

## Product Information Sheet

### Indications and Usage

iUPOD® is a self-assembling drug-free intrauterine device designed to modulate estrus behavior in mares. It may extend diestrus and reduce unwanted estrus behavior. This product requires *due diligence* and follow up to make absolutely sure that a mare is a candidate for its use.

### Items

The iUPOD® system consists of a self-assembling sterilized IUD and retriever, and an applicator which has been packed in a laboratory grade cleanroom facility.

### Contraindications

#### A. Horses that are not candidates for self-assembling iUPOD®:

- i) Mares having a previous or current history of uterine inflammation.
- ii) Mares with any uterine fluid during diestrus.
- iii) Mares with excessive uterine fluid during estrus (> 10 mm).
- iv) Mares with a history of pneumovagina or urine pooling.
- v) Mares with granulosa cell tumor.
- vi) Mares that had uterine glass marbles.
- vii) A previous IUD that has not been removed.
- viii) Mares with a *dysfunctional/stenotic cervix*. Mares (often maiden  $\geq 15$  years of age) that even in estrus present with a cervix that is very tight and fibrotic.
- ix) Hypersensitivity to any component of iUPOD®.
- x) Increased susceptibility to pelvic and uterine infections.
- xi) Pregnancy or suspicion of pregnancy.
- xii) Congenital or acquired uterine anomaly if it distorts the uterine cavity.
- xiii) Postpartum endometritis or infectious abortion in the past 6 months.
- xiv) Known or suspected uterine or cervical neoplasia.
- xv) Uterine bleeding of unknown etiology.
- xvi) Untreated acute cervicitis or vaginitis or other genital tract infections.

#### B. Instructions for inserting and retrieving the iUPOD®:

*Goal: minimal dilation of the cervix and distortion of the uterus.*

**Note:** The mare's perineum should be thoroughly scrubbed with a mild antiseptic Betadine solution before insertion or retrieval. Use a sterile iUPOD® and applicator, and sterile double glove technique (Portus et al. 2015). Sets are supplied sterile and are single use only. iUPOD® and retriever cannot be steam sterilized. The retriever can be gas sterilized.

#### Sedation/Uterine Relaxation –

- i) Sedation may be required based on the temperament of the mare.
- ii) Hyoscine Butylbromide can be used.

### iUPOD® Insertion –

- i) For mares with a pliable cervix e.g., estrus, or within 48 hours post-ovulation, use either the iUPOD® applicator with the 3 units (29x13 mm) loaded in tandem or manual insertion - please see below. The 3 units are pushed through the cervix until just clear the internal cervical os. Check the location of the devices with ultrasound. The iUPOD® will self-aggregate in the uterus in a “ring” configuration.
- ii) For mares with a closed cervix e.g., early estrus or diestrus and some mares (e.g., maiden) regardless of the stage of the cycle, insert individual units by hand. To do this, place the 3 units of the iUPOD® in one’s hand and push them through the cervix one by one. After the last device is pushed through, grab the cervix as it protrudes into the vaginal fornix, lift it up and side to side 2-3 times to make sure all the units slide through the internal os of the cervix. One can confirm this with the index finger.

Note: The devices have been cold sterilized with Chlorhexidine Gluconate 4% solution. You may consider inserting the devices as provided - the residual antiseptic may minimize putative bacterial seeding/contamination during the insertion procedure; rinse with sterile saline; or isopropyl alcohol; or both.

### iUPOD® Retrieval -

At the end of the 5-7 month period, induce estrus with an appropriate dose of prostaglandin. Retrieve the iUPOD® in mid estrus using the specially designed retriever with the applicator. Note: iUPOD® can also be retrieved at any stage of the estrous cycle without using prostaglandins to induce estrus, but that would involve a gentler and slower manual dilation of the cervix. The retriever is attached to a fluorocarbon line and/or umbilical tape. iUPOD® is located in the uterus with ultrasound. The applicator (with or without a sanitary sleeve) is inserted loaded with the retriever through the cervix and the uterus swept with the applicator and retriever until contact with the iUPOD®. Then, the retriever is pushed slowly into the uterus, making sure the retriever drops into the uterus; One can either i) keep the applicator in the cervix - after retrieving the plunger - as one pulls the tag line and feels the iUPOD® with the index finger at the end of the applicator, or ii) withdraw the applicator, leaving and holding on to the tag line, before pulling and feeling the weight of the iUPOD® attached to the retriever.

### **C. Recommendations:**

It is recommended that the iUPOD® is used for 5-7 months at a time during the performance season, when mares are likely to be cycling and able to produce endogenous progesterone, thus ineffective in transition mares.

Ultrasound the mare at least once - especially mares  $\geq 15$  years of age - during this period to confirm: a) the presence of the device (can be done routinely with an external metal detector and b) any excessive accumulation of uterine fluid. These devices are to be used by a licensed veterinarian only! **Disclaimer: This product, for the purpose of modulating estrus behavior in mares, expires within a year. It has a 1-year warranty. This product may not meet everyone’s (Owner/Trainers/Veterinarian’s) expectations, as it does not contain any drugs that could affect the estrous cycle. Some mares respond to it, some mares do not, and some mares may show no alteration in the interval between cycles yet, there is an overall improvement for the season in their level of disposition and/or rideability.** <https://doi.org/10.1016/j.jevs.2019.02.009> Note: In a normal population of mares 8% will fail to ovulate (most likely to recur) affecting the effectiveness of the iUPODs®. **It is recommended that the owner keep a meticulous record of the mare cycles/behavior. A Likert Scale is available at [iupod.org](http://iupod.org) for the owner’s reference.** Any feedback on this procedure/instructions, will be greatly appreciated: [gradil@iupod.org](mailto:gradil@iupod.org) Thank you kindly!

## iUPOD® IMPORTANT SAFETY INFORMATION

- If a mare has a pelvic infection, gets infections easily, or has certain cancers, don't use iUPOD®.
- iUPOD® is not appropriate for every mare. This product is not recommended for mares with an unhealthy reproductive tract.
- Do not use iUPOD® if there are signs of persistent abdominal/pelvic pain, colic or bloating.
- iUPOD® may become attached to, embedded in or go through the wall of the uterus. A migrating device can lead to internal injuries, multiple surgeries, pregnancy loss, and possible sterility. Risk may be increased if inserted in mares with previous uterine/cervical surgery.
  - *Note: Perforation has never been reported in mares using this device.*
- Pregnancy with iUPOD® is uncommon but may cause loss of pregnancy and fertility.
- iUPOD® may be partially or completely voided.
- Genital discharge and vulvovaginitis may occur.
- Streptococcal, Klebsiella, Pseudomonas infections have never been reported; However, strict aseptic technique is essential during insertion.
- Remove iUPOD® if pregnancy occurs with iUPOD® in place. If pregnancy occurs, there is increased risk of pregnancy loss, septic abortion (including septicemia, shock and death), premature labor and delivery, and loss of fertility
- iUPOD® does not protect against STD i.e., Equine Viral Arteritis, Equine Coital Exanthema, Contagious Equine Metritis and Dourine; and Equine Infectious Anemia.
- This is not a complete list of possible side effects with iUPOD®. Other medical events can occur. Please report side effects to the manufacturer/distributor [gradil@iupod.org](mailto:gradil@iupod.org)

### Additional information

- iUPOD® is only to be sold and inserted by licensed veterinarians.
- iUPOD® is to be used strictly according to instructions (Please see instructions for use Self-Assembling iUPOD® - item C).
- There is a cap of \$50,000.00 on the value of a horse to be fitted with iUPOD®. It will be the owner's responsibility to get extra insurance.
- Date and reference number will be included in the packing slip.
- iUPODs® Composition: magnetic metal core with plastic coating.
- Single use only.
- For animal use only.
- For intra uterine administration in mares only.
- Storage conditions - store at room temperature.
- No special disposal conditions. The material is a natural occurring rare earth mineral wrapped in a Teflon coating.
- Mares actively exposed by stallions will affect the effectiveness of the product.

## INFORMATION FOR MARE OWNERS

- iUPOD® is only to be sold and inserted by licensed veterinarians.
- iUPOD® is not appropriate for every mare. Share the mare reproductive health history with your veterinarian before placement of iUPOD®.
- iUPOD® is not recommended for mares with an unhealthy reproductive tract.
- If the mare is intended to be a brood mare, a negative uterine culture is recommended at the time of insertion.
- The iUPOD® may improve performance by reducing the number of heat cycles.
- Only you and your veterinarian can decide if iUPOD® is right for your mare.

## IMPORTANT SAFETY INFORMATION FOR MARE OWNERS

- If the mare has a pelvic infection, get infections easily, or has cancer, don't use iUPOD®.
- If the mare has persistent pelvic or abdominal pain or if iUPOD® comes out, tell your veterinarian.
- If the iUPOD® comes out, use a back-up plan for estrous control.
- iUPOD® is designed to be used ONLY in non-pregnant mares.
- The insertion of iUPOD® in a pregnant mare may result in loss of pregnancy or fertility.
- A mare with iUPOD® may conceive if bred or inseminated.
- iUPOD® does not protect against EIA or STDs.

## MARE OWNER Q and A

### What are the possible side effects of IUPODs® and what measures should be taken?

- Insertion of iUPODs® in mares with undiagnosed uterine infections increases the risk of endometritis and pyometra.
- *Endometritis/Pyometra.* Pyometra can cause serious problems such as infertility, or pelvic/abdominal pain that does not go away (a cause/effect attributed to this device has never been reported or proven). Endometritis is usually treated with antibiotics and prostaglandins. More serious cases of pyometra may require surgery. A hysterectomy (removal of the uterus) is sometimes needed. In rare cases, infections that start as endometritis can even cause death. *This condition has never occurred after extensive use of the device for the last 5 years.*
- Tell your veterinarian if you see any of these signs of endometritis/pyometra: unusual vaginal discharge, abdominal pain, or fever.
- Life-threatening infection. Life-threatening infection can occur within the first few days after the iUPOD® is placed. Call your Veterinarian immediately if the mare develops severe pain or fever shortly after the iUPOD® is placed.
- iUPOD® may become attached to (embedded) or go through the wall of the uterus. This is called perforation. If this occurs, iUPOD® may no longer modulate/affect the estrous cycle.

If perforation occurs, iUPOD® may move outside the uterus and can cause internal scarring, infection, or damage to other organs, and the mare may need surgery to have the device removed. The iUPOD® may attach to or go through the uterus and cause other problems.

- Perforation has never been reported. Nonetheless it is a possibility.
- Pain, bleeding or incoordination may occur during and after placement. If these symptoms do not stop 30 minutes after placement, iUPOD® may not have been placed correctly. Your Veterinarian should examine the mare to see if the iUPOD® needs to be removed or replaced.

#### **After the iUPOD® has been inserted, when should the mare owner call the veterinarian?**

- Call your veterinarian if you have any concerns about the iUPOD®. **Be sure to call if you:**
  - Think the mare was bred and is pregnant.
  - Have unusual vaginal discharge.
  - Have unexplained fever, discomfort or signs of colic.
  - Might have been exposed to sexually transmitted infections (STIs).
  - Have severe vaginal bleeding or bleeding that lasts a long time.

#### **What if the mare becomes pregnant while using iUPOD®?**

- If a mare is bred and gets pregnant while using an iUPOD® it will be very unlikely (due to anatomical conformation in these species compared to primates) that an ectopic pregnancy will occur. This condition has never been confirmed to occur in mares. However, unusual vaginal bleeding or abdominal pain may be a sign of ectopic pregnancy which is a medical emergency that often requires surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death.
- There are also risks if the mare gets pregnant while using an iUPOD®. Loss of pregnancy and premature delivery can occur with pregnancies that continue with an intrauterine device. Because of this, your veterinarian may try to remove the device, even though removing it may cause loss of pregnancy. If the iUPOD® cannot be removed, talk with your veterinarian about the benefits and risks of continuing the pregnancy.
- If the mare continues the pregnancy, see your veterinarian regularly. Call your veterinarian right away if the mare develops fever, cramping, pain, bleeding, vaginal discharge, or fluid leaking from the vagina. These may be signs of infection. It is not known if iUPODs® can cause long-term effects on the fetus if it stays in place during a pregnancy.

**These are not all the possible side effects of iUPOD®. For more information ask your Veterinarian.**

**iUPOD® will not work for every mare. Results may vary.**

## PRODUCT INFORMATION FOR VETERINARIANS

### Further information on iUPOD®

#### *Contra-indications*

#### **Absolute contra-indications**

Infection, pregnancy, uterine factors and gynecological cancers.

#### Infection

- History of pyometra, purulent cervicitis with signs of persistent infection - Not a candidate for the device!
- History of endometritis - the device may be inserted 3 months after infection, if there are no signs of persisting infection. Bi-monthly uterine ultrasound monitoring is recommended. If signs of recurring infection, retrieve the device immediately and treat accordingly.
- Septic abortion or postpartum endometritis in the previous 3 months.
- Endometritis, chronic infections and STDs. Recent exposure to STDs (CEM -*Taylorella equigenitalis*, EVA, Dourine, Coital exanthema, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*). Sexually transmitted endometritis can occur in any mare that is bred with semen contaminated with the incriminated organism. Bacteria (*S. Zooepidemicus*, *E. Coli*) yeast, fungi, and contaminants such as feces and urine are cleared from the uterus by a combination of cellular (neutrophils and phagocytes) and immunological processes (IgG, IgA and opsonization) that kill bacteria. If one of these processes malfunction the mare may not be able to overcome the infection. Indeed, in susceptible mares to endometritis, uterine defense mechanisms involving phagocytosis and opsonization by neutrophils, local synthesis of antibodies, mucociliary activity, vascular and myoelectric activity permeability are compromised, leading to fluid accumulation in response to inflammation, and infertility.
- Abnormalities of the cervix (adhesions or inflammation). Pyometra itself maybe a predisposing cause of cervical inflammation and adhesions.
- Older mares prone to uterine infections (through poor functional bacterial protection or due to inadequate natural uterine defense mechanism or both, are more susceptible and therefore, are not candidates for this device.
- The risk of endometritis in association with an iUPOD® is related to the insertion.
- The risk is higher than baseline for the first 3 weeks post-insertion, then should return to normal baseline levels after this.

#### Pregnancy

- Prior to insertion of the device confirm that the mare is not in foal.
- Devices should be removed prior to attempting to get the mare in foal.
- The presence of the device may result in early embryonic loss or abortion.

#### Removal and return to fertility

- Evidence suggests that the iUPOD® does not delay return to fertility after removal. The iUPOD® should be removed with estrus. <https://doi.org/10.1016/j.jevs.2019.02.009>

### Uterine factors

- Severe cervical stenosis.
- Uterine abnormality distorting the uterine cavity – Endometrial cysts, tumors.
- The device may be expelled, but may also be less effective (e.g., if placed in the cervix).
- Ovarian, cervical or endometrial tumors.
- Undiagnosed irregular vaginal bleeding/suspicion of genital malignancy.

### Gynecological cancers

- Uterine masses caused by hematomas, abscesses, or neoplasia (leiomyoma, adenocarcinoma), or cysts. Because uterine lymphatics are responsible for removing particulate material, the initiating factor in cyst development may be lymphatic damage that results in lymphatic accumulation and endometritis. The presence of a single large cyst near the tip of a uterine horn may be the result of trauma at the previous foaling. If the cyst locates to the myometrium, the seromuscular wall may be thinned on both its luminal and seromuscular aspects. The thin seromuscular wall of the cyst could fail, resulting in spillage of cyst fluid into the peritoneum and potentially peritonitis and uterine adhesions. Even if the cyst can be safely drained or ablated by heat, the thinned uterine wall could rupture at a subsequent foaling.
- After partial hysterectomy for treatment of mares with large intramural uterine cysts.

### Other factors

- Previous history of bacterial endocarditis.
- Significant immunosuppression.

### Relative contra-indications - usable with caution

- Nulliparous, young age i.e., < 2 years of age.
- Definite history of pelvic infection.
- Congenital abnormality of uterus, with marked distortion of the cavity.
- High risk of STI.
- Known EVA infection.
- Mare has a prosthesis which could be compromised by blood-borne infection.
- Between 48 hours and 4 weeks post pregnancy termination: the chances of expulsion post insertion are slightly increased in this period. It is recommended that the iUPOD® should only be inserted at this time if the client finds no other method acceptable and the operator is experienced.
- Pain during insertion is associated with a higher failure rate.
- Other factors relate to the experience of the veterinarian.
- Difficulties include problems passing the applicator or iUPOD® through the cervix and immediate expulsion.
- Age and time since last delivery increase the problems.
- Maiden mares are more likely to experience failed insertion, as the cervix is often more tightly closed, and the procedure more painful/less well tolerated.

### Syncope

- Syncope may be experienced at insertion secondary to vagal stimulation from the cervix.
- Bradycardia can occur especially in maiden mares.

### Suspected perforation at insertion

- The rate of perforation in experienced operators has not been reported per 1,000 insertions.
- The risk of perforation, whilst still small, may increase in lactating mares.

### Expulsion

- This can occur immediately. It is more likely where the procedure is less well tolerated in maiden mares but is also related to the skill of the operator.
- Most commonly in the first 4 weeks post insertion. Client may be unaware that expulsion has taken place.
- Expulsion is more common with younger mares and maiden mares.
- Expulsion is most likely to occur in the first 72 hours post-insertion and may in some cases relate to a widened cervical os.
- Maiden mares with painful estrus are more likely to void the device.

### Other considerations

#### Altered or abnormal bleeding

- The heavy bleeding should make the clinician consider the possibility of early pregnancy at the time of insertion.
- Abnormal bleeding beyond the first six months after insertion requires investigation for gynecological pathology.

#### Pelvic infection

- This is most strongly related to the insertion procedure and to the background risk of STIs.
- There is an increase in risk of PID in the first 3 weeks following insertion.
- If pelvic infection is suspected in a mare using an iUPODs® then antibiotics should be started.
- The device does not need to be removed unless symptoms fail to resolve within 72 hours.
- Follow up reproductive evaluation is recommended.
- Actinomyces-like organisms (ALOs): Infections are mainly caused by opportunistic or commensal microorganisms, e.g., *Proteus* spp., *Citrobacter* spp., of the female genital tract and have been identified in mares with and without iUPODs®. Their role in infection in mares using intrauterine iUPOD® is not clear.
- If ALOs are seen on a swab or smear, removal of the device is not indicated if the mare is asymptomatic.
- If symptoms of pelvic pain occur in conjunction with the presence of uterine infection removal of the device may be advisable.
- Other microorganisms like *Taylorella equigenitalis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are transmitted through venereal route. Regarding fungal endometritis, the most common fungi include *Candida* and *Aspergillus*. These microorganisms cause infertility as a result of repeated inseminations/treatments during the breeding season and proliferate when the natural immune system is weakened in mares with advanced age and multiparous, or after repeated use of antibiotics.

#### Post-insertion advice

- Check if the mare has recovered well enough to leave.



- Arrange follow-up for three-four months' time. This visit should be used to check for infection, perforation or expulsion. Further follow-up should occur if required.
- Please confirm that the client is aware of when the iUPOD® needs to be checked and when it will need to be retrieved.

### Documentation

It is advised that the following documentation be kept for iUPOD® insertion:

- Medical history and clinical assessment.
- Age.
- Reproductive history (including date of last estrus period).
- Previous iUPOD® used (including difficulty in iUPOD® insertion/retrieval).
- Obstetric history (including ectopic pregnancy – most unlikely).

### Additional Advice for Veterinarians

- Preferably, UPODs® should be inserted 2-4 days after ovulation.
- Anecdotal evidence in racing thoroughbred fillies, who may start teasing again sooner than expected, suggests that taking the devices out for two weeks then reinserting a new set may be helpful.
- Misoprostol/Prostaglandin E1 is an option in mares with tight cervixes.
- Some mares may pass the device on their own after prostaglandin administration.
- A Likert scale sheet to assess mare demeanor pre and post device insertion, may be helpful. This sheet is available to be downloaded from the website. [iupod.org](http://iupod.org)