Enzaprost® T
The natural Prostaglandin

Uterotonic and luteolytic, naturally
Enzaprosto\textsuperscript{T}: The uterotonic and luteolytic prostaglandin, naturally!

The active compound of Enzaprosto\textsuperscript{T} is Dinoprost, a tromethamine (organic buffered solution) salt of the native prostaglandin F\textsubscript{2\alpha}.

Prostaglandins (PGF\textsubscript{2\alpha}) of uterine origin are necessary to cause Corpus Luteum (CL) regression in bovines, which in turn will set the length of the oestrus cycle.

Dinoprost has luteolytic effect (causing the regression of the CL) and uterotonic effect (inducing myometrium contraction) as the natural PGF\textsubscript{2\alpha}.

Enzaprosto\textsuperscript{T} indications in cattle are:
1. Oestrus synchronisation.
2. Treatment of sub-oestrus or silent heat in cows which have a functional corpus luteum, but do not express behavioural oestrus.
3. Induction of abortion until day 120 of pregnancy.
4. Induction of parturition.
5. As an aid in the treatment of chronic metritis or pyometra where there is a functional or persistant corpus luteum.
Prostaglandins mode of action

Natural PGF2α half-life a natural protective mechanism!

Their main action is to cause luteolysis of a CL but it is important to highlight that newly formed CLs (less than 5 days old) are refractory to luteolytic effects of prostaglandins.

Mammals have developed mechanisms to avoid having excessive concentrations of PGF2α in blood for unnecessary periods. Therefore PGF2α is metabolized very rapidly after a single pass through the lungs. Thus, the short half-life of the natural PGF2α is in fact a protective mechanism of the normal physiology developed by mammals [1]. The natural PGF2α produced by the endometrium triggers a CL-induced oxytocin release in mature CLs, which in turn will cause more PGF2α release from the endometrium and this self-sustained endocrine loop (feedback loop, in blue in the picture shown below) will culminate with CL regression. Additionally, it has been recently demonstrated that PGF2α will induce PGF2α production in the CL in another self-sustained loop (Auto-amplification loop, in red in the picture shown below).

Analogues versus natural Prostaglandins

Prostaglandins can be natural like Enzaprost®T (dinoprost) or agonists like synthetic analogues.

Analogue compounds include cloprostenol and d-cloprostenol, luprostiol, etiprosten, alfaprostol and others and they are normally dosed at 2ml/animal.

Enzaprost®T (dinoprost) is a natural prostaglandin so it has an enhanced action on uterine contraction with an equivalent luteolytic effect. Dinoprost is dosed at 5ml/animal.

Enzaprost®T has a greater uterotonic effect than prostaglandin analogues with the same luteolytic effect!
1. Greater uterotonic effect!

Enzaprost®T exerts greater activity than d-cloprostenol and alfaprostol on both longitudinal and circular muscle of bovine myometrium during the luteal phase in an in vitro model [5].

An in vivo study measuring intra-uterine pressure, Dinoprost exerts greater uterotonic activity in all stages of the cycle particularly during dioestrus when there is an active corpus luteum [6]. Interestingly, the enhanced activity of the natural PGF2α is thought to be related to its much greater binding affinity to myometrial and CL cell receptors than for synthetic analogues. This affinity has been reported to be roughly 10 times greater than d-Cloprostenol for myometrial cells and staggeringly 150 times greater than dL-Cloprostenol for PGF2α receptors in CL cells [7].

2. Equivalent luteolytic effect in oestrus induction in beef cattle!

A very large (>1,000 animals enrolled) and well designed trial [8] to compare oestrus responses and conception results between dinoprost and cloprostenol using beef heifers as experimental units, found no significant effects on percentage and synchrony of oestrus or conception results for both PGF2α products tested.

3. Superior luteolytic effect in fixed-time artificial insemination in dairy cattle!

A recent publication [9] reporting results from two large field studies done in multiple herds in synchronised-lactating dairy cows showed a significant improvement in luteolysis rates in cows bearing a responsive CL that were treated with dinoprost as compared to cloprostenol (Exp 1: dinoprost 91.3% vs cloprostenol 86.6%, P<0.05). The same study also reported that dairy cows with unknown pregnancy status receiving a Re-synchronization program also presented greater (P<0.05) luteolysis rates after dinoprost treatment (78.5%) than after cloprostenol (69.1%).
Enzaprost®T uses

Most common uses of Enzaprost®T in bovine reproduction

- Uterine involution and treatment of uterine infections
- Induction of synchronous oestrus in non-pregnant/cycling cattle
- In synchronisation protocols for fixed-time insemination
- Improve luteolysis and conception
- Terminate undesirable pregnancies, induce labor, and other alternative uses during calving time

PGF2α used during Pre-synchronisation for 1st postpartum AI (artificial insemination)

PGF2α for cows detected non-pregnant and assigned to a Re-synch protocol for 2nd or later AIs

PGF2α towards the end of synchronisation programs for timed AI to induce CL regression

Uterotonic and luteolytic, naturally
References


ENZAPROST 5 mg/ml Solution for injection for cattle and pigs. COMPOSITION: Each 1ml contains: Active substance: Dinoprost (as trometamol) 5 mg. Excipients: Benzyl alcohol (E1519) 16.5 mg. INDICATIONS: The product is indicated for its luteolytic effects in cattle and pigs. Cattle: The luteolytic effect of the product can be exerted in the following therapeutic uses: 1. Oestrus synchronisation. 2. Treatment of sub-oestrus or silent heat in cows which have a functional corpus luteum, but do not express behavioural oestrus. 3. Induction of abortion until day 120 of pregnancy. 4. Induction of parturition. 5. As an aid in the treatment of chronic metritis or pyometra where there is a functional or persistent corpus luteum. Pigs: 1. Induction of parturition from day 111 of pregnancy. 2. Post partum use: reduction of the weaning to oestrus interval (WOI) and the weaning to fertile service interval (WFSI) in sows with puerperal problems such as metritis or uterine infections. CONTRA-INDICATIONS: Do not treat animals if they suffer from either acute or subacute disorders of the vascular system, gastro-intestinal tract or respiratory system. Do not administer to pregnant animals, unless it is desirable to induce parturition or interruption of pregnancy. Do not use in cases of known hypersensitivity to the active substance or to any of the excipients. ADVERSE REACTIONS: Cattle: The most frequently observed side-effect is increased rectal temperature. However, rectal temperature changes have been transient in all cases observed and have not been detrimental to the animal. Limited salivation has been seen in some instances. The side-effects disappear within one hour after the administration of PGF2α. In cattle, if used for induction of parturition, retained foetal membranes may occur more frequently, depending on the time of use of the product. Pigs: Transient side-effects consisting of increased body temperature, signs of pain at the site of injection, increased respiratory rate, increased salivation, stimulation of defecation and urination, flushing of skin and restlessness (arching of back, pawing, and rubbing and gnawing the crate), dyspnoea, slight ataxia, abdominal muscle spasms, vomiting and pruritus occur occasionally following the administration of dinoprost in pregnant sows and gilts. These effects tend to parallel the signs exhibited by sows prior to normal parturition, only they appear to be condensed in time. These effects are usually seen within 10 minutes of injection and disappear within 3 hours. Nest building is a common behaviour 5 to 10 minutes after the administration of prostaglandin s in sows that are housed in pen or pasture. In very rare occasions, anaphylactic-type reactions have been reported. If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon. DOSAGE, ROUTE AND METHOD OF ADMINISTRATION: Intramuscular use. Cattle: 1. Oestrus synchronisation. One administration of 25 mg of dinoprost (as trometamol), 5 ml of the product per animal, to be repeated, if necessary after 11 (10 to 12) days. Animals treated during dioestrous will normally return to oestrus and ovulate within two to four days after treatment. Animals treated with the product may be bred by natural service, artificial insemination on detected oestrus or at fixed time insemination (72 and 96 hours after the second injection is usually recommended). 2. Treatment of sub-oestrus or silent heat in cows which have a functional corpus luteum, but do not express behavioural oestrus. One administration of 25 mg of dinoprost (as trometamol), 5 ml of the product per animal, to be repeated, if necessary after 11 (10 to 12) days. Induction of abortion until day 120 of pregnancy. One administration of 25 mg of dinoprost (as trometamol), 5 ml of the product per animal. The product may be used to terminate pregnancy in cattle until day 120 of pregnancy through its luteolytic effect. 4. Induction of parturition. One administration of 25 mg of dinoprost (as trometamol), 5 ml of the product per animal on or after day 270 of gestation. The interval from administration to parturition is one to eight days (average three days). 5. For the aid in the treatment of chronic metritis or pyometra where there is a functional or persistent corpus luteum. One administration of 25 mg of dinoprost (as trometamol), 5 ml of the product per animal, to be repeated, if necessary after 11 (10 to 12) days. Pigs: To avoid excessive broaching of the stopper when treating large numbers of animals using the 50 ml pack size, the use of a multiple dose syringe with a draw-off needle is recommended. 1. Induction of parturition from day 111 of pregnancy. One administration of 10 mg of dinoprost (as trometamol), 2 ml of the product per animal within 3 days of expected parturition. Response to treatment by individual animals varies within a range of 24-36 hours from administration to parturition. This can be used to control the time of farrowing in sows and gilts in late gestation. Treatment earlier than 3 days prior to predicted farrowing date may induce weak piglets. 2. Post partum use: One administration of 10 mg of dinoprost (as trometamol), 2 ml of the product per animal 24 to 36 hours after parturition. ADVICE ON CORRECT ADMINISTRATION: Full aseptic precautions should be taken. Use a sterile syringe and needle and make the injection through an area of clean skin. Care should be taken to avoid injection through wet or dirty areas of skin. WITHDRAWAL PERIOD: Cattle: Meat and offal: 3 days. Milk: Zero hours. Pigs: Meat and offal: 2 days. SPECIAL STORAGE PRECAUTIONS: Keep out of the reach and sight of children. This veterinary medicinal product does not require any special storage conditions. Shelf-life after first opening the vial: 14 days. After first broaching the vial: do not store above 25°C. Do not use after the date shown following EXP: on the label. SPECIAL WARNINGS: Special warnings. The product is ineffective when administered prior to day 5 after ovulation. Special precautions for use in animals. Localised post injection bacterial infections that may become generalised have been reported. Aggressive antimicrobial therapy, particularly covering clostridial species, should be employed at the first sign of infection. Careful aseptic techniques should be employed to decrease the possibility of post injection bacterial infections. Do not administer by intravenous route. Induction of abortion or parturition by using exogenous substances may increase the risk for dystocia, fetal mortality, retention of the placenta and/or metritis. Special precautions to be taken by the person administering the veterinary medicinal product to animals Prostaglandins of the PGF2α type can be absorbed through the skin and may cause bronchospasm or miscarriage. Care should be taken when handling the product to avoid self-injection or skin contact. Accidental spillage on the skin, or accidental eye contact should be washed off immediately with clean water. Impervious gloves should be worn to avoid skin contact. Accidental injection may be a particular hazard to women who are pregnant, intending to become pregnant, or whose pregnancy status is unknown and to asthmatics and persons with bronchial or other respiratory problems. Asthmatics and persons with bronchial or other respiratory problems should handle the product with care to avoid accidental self-injection and skin contact. Pregnant women, men, women of child-bearing age, asthmatics and persons with bronchial and other respiratory problems should not use the product or should wear disposable plastic gloves. Use during pregnancy, lactation or lay. Pregnancy status should be determined prior to injection since Dinoprost has been demonstrated to result in abortion or parturition induction when administered at sufficiently high doses in many animal species. If pregnant, the unlikely possibility of uterine rupture should be borne in mind, especially if cervical dilation does not occur. Induction of parturition in pigs earlier than 72 hours prior to predicted farrowing date may result in reduced piglet viability. Interaction with other medicinal products and other forms of interaction. As non-steroidal anti-inflammatory drugs may inhibit the endogenous prostaglandin synthesis, concomitant administration of these compounds with the product may decrease the luteolytic effects. As oxytocics stimulate the production of prostaglandins, concomitant administration of these compounds with the product, may exacerbate the luteolytic effects. Overdose (symptoms, emergency procedures, antidotes), if necessary Increased rectal temperature and a slight transitory increase in heart rate can be observed at 5 or 10 times the recommended dosage in cows and heifers. In absence of compatibility studies do not mix with other veterinary medicinal products. PRESENTATIONS: Pack sizes: 10 vials of 5 ml, 5 vials of 10 ml, 1 vial of 30 ml, 1 vial of 50 ml. Not all pack sizes may be marketed. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER: CEVA SANTE ANIMALE - 10 av. de la Ballastière - 33500 LIBOURNE. 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