ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Synchromate 0.25mg/ml solution for injection for cattle, pigs and horses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Cloprostenol 0.25 mg
(corresponds to Cloprostenol sodium 0.263 mg)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Chlorocresol	1.0 mg
Citric acid monohydrate	-
Ethanol (96 per cent)	-
Sodium chloride	-
Sodium citrate	-
Water for injections	-

Clear colorless solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (cows), pigs (sows) and horses (mares)

3.2 Indications for use, for each target species, Cattle (Cows):

- Subestrous or silent oestrus
- Treatment of luteal cysts.
- Induction and synchronization of estrus
- Termination of pregnancy until day 150 of pregnancy
- Expulsion of mummified foetus
- Induction of parturition after 270 days of pregnancy
- Adjuvant treatment in chronic endometritis and pyometra.

Pigs (Sows):

- Induction of labor or synchronization of labor from day 114 of pregnancy (the last insemination day counted as the 1st day of pregnancy).

Horses (Mares):

- Induction of luteolysis.
- Treatment of persistent dioestrus.
- Treatment of pseudo-pregnancy.
- Treatment of lactation anestrus.
- Induction of estrous cycle.
- Induction of labour after 320 days of pregnancy.

3.3 Contraindications

- Do not administer to pregnant animals in which induction of abortion or parturition is not desired.
- Do not administer in case of spastic disease of the respiratory system and gastrointestinal tract and cardiovascular diseases.
- Do not use to induce abortion in case of dystocia due to mechanical obstruction or abnormal positioning of foetus.
- Do not use in case of known hypersensitivity to active substance or excipients.
- Do not administer intravenously.

3.4 Special warnings

Avoid induction of too early farrowing in multiparous and primiparous sows.
Induction of labour two days prior to the average duration of gestation can lead to an increase in stillbirth of piglets.

3.5 Special precautions for use

Special precautions for safe use in use in the target species:

- Induction of parturition and abortion may increase the risk of complications, retained placenta, foetal death and metritis.
- To reduce the risk of anaerobic infections, which might be related to the pharmacological properties of prostaglandins, care should be taken to avoid injection through contaminated areas of skin. Clean and disinfect injection sites thoroughly before administration.
- In case of oestrus induction in cows: from the 2nd day after injection, adequate heat detection is necessary.

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

- Prostaglandins of the F2α type, such as cloprostenol, 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, especially by pregnant women, women of child-bearing age, asthmatics and people with bronchial or other respiratory problems.
- Wear disposable impervious gloves when administering the veterinary medicinal product.
- Direct contact with the skin or eyes may cause irritation and allergic reactions.
- People with known hypersensitivity to cloprostenol or chlorocresol should avoid contact with the veterinary medicinal product.

- Accidental spillage on the skin or into the eyes should be washed off immediately with plenty of water.
  • In case of accidental self-injection or spillage on the skin, seek medical advice immediately, particularly as shortness of breath may occur, and show the package leaflet or the label to the physician.
  • Do not eat, drink or smoke while handling the veterinary medicinal product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cows

Common (1 to 10 animals / 100 animals treated):	- Retained placenta or Retained foetal membrane : (common in animals induced too early, usually more than 10 days before the calculated parturition date. Induction of parturition should take place as close as possible to the predicted calving date which is calculated based on actual conception date.)
Rare (1 to 10 animals / 10,000 animals treated):	- Injection site infection: (associated with proliferation of clostridia at the site of inoculation. Typical local reactions due to Anaerobic infection are inflammation and crepitus at the injection site. Adequate aseptic precautions are needed to avoid this adverse effect.) - Anaphylactic type reactions may be observed on rare occasions for a transient period within 15 minutes post-injection which usually disappear within an hour.
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	- Restlessness (observed within 15 minutes post-injection and usually disappear after an hour.) (Above signs may be observed within 15 minutes post-injection which usually disappear within an hour.)

Sows:

Common (1 to 10 animals / 100 animals treated):	- Retained placenta or Retained foetal membrane : (common in animals induced too early, usually more than 10 days before the calculated parturition date. Induction of parturition should take place as close as possible to the predicted calving date which is calculated based on actual conception date.)
Rare (1 to 10 animals / 10,000 animals treated):	- Injection site infection: (associated with proliferation of clostridia at the site of inoculation. Typical local reactions due to Anaerobic infection are inflammation and crepitus at the injection

	site. Adequate aseptic precautions are needed to avoid this adverse effect.) - Anaphylactic type reactions may be observed on rare occasions for a transient period within 15 minutes post-injection which usually disappear within an hour.
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	- Frequent urination, - Increased bowel movements - Behavioral disorder NOS (changes in behavior similar to those that occur before farrowing, which can go on for an hour) (Above signs may be observed within 15 minutes post-injection which usually disappear within an hour.)

Mares:

Common (1 to 10 animals / 100 animals treated):	- Retained placenta or Retained foetal membrane : (common in animals induced too early, usually more than 10 days before the calculated parturition date. Induction of parturition should take place as close as possible to the predicted calving date which is calculated based on actual conception date.)
Rare (1 to 10 animals / 10,000 animals treated):	- Injection site infection: (associated with proliferation of clostridia at the site of inoculation. Typical local reactions due to Anaerobic infection are inflammation and crepitus at the injection site. Adequate aseptic precautions are needed to avoid this adverse effect.) - Anaphylactic type reactions may be observed on rare occasions for a transient period within 15 minutes post-injection which usually disappear within an hour.
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	- Cold sweating - Colic - Prostration (Above signs may be observed within 15 minutes post-injection which usually disappear within an 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 also the last section of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Do not administer to pregnant animals unless the objective is to terminate the pregnancy.
The veterinary medicinal product can be used during lactation.

3.8 Interaction with other medicinal products and other forms of interaction

Simultaneous use of oxytocin and Cloprostenol increases the intensity and frequency of uterine contractions.In animals treated with a progestogen, a decreased response to progestogen is to be expected.
Do not administer together with Non-steroidal Anti-inflammatory Drugs (NSAID) as they inhibit endogenous prostaglandin synthesis.

3.9 Administration routes and dosage

Route of application : deep intramuscular injection.
To reduce the risk of anaerobic infection, thoroughly clean and disinfect the injection site before application.

Cattle (Cows):
0.5 mg Cloprostenol/animal corresponding to 2.0 ml product / animal
Subestrus or silent heat / oestrus induction **:** Administer the drug, after determining the presence of the *corpus luteum*. Heat is generally observed within 2-5 days after treatment. Inseminate at 72-96 hours.
Pregnancy interruption **:** The administration should be carried out between the first week and the day 150 gestation. Abortion occurs after 4-5 days.
Endometritis or pyometra **:** Administer a single dose of the drug. If necessary repeat treatment 10-14 days later.

Pigs (Sows):
0.175 mg Cloprostenol/animal corresponding to 0.7 ml of product / animal as a single dose.
Induction of labor must be performed within 24-48 hours prior to the expected date of the same to reduce the risk of mortality in piglets. Delivery usually occurs at 19-29 hours of its administration.

Horses (Mares):
- **Ponies:** single dose of 0.5-1.0 ml (equivalent to 125-250 mcg of cloprostenol) per animal.
- **Thoroughbreds, hunters and heavy horses:** single dose of 1-2 ml (equivalent to 250- 500 mcg cloprostenol) per animal.

For 20ml vials: “The bromobutyl rubber stoppers may be safely punctured up to 10 times with 16-gauge needle”.
For 10 ml vials: “Laminated elastomeric bromobutyl rubber stopper may be safely punctured up to 5 times with 16-gauge needle”.

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

In case of overdose, the following clinical signs may occur:
Increase in pulse and respiratory rate, bronchoconstriction, increase in body temperature, increased defecation and urination, salivation, nausea and vomiting.
In cattle, 200 times the dose of cloprostenol sodium caused only mild and transient scouring. In heifers, no adverse effects were noted after two intramuscular administrations, 11 days apart, of R-cloprostenol (as the sodium salt) at the recommended dose (150 µg) or at a ten-fold dose (1500 µg).
In sows, no adverse effects of R-cloprostenol (as the sodium salt) were reported after single intramuscular administration at the recommended dose (75 µg), at five-fold dose (225 µg) or at ten-fold dose (750 µg).

In horses transient clinical signs such as sweating, reduced rectal temperature, tachycardia, rapid breathing, movement incordination, colic, restlessness and depression may be observed disappearing within short time after application of the dose.

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

To be complete in accordance with national requirements. .

3.12 Withdrawal period

Cattle (cows):
Meat and offal: 2 days
Milk: Zero days

Pig (sows):
Meat and offal: 2 days
Horses (mares):
Meat and offal: 28 days

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QG02AD90

4.2 Pharmacodynamic

Cloprostenol is a synthetic analog of prostaglandins, structurally related with prostaglandin F 2α (PGF 2α). As a potent luteolytic agent, it causes regression functional and morphological of the *corpus luteum* and arrest of its secretory activity (Iuteolysis) followed by a return to estrus and a normal ovulation. It stimulates the uterine smooth muscles causing contraction and produces a relaxing effect on the cervix . Therefore, it causes the induction of heat in females with a normal estrous cycle or with *corpus luteum*.persistent, eliminating the effect of the negative feedback mechanism of the progesterone, and in pregnancy it induces labor or abortion. Its spasmogenic effect on smooth muscles also causes side effects such as: bronchoconstriction, increased blood pressure and stimulation of motility of the intestinal and urinary smooth muscles in some species.

4.3 Pharmacokinetic

The kinetic studies, in both domestic and laboratory species, indicate that the compound is rapidly absorbed from the site of injection, is metabolised followed by excretion in approximately equal proportion in urine and faeces. The major route of metabolism in all species appears to be ß-oxidation to the tetranor or dinor acids of cloprostenol. Peak values of radioactivity in blood were observed within 1 hour of a parenteral dose and declined with a t½ of between 1 - 3 hours depending on species.
In pigs, after a single intramuscular administration of 14C-cloprostenol (acid in the form of sodium salt) at a dose of 200 µg, the highest plasma level of radioactivity (0.70 ± 0.14 µg/l) was measured at 1 hour after dosing. At 24 hours post dosing, the levels were close to 0.04 µg/l. Fifty percent of

the dose administered was recovered either via urine or faeces. The major urinary metabolites were: the parent compound (approximately 10-14 %), the tetranor acid metabolite (approximately 37 %) and polar compounds (26-32 %). After intramuscular administration of 75 µg of R-cloprostenol to sows, the maximum concentration of R-cloprostenol in plasma was close to 2 µg/l and occurred between 30 and 80 minutes after injection. The half-life of elimination T1/2β was estimated to be 3 h 10 min.
In dairy cows, after a single intramuscular injection of 500 µg of free acid 14C-cloprostenol (specific activity 122 µCi/mg free acid), the highest plasma level (0.43 ± 0.043 µg free acid equivalent/l) was reached within 30 minutes after dosing. The concentrations were lower than 0.01 µg free acid equivalents/l at 24 hours post dosing. The T1/2β was 3 hours. The recovery of 14C in urine (52.5 ± 4.8 %) was achieved by 16 hours. Cloprostenol was extensively metabolised in the cow by β-oxidation to give the tetranor acid of cloprostenol, isolated as δ-lactone and as glucuronide conjugates (44 %). The parent compound represents 18 % of the radioactivity excreted.

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.
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5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: **2** years
Shelf life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

5.4 Nature and composition of immediate packaging

Contents 10 and 20 ml
For 20 ml: Clear glass vials of glass type I with Ph.Eur type I bromobutyl rubberstopper and aluminum cap
For 10 ml: Clear glass vials of glass type I with Ph.Eur type I laminated elastomeric bromobutyl rubber stopper and aluminum cap

Cardboard box containing 1vial of 10ml,
Cardboard box containing 5 vials of 10ml
Cardboard box containing 12 vials of 10ml
Cardboard box containing 1 vial of 20ml
Cardboard box containing 5 vials of 20ml
Cardboard box containing 12 vials of 20ml

Not all pack sizes may be marketed.

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

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

Alivira Animal Health Limited

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorization:

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

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.