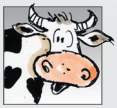
Gonavet Veyx®



GnRH-Analogue

- Ovulation induction/ synchronisation
- Fixed-time insemination
- Optimised reproductive performance
- Therapy of ovulation disorders

Gonadorelin[6-D-Phe] contained in the product Gonavet Veyx® is a synthetic derivative of the gonadotropin releasing hormone GnRH which develops naturally in the hypothalamus. Gonadorelin[6-D-Phe] triggers the same neuro-regulatory and endocrinal processes as the original GnRH. Thus, it induces the synthesis and release of the ovary regulating gonadotropic hormones LH and in a smaller amount FSH. These gonadotropins in turn stimulate follicular maturation, ovulation and the formation of the corpora lutea.
In comparison to the original GnRH, Gonadorelin[6-D-Phe] is characterised by a longer duration of action and a much greater affinity to the GnRH receptors in the pituitary gland. It also shows greater resistance to peptidases. The result is that Gonavet Veyx® shows approximately ten times the level of efficacy to that of natural GnRH.

Gonavet Veyx®, 50 µg/ml

Solution for injection for cattle, pigs and horses
Gonadorelin[6-D-Phe]

Active substance and other ingredients
Active substance:
Gonadorelin[6-D-Phe] 50.0 µg/ml
(equivalent to 52.4 µg/ml Gonadorelin[6-D-Phe]acetate)
Excipients:
Chlorocresol 1.0 mg/ml

Indications
Control and stimulation of reproduction in cattle and pigs. Treatment of ovarian-related fertility disorders or dysfunctions in cattle and horses.

Cattle (cows, heifers):
- Ovulation induction in case of delayed ovulation due to LH deficiency
- Induction/synchronisation within the framework of systems for timed inseminations
- Stimulation of the ovaries during the puerperal period from day 12 post partum
- Ovarian cysts (due to LH deficiency)

Pigs (sows, gilts):
- Induction/synchronisation of ovulation within the framework or systems for timed insemination and parturition synchronisation

Horses (mares):
- Acyclia and anoestrus due to LH-deficiency

Contraindications
Do not use in cows with a mature tertiary follicle ready to ovulate.
Do not use during infectious diseases and other relevant health disorders.
Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

Adverse reactions
None known.

Target species
Cattle (cows, heifers), pigs (sows, gilts), horses (mares)

Amounts to be administered and administration route
For intramuscular or subcutaneous injection. For intramuscular use, preferably in the neck region. The product is intended for single administration except when used as part of the "Ovsynch" timed artificial insemination protocol. Dosage in ml product and micrograms Gonadorelin [6-D-Phe] per animal.

Cattle (cows and heifers) by intramuscular injection: 1.0 – 2.0 ml
(corresponding to 50 – 100 µg of Gonadorelin[6-D-Phe])
- Ovulation induction in case of delayed ovulation due to LH-deficiency 2.0 ml
- Inductions/synchronisation of ovulation within the framework of systems for timed inseminations 1.0 – 2.0 ml
- Stimulation of the ovaries during the puerperal period from day 12 post partum 1.0 ml
- Ovarian cysts (due to LH-deficiency) 2.0 ml

Pigs (sows and gilts) by intramuscular or subcutaneous injection: 0.5 – 1.5 ml
(corresponding to 25 – 75 µg of Gonadorelin[6-D-Phe])
- Induction/synchronisation of ovulation within the framework of systems for timed inseminations and parturition synchronisation

Sows: 0.5 – 1.0 ml
Gilts: 1.0 – 1.5 ml

Horses (mares) by intramuscular injection: 2.0 ml
(corresponding to 100 µg of Gonadorelin[6-D-Phe])

The rubber stopper of the vial may be safely punctured up to 25 times. Otherwise, automatic syringe equipment, or a suitable draw-off needle, should be used for the 20 ml and 50 ml vials to avoid excessive puncturing of the closure.

Special information
Cattle:
For oestrus and ovulation synchronisation and timed artificial insemination (AI) in cattle the so called "Ovsynch-procedure" was developed, which consists of the combined use of GnRH and $PGF_{2\alpha}$. The following timed AI protocol has been commonly reported in the literature:

Day 0:	Inject 100 µg of Gonadorelin[6-D-Phe] per animal (2 ml of the product)
Day 7:	Inject $PGF_{2\alpha}$ or analogue (luteolytic dose)
Day 9:	Inject 100 µg of Gonadorelin[6-D-Phe] per animal (2 ml of the product)
AI:	16 – 20 hours later, or at observed oestrus if sooner

The Ovsynch-procedure may not be as efficacious in heifers as in cows.

Pigs:

The ovulation synchronisation system includes the administration of Peforelin or PMSG after the end of oestrus synchronisation with Altrenogest in gilts or after the weaning in adult sows and two timed artificial inseminations. In adult sows the time table depends on the duration of the suckling period. The following procedures are recommended:

	Gilts[1]	**Adult sows**[2]
Induction of oestrus	**Peforelin** 48 h or **PMSG (eCG)** 24 h – 48 h after last application of Altrenogest	**Peforelin** or **PMSG** application 24 h after weaning
Synchronisation of ovulation	**Gonadorelin[6-D-Phe]** 78 – 80 h after Peforelin or PMSG application	*Suckling period > 4 weeks:* **Gonadorelin[6-D-Phe]** 56 – 58 h after Peforelin or PMSG application *Suckling period 4 weeks:* **Gonadorelin[6-D-Phe]** 72 h after Peforelin or PMSG application *Suckling period 3 weeks:* **Gonadorelin[6-D-Phe]** 78 – 80 h after Peforelin or PMSG application
1st AI	24 – 26 h after **Gonadorelin[6-D-Phe]** application	24 – 26 h after **Gonadorelin[6-D-Phe]** application
2nd AI	40 – 42 h after **Gonadorelin[6-D-Phe]** application	40 – 42 h after **Gonadorelin[6-D-Phe]** application

[1] The preferred dose of Gonavet Veyx in gilts is 50 µg Gonadorelin[6-D-Phe]. However, the dose may be adjusted within the range of 50 - 75 µg to take into account farm-specific aspects or seasonal influences. The proposed time table should be strictly kept.

[2] The preferred dose of Gonavet Veyx in adult sows is 50 µg Gonadorelin[6-D-Phe]. However, the administration of 25 µg is also sufficient in case of sows with sow parity of more than 3 or during the mating period of September until May. The proposed time table should be strictly kept.

Advice on correct administration
None

Withdrawal periods

Cattle, horses, pigs:	Meat and offal	Zero days
Cattle, horses:	Milk	Zero hours

Special storage precautions
Store in a refrigerator (2 °C - 8 °C). Keep the vial in the outer carton in order to protect from light.
Do not store above 25 °C after opening.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and vial label after "EXP". The expiry date refers to the last day of that month. Shelf life after first opening the immediate packaging: 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
To maximise conception rates of cows to be treated with GnRH-$PGF_{2\alpha}$ based synchronisation protocols, the ovarian status should be determined and regular cyclic ovarian activity confirmed. Optimal results will be achieved in healthy normally cycling cows.

Special precautions for use
Special precautions for use in animals
Not applicable.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Administration should be performed with caution in order to avoid accidental self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician. As GnRH analogues can be absorbed through the skin, accidental spillage onto skin or into the eyes should be thoroughly rinsed off with water. The veterinary medicinal product should not be administered by pregnant women. Women of child-bearing potential should administer the product with caution. People with known hypersensitivity to GnRH should not use this veterinary medicinal product.

Use during pregnancy, lactation or lay

Pregnancy
Not applicable.

Lactation
Can be used during lactation.

Interaction with other medicinal products and other forms of interaction
A synergistic effect occurs in case of combined administration with FSH. Simultaneous use of human or equine chorionic gonadotropin may lead to ovarian over-stimulation.

Overdoses (symptoms, emergency procedures, antidotes, if necessary
None known.

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 veterinary medicinal product should be disposed of in accordance with local requirements.

To be supplied only on veterinary prescription.

Package sizes
10 ml, 20 ml and 50 ml vial

The information given in this product brochure corresponds to the state of knowledge upon completion. Please read the package leaflet before using the veterinary medicinal product.

Physiological basis

The reproductive process in mammals is an extraordinarily complexly controlled biological procedure. The central nervous system (CNS) and especially the hypothalamus play a decisive role. Neural structures have a primary influence, formed by the hypothalamus and its synaptic connections to the forebrain and midbrain and known as the limbic system. Thus the hypothalamus is an intermediary between the central nervous system and the endocrine system. It receives and transmits both the environmental stimuli received via the cerebral cortex and signals from the animal body (Fig. 1).

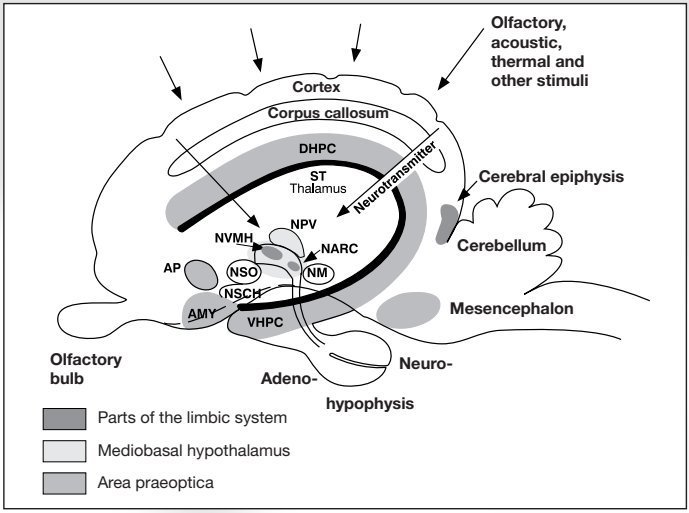


Fig. 1: Schematic depiction of the limbic system and the central nervouse structures, also, control of reproductive functions (acc. to BUSCH 1991 b)

DHPC = dorsal hippocampus; ST = Stria terminalis; AP = Area praeoptica; NVMH = Nucleus ventromedialis hypothalami; NPV = Nucleus paraventricularis; NARC = Nucleus arcuatus; NSO = Nucleus supraopticus; NM = Nucleus mamillaris; NSCH = Nucleus suprachiasmaticus; AMY = Amygdala; VHPC = ventral hippocampus

Additional components of a functional reproductive cycle are the gonads and the genital tract. The participating neural and humoral stages are organised hierarchically, however, the functions of the higher order organs are influenced by the subordinate organs.
The closely related interchange connections of this regulatory process are shown in Figure 2 and encompass:

- extra-hypothalamic structures of the central nervous system that exert influence on the secretion of GnRH (Gonadotropin-Releasing-Hormone), through exogenous and endogenous stimuli via the mediation of neurotransmitters, peptides and prostaglandins

- the hypothalamus, as the fundamental site of production of GnRH
- the adenohypophysis with the production of FSH (Follicle stimulating hormone) and LH (Luteinising hormone), as well as prolactin
- the ovary as the target organ of the gonadotropins (FSH, LH) and production site of oestrogens, androgens, gestagens and folliculostatin
- the uterus, on the one hand presented as an important effector organ of the ovarian hormones and on the other, where it exerts an immediate influence on the ovarian cycle via $PGF_{2\alpha}$ (Prostaglandin $F_{2\alpha}$).

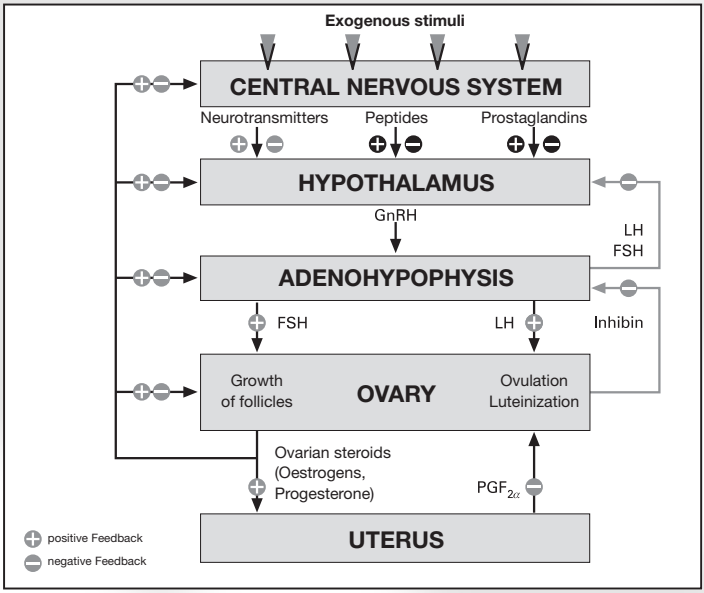


Fig. 2: Physiological control of reproduction in female animals (after DÖCKE 1994, simplified depiction)

GnRH is a key substance in the control of female sexual function. The neurohormone also known as gonadoliberin, luliberin or luteinising-hormone-releasing-hormone (LHRH) was initially detected in the rat in 1960 by McCANN's work group. GnRH is formed by hypothalamic neurons in all domestic mammals and undergoes pulsatile release. It reaches the pituitary via a special vascular system (hypothalamohypophysial-portal system). There, the formation and release of LH and in limited quantities also FSH is stimulated by GnRH. The released gonadotropins reach the ovaries via the blood circulation and there stimulate the growth of the follicle and ripening of the egg cell(s). The formation of gonadotropin receptors in the follicular epithelium is induced, which in turn initiates ovarian steroid synthesis. In this way the production of oestrogen is controlled by FSH. In turn an elevated blood progesterone level reduces the FSH secretion by a feedback mechanism. The high oestrogen level induces oestrus and via a positive feedback the LH-Peak, which leads to the ripening of the follicles and ovulation.

The ovulation inducing LH-Peak is subject to a rapid depletion. In the subsequent phase the pituitary gland is insensitive to a further stimulation by GnRH. This is especially significant for the practical application of GnRH for the induction of ovulation, as in this way, alongside the induction, an additional endogenous LH peak that could affect the ovarian and hormonal processes can be inhibited.
A corpus luteum (yellow body) develops from the ruptured follicle after ovulation and produces increasing quantities of progesterone. In non-pregnant animals the function of the corpus luteum is interrupted through the effects of $PGF_{2\alpha}$. This effects a morphological regression of the corpus luteum and the progesterone level falls. The reduction in progesterone effect then results once again in an increased release of FSH, achieving the prerequisites for a new oestrous cycle to commence. Further GnRH effects are found in the body organism, in addition to the stimulating effect on the pituitary gland gonadotropin secretion described here. This includes the increased level of sexual behaviour, which is probably induced via extra-hypothalamic areas of the brain. Moreover, GnRH may also affect the gonads directly, i.e. without mediation by gonadotropins. In female animals a primarily promoting influence on egg cell maturation, luteinising and the synthesis of progesterone in the granulosa cells of mature follicles has been observed.
Cognisance of the aforementioned relationships allow for various effects to be achieved through the administration of GnRH in cycling animals. For example, a single injection of GnRH at higher dosage rates induces the release of the ovulation triggering LH.

Chemistry

Gonavet Veyx® contains a synthetic derivative of the physiological gonadotropin releasing hormone GnRH. The chemistry involves a D-Phe^6-LHRH (D-Phe6-Luteinising-Hormone-Releasing-Hormone, Gonadorelin[6-D-Phe]), a highly effective peptide hormone (decapeptide) with the chemical formula

$C_{62}H_{80}N_{17}O_{13} \cdot x\ CH_3COOH$ (x = 1 to 2)

and a molar mass of 1271.4 g/mol (acetate free substance) along with the sequence:

PyroGlu-His-Trp-Ser-Tyr-D-Phe-Leu-Arg-Pro-$GlyNH_2$

The difference between the natural GnRH and the synthetic derivate is based on the fact that glycine has been substituted by D-Phenylalanine at position 6 of the amino acid sequence. In this way GnRH analogues are formed (GnRH-agonists) that are characterised by a long acting efficacy and a significantly higher affinity to the GnRH receptors of the pituitary gland. Moreover, they also exhibit a higher resistance to peptidases. This results in around a ten-fold more intensive effect for Gonavet Veyx® in comparison to natural GnRH. The Gonavet Veyx® preparation is a clear, almost colourless, aqueous solution, exhibiting a weak but characteristic acetic acid odour and has a pH value between 5.0 and 6.0.

Pharmacology

The effect of the Gonadorelin[6-D-Phe] contained in Gonavet Veyx® corresponds to that of the natural endogenous GnRH, whereby the intensity and duration of action in the synthetic analogue exhibit a considerable increase. Gonadorelin[6-D-Phe] stimulates to a large extent the synthesis and especially the release of gonadotropins from the pituitary gland. Thereby, the increase of the LH level in blood plasma following the application of Gonavet Veyx® is particularly noticeable. The LH peak occurring in a spontaneous cycle is imitated and effects all the physiological reactions involved with the follicle maturation and ovulation. The exogenously given Gonavet Veyx® in prooestrus or early oestrus is effective on the gonadotropin forming cells of the adenohypophysis. In these stages of the cycle, the disposition for reactivity by the pituitary gland and the ovary is particularly high. The release of LH commences immediately after the injection and develops into an LH peak within 1 to 2 hours. The initial values are only to be found again after about 7 to 8 hours.
The single exogenous supply of Gonavet Veyx® leads to a transitional release of LH. A simultaneously high GnRH level is physiologically abnormal and effects a desensitising of the gonadotropic cells as a result of a decline of GnRH receptors in the cell membrane. As a consequence, the release of Gonadotropins fails to occur. In figure 3 the LH profile of cows with a disturbed course of the puerperium is shown following a single application of 1 ml Gonavet Veyx®.

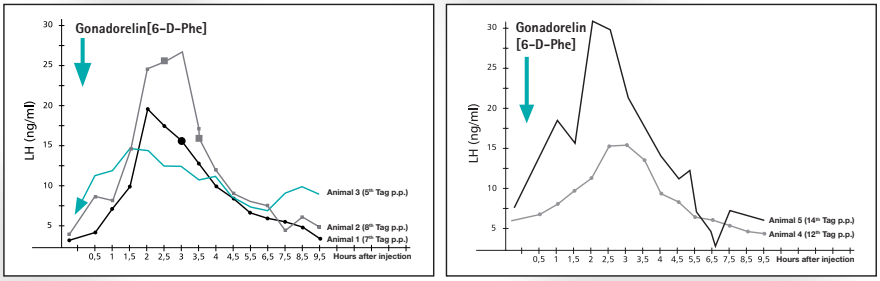


Fig. 3: LH blood level following a single application of 50 µg Gonadorelin [6-D-Phe] at differing times in the puerperium (BUSCH 1986)

Based on this Gonavet Veyx® has the ability to release LH from the adenohypophysis and to induce a characteristic LH progression curve in the blood plasma from already 5 days post-partum (BUSCH 1986). The peak value of the induced LH blood level values relates principally to the state of the individual neuro-endocrine development of the animal. Otherwise it is to be reckoned with that the 1st ovulation p. p. will be induced prematurely and to a large extent independent of the dosage of the applied preparation. Gonadorelin[6-D-Phe] stands out as having a very good tolerance level. It has low toxicity. The estimated LD_{50} following intravenous administration was 15.4 mg/kg live weight in rats. For the subacute toxicity tests (28-day application

duration) in rats showed that Gonavet Veyx® was harmless at application levels that corresponded to 50 times the therapeutic dosage. Gonadorelin[6-D-Phe] is completely metabolised within 10 hours following the injection. Intoxications cannot be achieved with the active substance, however, it has to be dosed precisely in the interests of achieving a timed and precise determinable effect.
Gonadorelin[6-D-Phe] is considered harmless from a biological residue perspective. The breakdown and inactivation of GnRH takes place very rapidly, so that its biological half-life is very short. In heifers, for example, the highest blood level was attained five minutes after an intravenous injection of 2.5 mg GnRH and the initial level was already achieved after 1.5 hours. Excretion of the metabolites occurs primarily via the kidneys. Therefore, there is no requirement for a withdrawal period.

Pharmacotherapy

Application in cattle

Gonavet Veyx® enables an effective therapy and prophylaxis for various disorders of the reproductive process in cattle. A significant improvement in the pregnancy rates, a reduction in the need for sterility treatments and low culling selection rates due to inability to breed are all confirmed in many scientific studies.
The tolerance to and efficacy of Gonavet Veyx® was determined and tested using around 2,900 cattle for indications with a very diverse range of diagnostic or therapeutic aspects. In contrast, about 1,800 control animals were used, i.e. cows that were kept under the same conditions and were not treated at all or given original GnRH.

1. Therapy of ovulation disorders
The secretion of LH induced by a single application of Gonavet Veyx® can be used to induce ovulation in cattle, insofar as a tertiary follicle exists on one of the ovaries. Disorders such as delayed ovulation and ovarian cysts that touch upon no timely release of LH or an LH deficiency, are thus indications for Gonavet Veyx®.

Delayed ovulation

In cattle the rupturing of the follicle is to be considered as delayed when it does not occur within 6 to 16 hours following the ending of standing oestrus.
The significance of delayed ovulation as a factor that reduces fertility is based on the fact that at the time of possible amphimixis, either the egg cell or the sperm are damaged or already dead.

Several clinical studies in cows with delayed ovulation have shown that the pregnancy rate significantly increases by 12 – 15 % after the application of Gonavet Veyx® compared to untreated control animals.
If delayed ovulation has been diagnosed or is assumed, a double insemination is always recommended (1st insemination in the second half of oestrus, 2nd insemination 24 hours later). If possible, Gonavet Veyx® should be administered at the time of the 1st insemination, at the latest, however, at the 2nd insemination).

Ovarian cysts

The efficiency of cyst treatment using Gonavet Veyx® has been determined in comprehensive clinical investigations. This showed that 60 % of the cows (n = 250) treated with the preparation were already in-calf to the first insemination. The overall pregnancy rate was about 80 %. Recidive cysts were observed in 11 % of the animals. The interval between the cyst treatment and the first AI (Artificial insemination) lay at 28.7 days. The interval between the treatment and pregnancy diagnosis was on average 48.3 days.
The Ovsynch procedure described in Section 3 has also proven successful for the therapy of ovarian cysts.
The fertility of the ovulated egg cells in the oestrus induced by the hormone treatment is significantly reduced. Thus the treated animal should be inseminated in the subsequent oestrus, i.e. 3 weeks later. Also, when following the treatment using the Ovsynch procedure, so that the pregnancy rate is comparable to other therapy procedures, it is an advantage that the majority of the animals remain cyclic.

2. Stimulation of the ovaries in the puerperium

In a number of studies involving large numbers of animals it was determined that the prophylactic application of Gonavet Veyx® in the clinical puerperium significantly reduced the frequency of endometritis and reduced the calving interval. The preparation should be injected 12 days post-partum. At this time the ovaries almost always exhibit an LH responsive follicle. It has proven effective to carry out a PGF_{2a} injection seven days after the application in order to induce a second oestrus. The treatment should ensure that a cyclic ovarian activity commences early in the puerperium. If the cycle has begun in the animals, then in most cases oestrus will occur at regular intervals. The insemination can then be carried out at the end of the planned calving to first insemination interval.

3. Ovulation synchronisation

Ovulation synchronisation is primarily suitable for units with problems with oestrus detection and low oestrus rates (HEUWIESER and MANSFELD 1999).

Ovsynch procedure

The Ovsynch procedure developed in the USA is by far the most widely used method of ovulation synchronisation in cattle. Animals included in the synchronisation procedure are initially administered a GnRH preparation, e.g. Gonavet Veyx®. They are given PGF_{2a} e.g. PGF Veyx® forte seven days later. Two days (30 – 48 hours) after the PGF_{2a} treatment, a second GnRH application is carried out. The animals involved can then be inseminated at a ‚fixed-time' without any preceding oestrus detection 8 – 24 hours later. (Fig. 4). However, it is the opinion of some authors that carrying out oestrus detection is to be recommended, as where an oestrus commences after the first injection, all subsequent injections can be avoided. Moreover, the timing of oestrus detection can be planned when using the Ovsynch procedure.

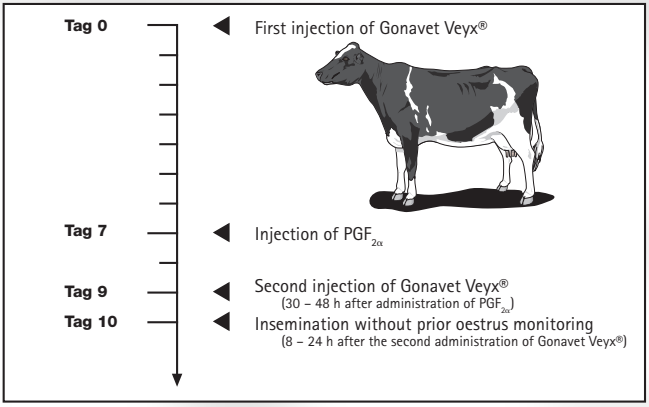


Fig. 4: Ovulation synchronisation with the Ovsynch procedure (acc. to WILTBANK 1998)

The mode of effect touches upon the following (HEUWIESER and MANSFELD 1999): The first GnRH administration leads to the ovulation of the dominant follicle within 24 – 32 hours and thereby to the formation of a new or an additional corpus luteum. This is why oestrus occurs only after the first PGF_{2a} administration. Within 1 – 2 days after the GnRH administration there is the development of a new follicle surge. One of the follicles achieves dominance and can be ovulated following the PGF_{2a} induced luteolysis. The second GnRH administration effects a synchronised ovulation.

Based on various investigations, the success rate for insemination in cows following the carrying out of the Ovsynch procedure and inseminated using a fixed-time insemination were only slightly lower than those for the respective control animals inseminated based on oestrus detection. In all studies published to date, it was determined consistently that this procedure produces better results in cows than in heifers.
It is recommended, when applying the Ovsynch procedure, that all animals to be synchronised undergo a gynaecological examination, in order to detect patients with pathological conditions of the reproductive organs and to exclude or treat them prior to synchronisation. SOBIRAJ and PRESCHE (1999) recommend that the Ovsynch procedure is carried out under veterinary supervision when they have not been detected as being in oestrus by the 60th day p.p. because of anoestrus or they are acyclic.
The Ovsynch procedure can also be successfully used to treat cows with ovarian cysts (see Section 1 of this brochure).

Presynch procedure (pre-synchronisation)
After application of the Ovsynch procedure, the rate of conception is highest when it is started 6 – 12 days after oestrus (HEUWIESER 2010). In order to achieve this in as many animals as possible, $PGF_{2\alpha}$ can be administered twice at an interval of 14 days for pre-synchronisation. The Ovsynch procedure is started within a period of 12 – 14 days after the last application of $PGF_{2\alpha}$.

Resynch procedure (post-synchronisation)
In order to optimise the time between a negative pregnancy diagnosis and repeat insemination, a post-synchronisation can be carried out (HEUWIESER 2010). This involves a regular Ovsynch protocol. It is timed so that the first GnRH administration is carried out already 7 days prior to the pregnancy diagnosis and an administration with $PGF_{2\alpha}$ for those with a negative result on the same day as the pregnancy test. The best insemination results are achieved when the resynch protocol is commenced 33 days after the insemination of the first Ovsynch protocol.

Ovulation synchronisation BUSCH
As an alternative to the aforementioned application possibilities, according to BUSCH (1999) Gonavet Veyx® can also be used as follows: Animals that do not exhibit oestrus within the scope of oestrus synchronisation using a PGF_{2a} injection receive a further PGF_{2a} administration 11 days after the first injection. Where there is no detectable oestrus after the second application, then an application of Gonavet Veyx® occurs on the morning of the 3rd day after the repeat injection with a subsequent fixed-time insemination without consideration of any signs of oestrus. The prerequisite for success for such a procedure is the strict carrying out of puerperal controls and the treatment of diseased animals. The procedure should be carried out at the earliest from 55 to 60 days p.p.

Application in pigs

Gonavet Veyx® allows for controlling the onset of ovulation, following a preceding oestrus synchronisation in adult sows and gilts, so that the insemination of batches of animals can be pre-planned precisely (fixed-time insemination). The ovulation synchronisation of batches of animals has for many years presented a proven method of controlling reproduction. The resulting advantages in terms of production technology, hygiene, and labour economics help to improve management and to increase the output in piglet production farms.
Ovulation synchronisation allows for semen to be previously sourced and more easily planned. Moreover, checking for returns to oestrus is simplified. The group of inseminated breeding sows then follow the same sequence during gestation and will farrow within a few days of each other. The application of $PGF_{2\alpha}$ (PGF Veyx®) and the long acting oxytocin Hypophysin® LA ensures that the commencement of birth in this sow group is concentrated within a short time frame. This allows for the observation and assistance at farrowing to be reduced from many days and nights to just a few. Piglet care (e.g. iron administration, vaccinations) can be carried out at predetermined times with large groups of piglets. The basic principles of health and hygiene in pig production and weaner rearing are better realised. Use of reproduction control methods has the following advantages for the sow breeder:

- Potentially simultaneous occupation and clearance of stall units (all-in-all-out-principle)
- Better organisation of work and production steps
- Production of uniform piglet lots with the same genetic structure and the resulting market advantages
- Reduction of expenses for keeping of teaser and breeding boars
- Reliable integration in groups of replacement sows in periodic farrowing systems
- More efficient planning and control of gilt stock management.

Essential prerequisites for the efficacy of systems that control reproduction are the correct timing and preparation of batches of healthy and reproductively primed breeding animals, as well as high levels of provision and care. However, the application of medications to control reproduction cannot compensate for serious deficiencies in nutrition, housing, health related deficiencies, or bad management. The synchronised ovulation procedure with Gonavet Veyx® differs according to whether gilts or adult sows are to be included (Fig. 5). The procedures listed here can be applied without problem to specific unit circumstances (e.g. choice of weekday when weaning and insemination is to be carried out).

			Adult sows (4-week suckling)	Gilts
Day 0	Tuesday	a. m.		Last Altrenogest admin.
		p. m.		
Day 1	Wednesday	a. m.		24 – 48 hours
		p. m.	weaning	
Day 2	Thursday	a. m.	24 hours	Oestrus induction
		p. m.	Oestrus induction	
Day 3	Friday	a. m.		
		p. m.		78 – 80 hours
Day 4	Saturday	a. m.	72 hours*	
		p. m.		
Day 5	Sunday	a. m.		
		p. m.	Gonavet Veyx®	
Day 6	Monday	a. m.		
		p. m.	24 – 26 hours: AI_1	AI_1: 24 – 26 hours
Day 7	Tuesday	a. m.	16 hours: AI_2	AI_2: 16 hours
		p. m.		
a. m. = morning; p. m. = afternoon * 3-week suckling 78 – 80 hours				

Fig. 5: Methods of ovulation synchronisation and fixed-time insemination in adult sows and gilts

1. Ovulation synchronisation in adult sows

HCG was initially used to achieve a biological synchronisation of ovulation in group housed breeding sows. Its antigenic and immunogenic properties proved to be a particular disadvantage. Therefore, today, the very well tolerated Gonavet Veyx® is used for ovulation synchronisation in adult sows following an oestrus induction after weaning. Maprelin® or preparations with the active substance PMSG (Pregnant Mare's Serum Gonadotropin, Synonym eCG = equine chorionic gonadotropin) are available to stimulate follicular growth and development. The latter have similar properties to hCG products, as both active substances are harvested from biological material. Maprelin® contains the very well tolerated synthetic active substance Peforelin. This involves a GnRH analogue, which in contrast to the active substance contained in Gonavet Veyx®, does not stimulate LH secretion, but FSH secretion.

Thus Maprelin®, just like PMSG (eCG), is suitable for stimulating oestrus and thereby fulfils the necessary prerequisites for favourable endocrine conditions for the fixed-time induction of ovulation and insemination.

The best results are produced by animals that exhibit a strong standing reflex at the time of insemination. Oestrus detection is therefore also to be recommended for fixed-time inseminations. Evaluation of the standing reflex behaviour can be helpful in optimising ovulation synchronisation and adapting to individual unit conditions.

Ovulation synchronisation is carried out as follows in adult sows:
- Simultaneous weaning off of the piglets
- 24 hours after weaning, oestrus induction using Peforelin or PMSG (eCG). The dosage is based on parity (litter no.): Sows weaned off their first litter, receive 37.5 µg Peforelin, equivalent to 0.5 ml Maprelin®, or 750 – 1000 IU PMSG (eCG). Sows that have weaned more than one litter receive 150 µg Peforelin, equivalent to 2 ml Maprelin® or 750 – 1000 IU PMSG (eCG).
- Injection of 1 ml Gonavet Veyx® (in exceptional circumstances 0.5 ml is enough) at times following oestrus induction that are dependent on the duration of suckling:
  - for > 4 week suckling period = 56 - 58 hours after oestrus induction
  - for 4 week suckling period = about 72 hours after oestrus induction
  - for 3 week suckling period = 78 – 80 hours after oestrus induction
- Fixed-time insemination:
  - AI_1: 24 hours after Gonavet Veyx® administration
  - 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.

In comparison to the control treatments using hCG or combinations of hCG and GnRH following oestrus induction carried out by giving PMSG, Gonavet Veyx® proved superior in respect of the synchronisation effect and the farrowing results (Table 1).

Table 1: Fertility performance of adult sows after oestrus induction using PMSG and ovulation synchronisation with hCG or Gonavet Veyx® (HÜHN and BRÜSSOW 1997, BRÜSSOW and WÄHNER 2005)

	Number of animals	Pregnancy rate (%)	PBA/litter	Piglet index
hCG	30973	80.7[b]	10.9	880[b]
Gonavet Veyx®	20701	83.0[a]	11.0	913[a]

[a], [b]: Differences between the groups were significant ($p < 0.05$).
PBA = piglets born alive; Piglet index = piglets born alive per 100 first inseminations

Practical experience is now available for oestrus induction using Maprelin® from a large number of pig units.

In comparison to ordinary methods based on the use of PMSG, comparably good results are achieved with Maprelin®, as is illustrated in the following example:

In a unit in Thuringia with a weekly farrowing pattern and a 3 week suckling period, different timings of the Gonavet Veyx® injection after the Maprelin® administration were tested. Most of the parameters encompassed in the four groups were similar and did not differ significantly (Table 2). However, there was a tendency for better results in regard to the rate of oestrus and farrowing rate in the Maprelin® treated groups. Significant differences were found in respect of live born piglets and piglet index between the two Maprelin® groups as well as for the piglet index between both PMSG groups ($p < 0.05$). In summary it could be determined that the best results were achieved with a 78 hour interval between the Gonavet Veyx® and the Maprelin® administration.

Table 2: Performance data of adult sows after fixed-time insemination

Interval Gonavet Veyx®	74 hours		78 hours	
	PMSG (eCG)	Peforelin	PMSG (eCG)	Peforelin
Number of animals	61	63	64	65
Oestrus rate (%)	93.4	95.2	90.6	92.3
Farrowing rate (%)	84.2	90.0	81,0	85.0
PBA/litter ($\bar{x} \pm s$)	11.02 ± 2.97^{ab}	10.06 ± 2.45^{b}	10.96 ± 2.78^{ab}	11.08 ± 2.77^{a}
Piglet index$_{PGA}$	928^{c}	905^{bc}	888^{b}	942^{ac}

^{a}, ^{b}, ^{c}: Differences between the groups were significant ($p < 0.05$).
PBA = piglets born alive; Piglet index = piglets born alive per 100 first inseminations

2. Ovulation synchronisation in gilts

Sexual maturity is an important prerequisite for all medicated measures to control reproduction in gilts. In order to achieve this, replacement gilts not home reared should be purchased in good time. In general, stimulation procedures should be carried out at an early stage. In general, regular boar contact should commence from 180 days of age and frequent changes in housing and mixing groups of gilts is recommended to stimulate the natural triggers for puberty. Oestrus detection measures must be carried out and recorded in order to document puberty as defined by the observation of the first standing oestrus. When the animals have had at least one oestrus and are at least 220 days old – some breeding organisations recommend 250 days – and have a weight of at least 115 kg, hormonal control measures can commence. Initially the oestrous cycle is inhibited temporarily by administering Altrenogest. After this, an oestrus induction is carried out using PMSG or Maprelin® treatments. Subsequently, ovulations can be synchronised.

Ovulation synchronisation is carried out as follows in sexually mature gilts:
- oral treatment of 20 mg Altrenogest daily over 18 days
- oestrus induction after the final Altrenogest treatment, e.g. by administering 150 µg Peforelin (equivalent to 2 ml Maprelin®) 48 hours after the final Altrenogest treatment or through the administration of 750 – 1000 IU PMSG (eCG) 24 – 48 hours after the final Altrenogest treatment
- 78 – 80 hours after oestrus induction, the treatment with 1 ml Gonavet Veyx® is carried out
- Fixed-time insemination:
- AI_1: 24 – 26 hours after Gonavet Veyx® administration
- AI_2: at the latest 40 hours after the Gonavet Veyx® administration
- AI_3: when required, gilts with a longer oestrus: approx. 6 – 8 hours after AI_2.

Gonavet Veyx® also proved more suitable for synchronising ovulation in gilts than hCG (Table 3).

Table 3: Fertility performance of gilts after oestrus induction using PMSG and ovulation synchronisation with hCG or Gonavet Veyx® (HÜHN and BRÜSSOW 1997, BRÜSSOW and WÄHNER 2005)

	Number of animals	Pregnancy rate (%)	PBA/litter	Piglet index
hCG	1459	74.4[b]	9.8	728[b]
Gonavet Veyx®	1285	78.8[a]	9.9	779[a]

[a, b]: Differences between the groups were significant ($p < 0.05$).
PBA = piglets born alive; Piglet index = piglets born alive per 100 first inseminations

Fixed-time insemination is also possible in gilts following oestrus induction using Maprelin®, as has been shown based on practical experience on numerous units. The fertility performance in these cases is of the same level as when PMSG is used, as illustrated in the following example:
A 760 sow herd in Bavaria treated pubertal gilts over 18 days using 20 mg Altrenogest orally per day. A group of 85 gilts was treated after 39 hours with PMSG and 79 hours later administered Gonavet Veyx®. Another 98 animals received a Maprelin® administration 48 hours after the final Altrenogest treatment and 80 hours subsequently the Gonavet Veyx® administration. The gilts underwent fixed-time insemination in the presence of a mature working boar at 25 hours and 41 hours, respectively, after the Gonavet Veyx® administration.

Overall the performances were of a very high level and similar in both groups ($p > 0.05$; Table 4). However, there was a tendency for higher farrowing rates following the Maprelin® treatment and higher litter sizes following PMSG treatment.

Table 4: Performance data of gilts after fixed-time insemination

	PMSG (eCG)	Peforelin
Gilts inseminated	85	98
Standing reflex rate AI_1	85.88 %	85.71 %
Standing reflex rate AI_2	97.65 %	98.98 %
Pregnancy rate	96.47 %	98.98 %
Farrowing rate	92.94 %	98.98 %
PBA/litter ($\bar{x} \pm s$)	12.66 ± 2.68	11.98 ± 2.52
Piglet $index_{PBA}$	1192	1186

Differences between the groups were significant ($p < 0.05$).
PBA = piglets born alive; Piglet index = piglets born alive per 100 first inseminations

Summary

Based on the result of the clinical test program and subsequent field studies as well as years of experience with the product in livestock practice, it can be established that Gonavet Veyx® is well-suited for the use in ovulation synchronisation in oestrus induced adult sows and gilts. Gonavet Veyx® leads to a higher synchronisation effect following a preceding induction of the oestrus cycle than is the case with other active substances used for this indication (hCG or combinations of hCG and GnRH). With the new active substance Peforelin in the Maprelin® preparation, fixed-time insemination can be carried out just as successfully as with the previously applied PMSG method. It is generally considered advisory to also carry out oestrus detection with fixed-time insemination, as the best results are to be expected from inseminations that take place when there is a standing reflex.

Application in horse

The horse belongs to the seasonally polyoestrous animals, whereby they come into oestrus as a result of increasing daylight (day length) also known as "long day breeders". The oestrous cycle of the mare lasts on average for 22 days, but the duration of oestrus is very variable. Ovulatory short oestruses lasting 2 to 3 days can occur as well as fertile long oestruses lasting 8 to 12 days. Oestruses occur more or less at regular intervals during the breeding season. Signs of oestrus are usually exhibited for 1 to 2 days after ovulation, the majority occurring between the 4th and 6th day of oestrus. Matings that occur later than 6 hours after the release of the ovum and at the end of oestrus, frequently no longer lead to conception.

The reproductive performance of the mare can be influenced in respect of the commencement of oestrus through measures such as feeding correctly according to condition, good housing and husbandry, as well by the stimulating effect of the stallion. Moreover, oestrus can be induced and the time of ovulation influenced by medication.

The use of Gonavet Veyx® in the mare involves correcting gonadotropic deficiency conditions where there are insufficiencies in the central control mechanisms of the oestrous cycle and its regulation. In particular, administering Gonavet Veyx® can be used therapeutically and as part of a breeding programme to induce the release of LH to promote the follicles to mature and trigger ovulation. To this end, the slower metabolic breakdown of Gonavet Veyx®, which ends only after about 10 hours, is particularly important for the reproductive biological hormone profile of the mare.

Generally, a single administration of the 2 ml therapeutic dose is sufficent to achieve the desired effect. In cases of anoestrus and acyclic animals (centrally dependent LH deficit-induced insufficiency of the oestrous cycle) the treatment can be repeated where there is no success after 10 to 20 days using the aforementioned dose.

For the induction of ovulation (shortening the duration of oestrus) in relation to mating, it is recommended that Gonavet Veyx® is administered at the first mating. In case of long lasting oestruses, injections given later can speed up ovulation by around 1 to 2 days.

In contrast to the cow, there is currently no practically relevant indication for medication using Gonavet Veyx® during the puerperium, because the oestrous cycle in the mare as a rule already commences spontaneously about a week after foaling (foal heat).

1. Treatment of anoestrus and acyclic states

Both cycle disorders are discussed together, because the symptoms are the same (absence of oestrus). A differentiation is mostly possible through repeated examination of the ovaries. In acyclic cases both ovaries are small, solid and smooth, without the presence of cyclic formations. In case of anoestrus, in contrast, subclinical cyclic processes occur that can even include attaining the development of a graffian follicle with the capacity to ovulate. However, such cases are better categorised as suboestrus or still heats. For a true case of anoestrus, mostly relatively small (chestnut to a maximum hen's egg size), slightly bumpy ovaries are determined, on which numerous tertiary follicles can be found, which as a rule are atrophying. Absence of oestrus caused by a persistent corpus luteum must be considered separately. In the narrowest sense, the differentiation of anoestrus has therapeutic significance, as a decision between the use of prostaglandins and Gonavet Veyx® must be taken. The differentiation can be carried out through the determination of progesterone levels in the blood and through sonographic portrayal of the corpus luteal tissues.

The pathological conditions, the November to February period of "winter anoestrus" must be kept separate, which is to be seen as normal and a characteristic of the seasonal cycle in the mare. Only sporadic success is to be reckoned with when attempts are made, upon the request of the owner, to influence heat inducement by therapeutic means during this period.

Prior to a medicated treatment for anoestrus and acyclic states, it must be checked whether feed or husbandry deficiencies exist, or the affected mare is suffering an extra-genital illness. In such cases, the respective deficiencies or health disorders must be corrected prior to a hormonal therapy.

The efficacy of Gonavet Veyx® in alleviating anoestrus and acyclic states was tested in a variety of studs and large horse breeding farms over a period of 3 years. Altogether, 118 mares that showed anoestrus over an extended period and had a relevant ovary diagnosis were tested under various feeding, husbandry and environmental conditions primarily during the periods from beginning of April until end of May and from the beginning of September until end of October. The results achieved for oestrus induction are presented in Table 5. Table 6 shows the pregnancy results following induced oestrus.

Table 5: Application of Gonavet Veyx® for anoestrus and acyclic states in the mare

No. of animals	Indication	Oestrus induction (n/%)		Oestrus commences (days after injection)	Duration of oestrus (days)
		yes	no		
118	100 An, 18 Ac	100/84.7	18/15.3	1 – 23	1 – 14 ø 6.4

An = Anoestrous; Ac = Acyclic; ø = mean average

Table 6: Pregnancy results after oestrus induction using Gonavet Veyx® in the mare

Mares with oestruses commenced (n)	Matings after oestrus induction (n)	PD + (n/%)	PD – (n/%)	Returns to oestrus repeat matings (n)	Pregnancy rates after repeat matings
100	1 – 5 ø 2.6	62/62 5 PP ?	33/33	20	8 PP + 6 PP - 6 PP ?

PD + = pregnant; PD – = non-pregnant; PP ? = probable PD

It can be seen from the tables that in almost 85 % of the cases, oestrus could be induced within the normal oestrous cycle of about 3 weeks, whereby the commencement of oestrus was widely spread between 1 and 23 days post injection. A cluster was found to some extent between the 7th and 12th day post injection. The average duration of oestrus at 6 to 7 days lies within the normal range, whereby however, numerous long duration oestruses of 10 to 14 days pushed the result towards the upper limit. Nevertheless, with on average 2.6 matings in the induced oestruses a pregnancy rate of 62 % was achieved. Compared to results for first matings in healthy herds without fertility problems these results are to be evaluated as very good and significantly above average. From 20 returns to mating that were re-mated in these spontaneous returns to oestrous, 8 were certainly pregnant and 6 were considered as probables. Hence, the overall percentage of pregnant mares from the first and second matings increased the pregnancy rate to on average 76 %. Thus, the induced and subsequent oestruses proved exceptionally fertile. From the 118 mares exhibiting anoestrus or acyclic states treated once with Gonavet Veyx®, 76 in total (64.4 %) were pregnant in the 1st to 2nd oestrus. The broad consistency of the results in all three years was striking. This repeatability alludes to the assured and consistent mode of effect of Gonavet Veyx®.

With an average oestrus rate of 84.7 % (79.5 – 88.3 % between the years) and an achieved pregnancy rate of 62 % after a single treatment, Gonavet Veyx® proves to be effective in overcoming anoestrus and acyclic states in the mare.

2. Ovulation induction in spontaneous oestrus/shortening oestrus

The LH releasing effect of Gonavet Veyx® can not only be used therapeutically for cyclopathy, but can also be used in oestruses that progress normally, in order to allow the breeder to increase the chances of conception and boost business profitability. Due to the widespread practice to place the semen artificially in the horse, it is furthermore required to arrange for the order and delivery of semen in view of the time of ovulation. Administration of GnRH preparations allow for oestrus to be shortened and the time of ovulation to be planned.

The reduction in the length of oestrus and bringing forward the time of ovulation by 1 or 2 days can allow for better ordering of semen and a reduction in the number of gynaecological examinations required.

As GnRH is naturally released in a pulsatile way, repeated injections of Gonavet Veyx® are recommended at 12 hour intervals and when the dominant follicle has attained a 3.5 cm diameter. An ovulation is to be expected within 48 hours of commencing the treatment. The pregnancy rate after induced ovulation corresponds to that of mares with a spontaneous ovulation.

It can also make sense to reduce the length of oestrus through induced ovulation for natural matings. In terms of reproductive biology it is of great importance that the germ proliferation in the genitals may increase with growing numbers of matings, thus raising the risk of developing endometritis.

The suitability of Gonavet Veyx® for the reduction in the length of oestrus was tested on 174 mares compared to 72 control animals in 3 replicated experiments. Thereby treatments were carried out, separated on the basis of breed, method of breeding, type of husbandry, timing of injection and dosage, from which differing analysis criteria were also derived.

First series of tests

In a trotting horse stud, 2.0 ml Gonavet Veyx® were applied intramuscularly in 26 mares on the day of the first matings during the natural oestrus. Compared to 12 untreated control mares, the end of oestrus was brought forward from 5.0 to 2.8 days and thus the duration of oestrus shortened from 8.8 to 5.8 days (Table 7). The number of matings per oestrus was reduced from 3.0 to 1.9. Thus with Gonavet Veyx® oestrus ended 2 days earlier, its total length was reduced by 3 days and one less mating was necessary. The reduction effect in this breeding stud is particularly high due to the abnormally long duration of oestrus found at this location.

Table 7: Use of Gonavet Veyx® on the day of the first mating to induce ovulation and to reduce the length of oestrus

	Number of animals	ø End of oestrus after 1st mating (days after injection)	ø Oestrus length (days)	ø Number of matings
Gonavet Veyx®	26	2.8	5.8	1.9
Controls (untreated)	12	5.0	8.8	3.0

ø = average

Second series of tests

Under commercial stud conditions, 18 English thoroughbreds were also administered 2.0 ml Gonavet Veyx® already on 1st day of oestrus as an intramuscular injection. Compared to 21 control mares, the overall length of oestrus was shortened on average from 4.7 to 3.7 days (Table 8). Thus, with an already very short average length of oestrus, Gonavet Veyx® treatment could achieve a one day reduction.

Table 8: Use of Gonavet Veyx® on the 1st day of oestrus to induce ovulation and to reduce the length of oestrus

	Number of animals	ø Oestrus (days)
Gonavet Veyx®	18	3.7
Controls (untreated)	21	4.7

ø = average

Third series of tests

In a breeding stud, 130 warmblood mares from differing housing and husbandry systems were tested for a dosage dependent influence of Gonavet Veyx® on the length of oestrus. Dosages of 1.5 ml, 2.0 ml and 2.5 ml were selected for intramuscular application (Table 9). It was demonstrated that with increasing dosage the length of oestrus fell. Whilst no significant effect could be achieved with the lower dosage (1.5 ml), the mid dose (2.0 ml) reduced oestrus by about one day. The higher dosage (2.5 ml) actually achieved an average reduction of 1.5 days. These values were compared with the oestrus lengths of 39 untreated mares.

Table 9: **Use of Gonavet Veyx® on the day of the first mating to induce ovulation and to reduce the length of oestrus**

	Number of animals	ø Oestrus (days)
1.5 ml Gonavet Veyx®	46	5.9
2.0 ml Gonavet Veyx®	44	5.1
2.5 ml Gonavet Veyx®	40	4.7
Controls (untreated)	39	6.2

ø = average

In summary, the following can be determined: The application of Gonavet Veyx® at the beginning of oestrus, i.e. on the 1st day of oestrus or on the day of the first mating, can reduce its length by 1 to 2 days (in extremely long oestruses, even by 3 days) with high level of efficacy assured. The investigations have shown that as a result of induced LH release the follicle maturation and ovulation can be accelerated. As a result of the earlier occurrence of ovulation, the overall length of oestrus is reduced. The pregnancy results achieved correspond to the current situation on the unit and thus allude to a completely normal fertility for the oestruses hormonally shortened using Gonavet Veyx®. The results allow for the recommendation for the use of the Gonavet Veyx® preparation to bring forward ovulation and thus to reduce the length of oestrus within a normal oestrous cycle, in the interest of an easier work load for the stallion in both natural mating or insemination and assuring and maintaining higher reproductive health, as well as economic benefits. Moreover, the advantage of a reduction in the length of oestrus also ensures that the mare incurs lower stabling costs at the horse breeding station or stud.

The information given in this product brochure conforms to the state of knowledge upon completion. Please read the package leaftlet before using the veterinary medicinal product.

Authors:
Priv. Doz. Dr. Dr. habil. Wolfgang Zaremba
Dr. Silke Engl
Prof. Dr. Axel Wehrend

Literature is available upon request.

Veyx-Pharma is GMP- and QS-certified.

Veyx-Pharma GmbH · Soehreweg 6 · 34639 Schwarzenborn · Germany
Phone 0049 5686 99860 · Fax 0049 5686 1489 · E-Mail zentrale@veyx.de
www.veyx.com

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