the studies carried out under field conditions, numerous sows of various age classes were included. Initially, extensive investigations were performed to determine the dosage and to determine the appropriate application time after weaning off the piglets and after ending a medication for the inhibition of the cycle, respectively. The functional status of the ovaries was hereby assessed using sonography or within the scope of diagnostic slaughter.

With regard to the question of why a considerably lower dosage is required in primiparous sows; on the basis of the current state of knowledge we can only make speculations. Possibly, the endocrinological processes that activate the release of FSH are only harmonised through 0.5 ml Maprelin® (37.5 µg Peforelin) (in comparison to higher dosages with a lower FSH secretion of shorter duration, see Figure 1). The fact that primi- and pluriparous sows differ in their responsiveness towards exogenously delivered endocrine effective substances is also described in the reference literature.

Insemination based on the test for standing reflex
Initially the studies were focussed on the application of Maprelin® for the stimulation of oestrus with subsequent insemination based on the test for standing reflex. From the extensive efficacy studies carried out for this, there follows below a more detailed look at three study examples.

In a study in pluriparous sows, 2 ml Maprelin® were used to test a comparison with 800 IU PMSG, as well as with a placebo (Table 1). The sows included in the study were treated with the named substances 24 hours after weaning off the piglets.
It could be demonstrated that Maprelin® is suitable to effectively stimulate oestrus in pluriparous sows. In comparison to the control animals (placebo treatment), an oestrus rate was achieved with the Maprelin® treatment that was 14.5 % higher; moreover, the farrowing rate was also significantly increased. Furthermore, compared to the control group the piglet index was significantly increased, i.e. for each 100 first inseminations, 100 more live born piglets were produced.

On the basis of the studies presented Maprelin® and PMSG are equally suitable for the stimulation of oestrus in pluriparous sows (oestrus rate with Maprelin® 95.1 %, and with PMSG 96.3 %). The pregnancy and farrowing rates were also the same.

Table 1: Fertility performance of pluriparous Sows

	Maprelin® (n = 103)	PMSG (n = 107)	Placebo (n = 103)
Oestrus rate (%)	95.1[b]	96.3[b]	80.6[a]
Farrowing rate* (%)	96.9	97.1	91.6
TPB/litter	11.7 ± 2.3	12.0 ± 2.6	11.6 ± 2.0
PBA/litter	11.2 ± 2.4	11.4 ± 2.5	10.7 ± 3.0
Piglet index	1082[a]	1105[a]	978[b]

a, b: differences between the groups were significant ($p \leq 0.05$).
Values relating to animals exhibiting oestrus by the 7th day after weaning.
* percentage of sows that farrowed from the sows inseminated;
TPB = total number of piglets born; PBA = piglets born alive;
Piglet index = piglets born alive per 100 first inseminations

As already mentioned, in primiparous sows a dosage rate of only 0.5 ml Maprelin® is required. Studies with primiparous sows using this dosage 24 hours after weaning off the piglets produced results that demonstrated that Maprelin® leads to a significant increase in the oestrus, gestation and farrowing rate in comparison to untreated sows (Table 2).

Whilst the untreated animals exhibited an 85.8 % oestrus rate, the sows that received Maprelin® achieved 94.0 %. Also in relation to the piglet index, there existed significant differences in favour of the Maprelin® treatment (105 more live born piglets per 100 first inseminations).

The studies confirm that Maprelin® can also be used effectively to stimulate oestrus in primiparous sows.

Table 2: Fertility performance of primiparous sows

	0.5 ml Maprelin® (n = 434)	untreated (n = 493)
Oestrus rate (%)	94.0[a]	85.8[b]
Farrowing rate* (%)	77.9[a]	71.9[b]
TPB/litter	12.5 ± 3.1	12.4 ± 3.3
PBA/litter	11.9 ± 3.1	11.7 ± 3.3
Piglet index	928[a]	823[a]

a, b: differences between the groups were significant ($p \leq 0.05$).
Values relating to animals exhibiting oestrus by the 7th day after weaning.
* percentage of sows that farrowed from the sows inseminated;
TPB = total number of piglets born; PBA = piglets born alive;
Piglet index = piglets born alive per 100 first inseminations

On the basis of perceptions gained from pre-trials a study in gilts was carried out using 2 ml Maprelin® 48 hours after the ending of a medication for the inhibition of the cycle with Altrenogest (20 mg each daily for 18 days). Gilts served as controls that were given exclusively Altrenogest, i.e. they did not receive any substance to stimulate oestrus (Table 3).

Gilts that received Maprelin®, exhibited a significantly higher rate of oestrus than the animals without oestrus stimulation. Thereby the interval from the last Altrenogest treatment to the onset of oestrus was reduced significantly following Maprelin® treatment and the inseminations carried out in a narrower time frame (Table 2). As with regard to the gestation rate there were no significant differences although the animals treated with Maprelin® had a tendency to have better results. From the total number of sows inseminated (AO_{all}) 9 animals returned to oestrus respectively in both the treated and control groups, 5 control and 3 Maprelin® treated sows aborted. Moreover, PCV and PRRS were diagnosed on the pig breeding unit.

38 litters were produced by Maprelin® treated animals and 32 in the control animals, from the gilts that exhibited oestrus within 8 days after the final Altrenogest treatment. There was no difference in the farrowing rate between the groups and it was at a low level*. The total numbers born and numbers born alive were similar in both groups ($p > 0.05$), but the piglet index of those treated with Maprelin® was increased ($p \leq 0.05$).

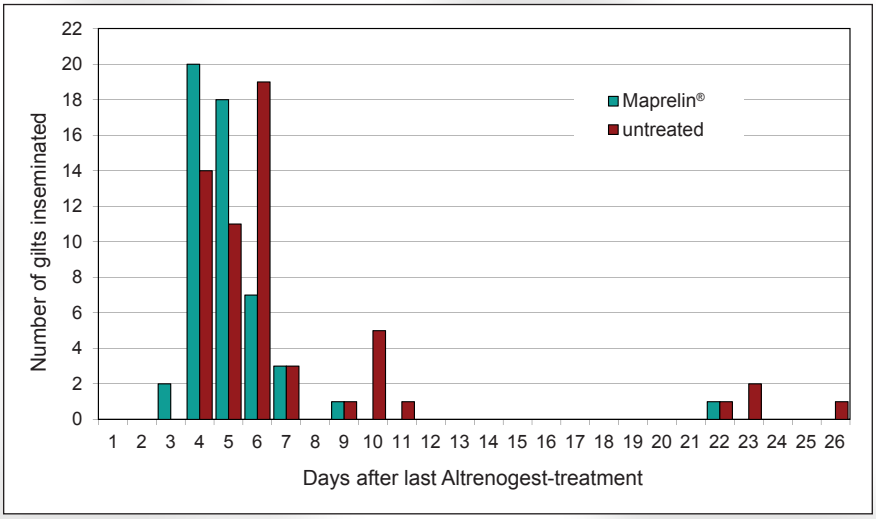
* The litters in this unit were characterized by a low farrowing rate, as well as a high rate of abortion and sows returning to oestrus. However, the litter size was in line with what was expected for this breed of sows. Moreover, PCV and PRRS were diagnosed. Once the herd had undergone a vaccination programme, subsequently, the number of returns to oestrus and abortions could be significantly reduced.

Table 3: Fertility performance of gilts

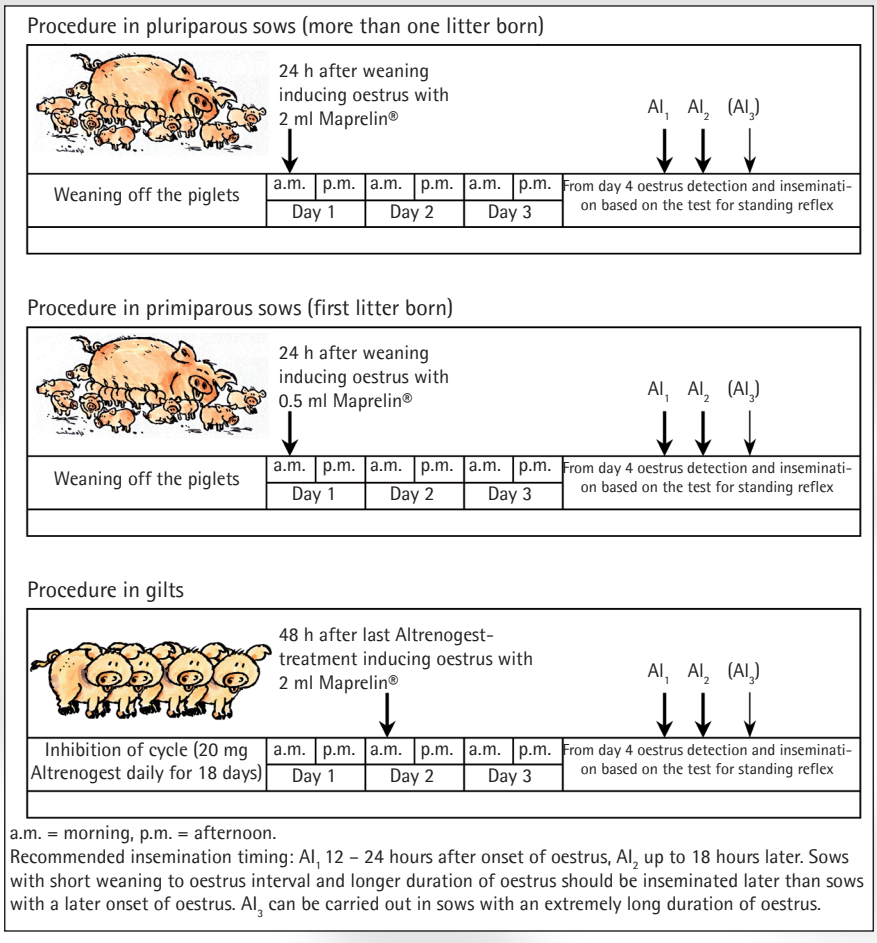
	Maprelin® (n = 58)	untreated (n = 52)
Oestrus rate*	96.2 %[a]	81.0 %[b]
AO_{8d} ($\bar{x} \pm s$)*	4.78 ± 0.95[b]	5.23 ± 0.96[a]
AO_{all} ($\bar{x} \pm s$)*	5.19 ± 2.62[b]	7.07 ± 4.87[a]
Pregnancy rate*	88.0 %	83.0 %
Farrowing rate*	76.0 %	68.1 %
TPB/litter ($\bar{x} \pm s$)*	14.11 ± 3.95	13.81 ± 2.35
PBA/litter ($\bar{x} \pm s$)*	13.03 ± 3.61	12.22 ± 3.55
Piglet $index_{IGF}$*	1072[a]	940[b]
Piglet $index_{LGF}$*	990[a]	832[b]

a, b: Differences were significant between the groups ($p \leq 0.05$).
* Values relate to animals in oestrus by the 8th day after the last Altrenogest treatment
AO^{8d} = Interval from last Altrenogest treatment to onset of oestrus for sows with oestrus by the 8th day after the last Altrenogest treatment; AO_{all} = same as AO^{8d}, but for all sows, also with later oestrus; pregnancy rate = proportion of inseminated gilts that were detected as pregnant by sonography in the 4th week after insemination; farrowing rate = percentage of inseminated gilts that farrowed;
TPB = total number of piglets born; PBA = piglets born alive;
Piglet index = piglets born alive per 100 first inseminations.

Figure 2: Distribution of first inseminations in gilts



In Figure 3 recommendations are given derived from the clinical studies presented for the use of Maprelin® for the stimulation of oestrus with subsequent insemination based on the test for standing reflex.



a.m. = morning, p.m. = afternoon.
Recommended insemination timing: AI_1 12 – 24 hours after onset of oestrus, AI_2 up to 18 hours later. Sows with short weaning to oestrus interval and longer duration of oestrus should be inseminated later than sows with a later onset of oestrus. AI_3 can be carried out in sows with an extremely long duration of oestrus.

Figure 3: Recommendations for the application of Maprelin® for inducing the oestrous cycle with subsequent insemination based on the test for standing reflex

Fixed-time insemination

A considerable amount of practical experience is available from numerous pig units in relation to oestrus induction using Maprelin® with subsequent synchronised ovulation. As the following examples show, equally good results are achieved using Maprelin® compared to ordinary methods using PMSG:

Different timings of the Gonavet Veyx® injection in sows following the Maprelin® administration were tested on a unit in Thuringia, Germany, with a weekly farrowing pattern and three week lactation period. Sows that received PMSG at the same time served as controls. Most of the parameters included were similar in the four groups and did not differ significantly (Table 4). However, there was a tendency for better oestrus and farrowing rates in the groups treated with Maprelin®. Significant differences existed in relation to live born piglets and the piglet index between both Maprelin® groups, as well as for the piglet index between both PMSG groups ($p < 0.05$).

In summary, it can be determined that the best results were achieved with a 78 hour interval between Gonavet Veyx® treatment and the administration of Maprelin®.

Table 4: Sow performance after fixed-time insemination

Interval Gonavet Veyx®	74 hours		78 hours	
	Maprelin® (n = 63)	PMSG (n = 61)	Maprelin® (n = 65)	PMSG (n = 64)
Oestrus rate (%)	95.2	93.4	92.3	90.6
Farrowing rate (%)	90.0	84.2	85.0	81.0
PBA/litter ($\bar{x} \pm sd$)*	10.06 ± 2.45^{b}	11.02 ± 2.97^{ab}	11.08 ± 2.77^{a}	10.96 ± 2.78^{ab}
Piglet index	905^{bc}	928^{c}	942^{ac}	888^{b}

a, b, c: Differences between the groups were significant ($p < 0.05$).
Values relating to animals exhibiting oestrus by the 7th day after weaning.
* percentage of sows that farrowed from the sows inseminated
PBA = Pigs born alive; Piglet index = PBA per 100 first inseminations

In a 760 sow breeding herd in Bavaria, gilts that had attained puberty were orally administered 20 mg Altrenogest for 18 days. Thereby, one group of 98 gilts were administered Maprelin® after 48 hours and 80 hours later Gonavet Veyx®. In 85 other animals, PMSG was administered 39 hours after the Altrenogest treatment and 79 hours later were given Gonavet Veyx®. The gilts were fixed-time inseminated in the presence of a mature breeding boar at 25 hours and 41 hours, respectively, after the Gonavet Veyx® administration.

The results were of a very high level overall and similar in both groups ($p > 0.05$; Table 5). But, there was a tendency for higher farrowing rates following the Maprelin®-treatment and higher litter sizes following PMSG administration.

Table 5: Performance of gilts after fixed-time insemination

	Maprelin® (n = 98)	PMSG (n = 85)
Gilts inseminated	98	85
Standing reflex AI_1	85.71 %	85.88 %
Standing reflex AI_2	98.98 %	97.65 %
Conception rate	98.98 %	96.47 %
Farrowing rate	98.98 %	92.94 %
PBA/litter ($\bar{x} \pm$ sd)*	11.98 ± 2.52	12.66 ± 2.68
Piglet index	1186	1192

There were no significant differences between the groups ($p > 0.05$).
Conception rate = percentage of gilts that were found pregnant using sonography in the 4th week after insemination; Farrowing rate = percentage farrowed per gilt inseminated; PBA = pigs born alive; Piglet index = PBA/100 sows/gilts inseminated

In summary, it can be concluded that fixed-time insemination following oestrus induction can be carried out equally successfully using Maprelin® as when using the traditional method based on PMSG. It is generally considered advisable to carry out oestrus detection, because the best results are to be expected when there is a standing reflex at the time of insemination. It is also especially useful to check the timing of the insemination when the system operating on the unit is changed or modified.

The following procedure is generally recommended:
Adult sows:
- Weaning the piglets off the sows should be carried out simultaneously
- 24 hours after weaning – induce oestrus using 0.5 ml (primiparous sows), or 2 ml Maprelin® (pluriparous sows)
- Injection of the ovulation synchronising substance (e. g. 1 ml Gonavet Veyx®) at intervals after oestrus induction based on the length of the suckling period:
  - for > 4 week lactation = 56 – 58 hours after oestrus induction
  - for 4 week lactation = about 72 hours after oestrus induction
  - for 3 week lactation = 78 – 80 hours after oestrus induction
- Fixed-time insemination:
  AI_1: 24 hours following the injection of the ovulation synchronising substance
  AI_2: at the latest 16 hours after AI_1
  AI_3: recommended in sows with longer oestrus duration, approx. 6 – 8 hours after AI_2

Gilts:

- Oral administration of 20 mg Altrenogest daily over 18 days
- Oestrus induction by administering 2 ml Maprelin® 48 hours after the final Alt renogest treatment
- 78 – 80 hours after oestrus induction – injection takes place for the ovulation synchronising substance (e. g. 1 ml Gonavet Veyx®)
- Fixed-time insemination:
  AI_1: 24 – 26 hours following the injection of the ovulation synchronising substance
  AI_2: at the latest 40 hours following the injection of the ovulation synchronising substance
  AI_3: when required in gilts with longer oestrus duration – approx. 6 – 8 hours after AI_2

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Veyx-Pharma is GMP-, QS- and VLOG-certified.

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