ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cyclix 250 µg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Cloprostenol 250 µg
as Cloprostenol sodium 263 µg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl alcohol (E1519)	20 mg
Citric Acid Monohydrate (as a pH adjuster)	
Sodium Citrate	
Sodium Chloride	
Sodium Hydroxide (as a pH adjuster)	
Water for injections	

Colourless solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (cows).

3.2 Indications for use for each target species

Cattle (cows):
- Oestrus induction and synchronisation in cows with a functional corpus luteum.
- Induction of oestrus as an aid to management of suboestrus (‘silent heat’).
- Treatment of clinical and subclinical endometritis in the presence of a functional corpus luteum.
- Treatment of ovarian luteal cysts.
- Induction of parturition after day 270 of gestation.
- Induction of abortion up to day 150 of gestation.

3.3 Contraindications

Do not use in pregnant animals in which the induction of abortion or parturition is not intended.

Do not administer to induce parturition in animals with suspected dystocia due to mechanical obstruction or abnormal position, presentation and/or posture of the foetus.
Do not use in animals with compromised cardiovascular function, bronchospasm or gastrointestinal dysmotility.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

There is a refractory period of four to five days in cattle after ovulation, when females are insensitive to the luteolytic effect of prostaglandins.
For the termination of gestation in cattle, best results are obtained before day 100 of gestation. Results are less reliable between day 100 and 150 of gestation.

3.5 Special precautions for use

Special precautions for safe use in the target species:
To reduce the risk of anaerobic infections arising from vasoconstriction at the injection site, injections into contaminated (wet or dirty) skin areas should be avoided. Thoroughly clean and disinfect injection sites prior to administration.
Do not administer intravenously.
All animals should receive adequate supervision after treatment.
Induction of parturition or abortion may cause dystocia, stillbirth and/or metritis. The incidence of retained placenta may be increased depending on the time of treatment relative to the date of conception.
Injection into adipose tissue can result in incomplete absorption of the veterinary medicinal product.
Cloprostenol may cause effects related to Prostaglandin F2α activity in the smooth muscles, such as increased frequency of urination and defecation.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Prostaglandins of the F2α type, such as cloprostenol, may be absorbed through the skin and may cause bronchospasm or miscarriage. Care should be taken when handling the veterinary medicinal product to avoid self-injection or skin contact.

Pregnant women, women of childbearing age, asthmatics and persons with other respiratory tract diseases should avoid contact when handling this veterinary medicinal product. Personal protective equipment consisting of impervious gloves should be worn when handling the veterinary medicinal product.

Accidental spillage on the skin should be washed immediately with soap and water. In case of accidental self-injection or spillage onto the skin seek medical advice immediately, particularly as shortness of breath may occur, and show the package leaflet or label to the physician.

This veterinary medicinal product may cause hypersensitive reactions. People with known hypersensitivity to benzyl alcohol should avoid contact with the veterinary medicinal product.

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle (cows):

Rare (1 to 10 animals / 10,000 animals treated)	Injection site infection[1]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anaphylaxis[2]; Increased respiratory rate[3]; Increased heart rate[3]; Abdominal pain[3], Diarrhoea[3,5]; Incoordination[3]; Lying down[3]; Retained placenta[4], Metritis[4], Dystocia[4], Stillbirth[4]; Restlessness, Frequent urination[3,5];

[1] May occur if anaerobic bacteria enter the injection site, especially following intramuscular injection, and may become generalized. Aggressive antibiotic 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 these infections.

[2] Requiring immediate medical attention. Can be life-threatening.

[3] Cloprostenol may cause effects similar to Prostaglandin F2α activity in the smooth muscles.

[4] May be caused by induction of parturition or abortion. As part of induction of parturition, depending on the date of treatment versus the date of conception, the incidence of placental retention may be increased.

[5] In case of occurrence, these effects are observed within 15 minutes post-injection and usually disappear after one hour.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy:
Do not use in pregnant animals in which the induction of abortion or parturition is not intended.

Lactation:
The veterinary medicinal product can be used during lactation.

Fertility:
Cloprostenol has a large safety margin and does not negatively affect fertility in cattle. Nor have any harmful effects been reported in the offspring of an insemination or mating following treatment with this veterinary medicinal product for conception products obtained after treatment.

3.8 Interaction with other medicinal products and other forms of interaction

The concomitant use of oxytocin and cloprostenol increases the effects on the uterus.
The concomitant use of progestogens decreases the effect of cloprostenol.
Do not administer with non-steroidal anti-inflammatory drugs (NSAIDs) since they inhibit endogenous prostaglandin synthesis.

3.9 Administration routes and dosage

Intramuscular use.

One dose equals 500 micrograms of cloprostenol per animal, corresponding to 2 ml of the veterinary medicinal product.

Oestrus induction and synchronisation:
Administer one dose per animal. When no oestrus symptoms are observed, a second dose can be administered after 11 days.

Treatment of clinical and subclinical endometritis in the presence of a functional corpus luteum.:
Administer one dose per animal. If necessary, repeat the treatment 10-14 days later.

Treatment of ovarian luteal cysts:
Administer a single dose per animal.

Induction of parturition
Administer a single dose per animal, not earlier than 10 days before the expected date of calving.

Induction of abortion up to day 150 of gestation:
Administer a single dose per animal, between the 5th and the 150th day of gestation.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

At 5x to 10x overdose the most frequent side effect is increased rectal temperature. This is usually transient, however, and not detrimental to the animal. Limited salivation or transient diarrhoea may also be observed in some animals.

There are no antidotes available, treatment should be symptomatic, assuming that prostaglandin F2α influences the smooth muscle cells.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Meat and offal: 1 day.
Milk: Zero hours.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QG02AD90

4.2 Pharmacodynamics

Cloprostenol sodium, a (racemic) analogue of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), is a very potent luteolytic agent. It causes functional and morphological regression of the corpus luteum (luteolysis) followed by return to oestrus and normal ovulation.
Furthermore, this group of substances has a contractile effect on the smooth muscles (uterus, gastro-intestinal tract, respiratory tract, vascular system).
The veterinary medicinal product does not demonstrate any androgenic, oestrogenic or anti progesterone activity and its effect on pregnancy is due to its luteolytic property.
Unlike other prostaglandin analogues, cloprostenol has no thromboxane A_2 activity and does not cause platelet aggregation.

4.3 Pharmacokinetics

Metabolism studies, using 15-^{14}C-cloprostenol have been performed (by IM administration) to determine residue levels.
The kinetic studies indicate that the compound is rapidly absorbed from the site of injection, is metabolised then excreted in approximately equal proportion in urine and faeces. Less than 1% of the administered dose is eliminated via milk. The major route of metabolism appears to be β-oxydation to the tetranor or dinor acids of cloprostenol.
Following intramuscular injection, cloprostenol is rapidly adsorbed and peak cloprostenol concentrations are generally reached within the first 15 minutes after injection. Blood cloprostenol concentrations steadily decrease with a mean half-life of approx. 56 min.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life of the veterinary medicinal product after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

Keep the vial in the outer carton.
Protect from light.

5.4 Nature and composition of immediate packaging

20 ml and 50 ml colourless glass vials (glass type I, Ph.Eur.) closed with a halogenobutyl rubber stopper, with or without teflon coating.
An aluminium crimp cap with an integral plastic tamper-evident cover is fixed over the rubber stopper.
Secondary packaging: cardboard box.

Not all pack sizes may be marketed

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

The veterinary medicinal product should not enter water courses as cloprostenol may be dangerous for fish and other aquatic organisms.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

VIRBAC

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

9 DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.
Detailed information on this veterinary medicinal product is available in the Union Product Database (*https://medicines.health.europa.eu/veterinary*).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Box containing a vial of 20 ml or 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cyclix 250 µg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Cloprostenol 250 µg/ml
as Cloprostenol sodium 263 µg/ml

3. PACKAGE SIZE

20 ml
50 ml

4. TARGET SPECIES

Cattle (cows).

5. INDICATION(S)

6. ROUTES OF ADMINISTRATION

Intramuscular use.

7. WITHDRAWAL PERIODS

Withdrawal period: Meat and offal: 1 day.
Milk: Zero hours.

8. EXPIRY DATE

Exp. {mm/yyyy}
Once opened, use within 28 days.

Once broached, use by:

9. SPECIAL STORAGE PRECAUTIONS

Keep the vial in the outer carton.
Protect from light.

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

VIRBAC

14. MARKETING AUTHORISATION NUMBER(S)

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial of 20 ml or 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cyclix

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

250 µg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

1. Name of the veterinary medicinal product

Cyclix 250 µg/ml solution for injection for cattle

2. Composition

Each ml contains:

Active substance:
Cloprostenol 250 µg
as Cloprostenol sodium 263 µg

Excipients:
Benzyl alcohol (E1519) 20 mg

Colourless solution.

3. Target species

Cattle (cows).

4. Indications for use

Cattle (cows):
- Oestrus induction and synchronisation in cows with a functional corpus luteum.
- Induction of oestrus as an aid to management of suboestrus (‘silent heat’).
- Treatment of clinical and subclinical endometritis in the presence of a functional corpus luteum (inflammation of the uterus).
- Treatment of ovarian luteal cysts.
- Induction of parturition after day 270 of gestation.
- Induction of abortion up to day 150 of gestation.

5. Contraindications

Do not use in pregnant animals in which the induction of abortion or parturition is not intended.
Do not administer to induce parturition in animals with suspected dystocia (difficult parturition) due to mechanical obstruction or abnormal position, presentation and/or posture of the foetus.
Do not use in animals with compromised cardiovascular function, bronchospasm or gastrointestinal dysmotility.
Do not use in case of hypersensitivity to the active substance or to any of the excipients.

6. Special warnings

There is a refractory period of four to five days in cattle after ovulation, when females are insensitive to the luteolytic effect of prostaglandins.
For the termination of gestation in cattle, best results are obtained before day 100 of gestation. Results are less reliable between day 100 and 150 of gestation.

Special precautions for safe use in the target species:

To reduce the risk of anaerobic infections arising from vasoconstriction at the injection site, injections into contaminated (wet or dirty) skin areas should be avoided. Thoroughly clean and disinfect injection sites prior to administration.
Do not administer intravenously.
All animals should receive adequate supervision after treatment.
Induction of parturition or abortion may cause dystocia (difficult parturition), stillbirth and/or metritis (inflammation of the uterus). The incidence of retained placenta may be increased depending on the time of treatment relative to the date of conception.
Injection into adipose tissue can result in incomplete absorption of the product.
Cloprostenol may cause effects related to Prostaglandin F2α activity in the smooth muscles, such as increased frequency of urination and defecation.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Prostaglandins of the F2α type, such as cloprostenol, may be absorbed through the skin and may cause bronchospasm or miscarriage. Care should be taken when handling the veterinary medicinal product to avoid self-injection or skin contact.
Pregnant women, women in childbearing age, asthmatics and persons with other respiratory tract diseases should avoid contact when handling this veterinary medicinal product. Personal protective equipment consisting of impervious gloves should be worn when handling the veterinary medicinal product.
Accidental spillage on the skin should be washed immediately with soap and water. In case of accidental self-injection or spillage onto the skin seek medical advice immediately, particular as shortness of breath may occur, and show the package leaflet or label to the physician.
This veterinary medicinal product may cause hypersensitive reaction. People with known hypersensitivity to benzyl alcohol should avoid contact with this veterinary medicinal product.
Wash hands after use.

Pregnancy:

Do not use in pregnant animals in which the induction of abortion or parturition is not intended.

Lactation:

The veterinary medicinal product can be used during lactation.

Fertility:

Cloprostenol has a large safety margin and does not negatively affect fertility. Nor have any harmful effects been reported in the offspring of an insemination or mating following treatment with this veterinary medicinal product for conception products obtained after treatment.

Interaction with other medicinal products and other forms of interaction:

The concomitant use of oxytocin and cloprostenol increases the effect on the uterus.
The concomitant use of progestogens decreases the effect of cloprostenol.
Do not administer with non-steroidal anti-inflammatory drugs (NSAIDs) since they inhibit endogenous prostaglandin synthesis.

Overdose:

At 5x to 10x overdose the most frequent side effect is increased rectal temperature. This is usually transient, however, and not detrimental to the animal. Limited salivation or transient diarrhoea may also be observed in some animals.

There are no antidotes available, treatment should be symptomatically, assuming that prostaglandin F2α influences the smooth muscle cells.

Major incompatibilities:

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

7. Adverse events

Cattle (cows):

Rare (1 to 10 animals / 10,000 animals treated)	Injection site infection[1]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anaphylaxis[2]; Increased respiratory rate[3]; Increased heart rate[3]; Abdominal pain[3], Diarrhoea[3,5]; Incoordination[3]; Lying down[3]; Retained placenta[4], Metritis[4], Dystocia[4], Stillbirth[4]; Restlessness, Frequent urination [3,5];

[1] May occur if anaerobic bacteria enter the injection site, especially following intramuscular injection, and may become generalized. Aggressive antibiotic 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 these infections.
[2] Requiring immediate medical attention. Can be life-threatening.
[3] Cloprostenol may cause effects similar to Prostaglandin F2α activity in the smooth muscles.
[4] May be caused by induction of parturition or abortion. As part of induction of parturition, depending on the date of treatment versus the date of conception, the incidence of placental retention may be increased.
[5] In case of occurrence, these effects are observed within 15 minutes post-injection and usually disappear after one hour.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system.

8. Dosage for each species, routes and method of administration

Intramuscular use.

Cattle (cows):
One dose equals 500 micrograms of cloprostenol per animal, corresponding to 2 ml of the veterinary medicinal product.

Oestrus induction and synchronisation:
Administer one dose per animal. When no oestrus symptoms are observed, a second dose can be administered after 11 days.

Treatment of clinical and subclinical endometritis in the presence of a functional corpus luteum (inflammation of the uterus):
Administer one dose per animal. If necessary, repeat the treatment 10-14 days later.

Treatment of ovarian luteal cysts:
Administering a single dose per animal.

Induction of parturition
Administer a single dose per animal, not earlier than 10 days before the expected date of calving.

Induction of abortion up to day 150 of gestation:
Administer a single dose per animal between the 5th and the 150th day of gestation.

9. Advice on correct administration

10. Withdrawal periods

Meat and offal: 1 day.
Milk: Zero hours.

11. Special storage precautions

Keep out of the sight and reach of children.
Keep the vial in the outer carton.
Protect from light.
Do not use this veterinary medicinal product after the expiry date which is stated on the label and the outer carton after Exp. The expiry date refers to the last day of that month.
Shelf life after first opening the immediate packaging: 28 days.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

The veterinary medicinal product should not enter water courses as cloprostenol may be dangerous for fish and other aquatic organisms.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Cardboard box with 1 x 20 ml or 1 x 50 ml vial.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{MM/YYYY}
Detailed information on this veterinary medicinal product is available in the Union Product Database (*https://medicines.health.europa.eu/veterinary*).

16. Contact details

Marketing authorisation holder and manufacturer responsible for batch release:

VIRBAC
1ère avenue – 2065 m – LID
06516 Carros
FRANCE

Local representative(s) and contact details to report suspected adverse reactions: