

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

RELOSYL 50 micrograms/ml solution for injection for cattle.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Gonadorelin (as gonadorelin acetate).....50 µg

Excipients:

Benzyl alcohol (E1519)9 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless or almost colourless solution free from visible particles.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle: cows, heifers.

4.2 Indications for use, specifying the target species

Cattle: cows and heifers

Treatment of ovarian follicular cysts.

In association with artificial insemination to optimise the time of ovulation.

Induction and synchronisation of oestrus and ovulation in combination with prostaglandin F_{2α} (PGF_{2α}) with or without progesterone as part of Fixed Time Artificial Insemination (FTAI) protocols:

-In cycling cows. To be used in combination with PGF_{2α} or analogue.

-In cycling and non-cycling cows and heifers. To be used in combination with PGF_{2α} or analogue and progesterone releasing device.

4.3 Contraindications

Do not use in animals with known hypersensitivity to gonadorelin or to any of the excipients.

4.4 Special warnings for each target species

In the treatment of cystic ovaries, the condition of ovarian follicular cysts should be diagnosed by rectal palpation revealing the presence of persisting follicular structures with a diameter over 2.5 cm and should be confirmed by the use of plasma or milk progesterone assay.

The product should be administered at least 14 days after calving due to the absence of receptivity of the hypophysis before that time.

For induction and synchronisation of oestrus and ovulation in Fixed Time Artificial Insemination (FTAI) protocols, the product should be administered at least 35 days after calving. The response of cows and heifers to synchronisation protocols is influenced by the physiological state at the time of treatment. Responses to treatment can vary either across herds or across cows within herds. However,

the percentage of cows displaying oestrus within a given period is usually greater than in untreated cows and the subsequent luteal phase is of normal duration.

For protocol that only includes PGF_{2α} recommended for cycling cows: To maximise conception rates of cows to be treated, the ovarian status should be determined and regular cyclic ovarian activity confirmed. Optimal results will be achieved in healthy normally-cycling cows.

4.5 Special precautions for use

Special precautions for use in animals

Animals in poor condition, whether from illness, inadequate nutrition, or other factors, may respond poorly to treatment.

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

Care should be taken when handling the product to avoid self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Accidental spillage on the skin or eyes should be washed off with plenty of water.

Gonadorelin is a Gonadotropin Releasing Hormone (GnRH) analogue which stimulates the re-lease of sex hormones. The effects of accidental exposure to GnRH analogues in pregnant women or in women with normal reproductive cycles are unknown; therefore it is recommended that pregnant women should not administer the product, and that women of child-bearing age should administer the product with caution.

People with known hypersensitivity to GnRH analogues and benzyl alcohol, should avoid contact with the veterinary medicinal product.

4.6 Adverse reactions (frequency and seriousness)

None.

4.7 Use during pregnancy, lactation or lay

Not indicated for use during pregnancy.

No contraindications have been described during lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Not known.

4.9 Amounts to be administered and administration route

Intramuscular use.

- **Treatment of ovarian follicular cysts:** 100-150 micrograms of gonadorelin (as acetate) per animal (i.e. 2- 3 ml of the product per animal). If necessary, treatment can be repeated at intervals of 1-2 weeks.

- **In association with artificial insemination to optimise the time of ovulation,** improving the chances that the treated cow will become fertile: 100 micrograms of gonadorelin (as acetate) per animal (i.e. 2 ml of the product per animal). It must be administered at the same time as artificial insemination and/or 12 days after this.

The following timing of injection and insemination should be followed:

- Injection should be performed between 4 and 10 hours after oestrus detection.
- An interval of at least 2 hours between the injection of GnRH and artificial insemination is recommended.

- Artificial insemination should be carried out in accordance with the usual field recommendations, i.e., 12 to 24 hours after oestrus detection.

• **Induction and synchronisation of oestrus and ovulation in combination with prostaglandin F_{2α} (PGF_{2α}) with or without progesterone as part of Fixed Time Artificial Insemination (FTAI) protocols:**

The following FTAI protocols have been commonly reported in the literature:

In cycling cows:

- Day 0 Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product)
- Day 7 Inject PGF_{2α} or analogue (luteolytic dose)
- Day 9 Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product)
- Artificial insemination 16–20 hours later, or at observed oestrus if sooner.

Alternatively:

- Day 0 Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product)
- Day 7 Inject PGF_{2α} or analogue (luteolytic dose)
- Artificial insemination and injection of 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product) 60–72 hours later, or at observed oestrus if sooner.

In cycling and non-cycling cows and heifers:

- Insert intravaginal progesterone releasing device for 7-8 days.
- Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product) at progesterone device insertion.
- Inject a luteolytic dose of PGF_{2α} or analogue 24 hours prior to device removal.
- FTAI 56 hours after removal of the device, or
- Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product) 36 hours after progesterone releasing device removal and FTAI 16 to 20 hours later.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

At up to 5 times the recommended dose and in a regimen extended from one to three daily administrations, no measurable signs of either local or general clinical intolerance were observed.

4.11 Withdrawal period(s)

Meat and offal: zero days.

Milk: zero hours.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Hypothalamic hormones. Gonadotropin-releasing hormones.

ATCvet code: QH01CA01.

5.1 Pharmacodynamic properties

Gonadorelin (as acetate) is a synthetic gonadorelin (“Gonadotropin Releasing Hormone” GnRH) physiologically and chemically identical to the natural gonadorelin released by the hypothalamus in mammalian species.

Gonadorelin stimulates the synthesis and release of the pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). Its action is mediated by a specific plasma membrane receptor. Only 20% GnRH receptor occupancy is required to induce 80% of the maximum biological response. The binding of GnRH to its receptor activates protein kinase C (PKC) and also mitogen-activated protein kinase (MAPK) cascades which provide an important link for the transmission of signals from the cell surface to the nucleus allowing synthesis of the gonadotropin hormones.

Repeat breeding may be affected by multiple factors, including feeding and husbandry practices. Also, one of the most prominent findings in repeat breeding animals is the delayed and smaller preovulatory LH surge leading to delayed ovulation. Injection of GnRH during oestrus increases the spontaneous LH peak and prevents delay in ovulation in repeat breeding animals.

5.2 Pharmacokinetic particulars

Absorption

After intramuscular administration in cows, gonadorelin is rapidly absorbed from the injection site, with a plasma half-life of approximately 20 minutes.

Distribution

An increase in the level of LH is detected thirty minutes after the administration, demonstrating fast distribution to the adenohypophysis.

Metabolism

The compound is rapidly metabolized into smaller inactive peptides and aminoacids.

Elimination

The main excretion route is renal, although a significant proportion is also excreted in expired air.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E 1519)

Potassium dihydrogen phosphate

Dipotassium phosphate

Sodium chloride

Water for injections

6.2 Major incompatibilities

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

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.

Shelf life after first opening the immediate packaging: 28 days.

6.4. Special precautions for storage

Do not store above 25 °C.

Keep the vial in the outer carton.

6.5 Nature and composition of immediate packaging

Type II colourless glass vials fitted with a type I bromobutyl rubber stopper and sealed with an aluminium cap.

Pack sizes

Cardboard box with 1 vial of 6 ml
Cardboard box with 1 vial of 20 ml
Cardboard box with 1 vial of 50 ml
Cardboard box with 1 vial of 100 ml
Cardboard box with 10 vials of 6 ml

Not all pack sizes may be marketed.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratorios SYVA S.A.
Calle Marqués de la Ensenada, 16
28004 Madrid
Spain

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

Date of last renewal: DD/MM/YYYY}.

10. DATE OF REVISION OF THE TEXT

{Month YYYY}

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be supplied only on veterinary prescription

To be administered exclusively by a veterinarian (in the case of intravenous administration).

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE AND IMMEDIATE PACKAGE

{box with 1 vial of 6, 20, 50, 100 ml and box with 10 vials of 6 ml. Vials of 50 and 100 ml }

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

RELOSYL 50 micrograms /ml solution for injection for cattle.

Gonadorelin (as acetate).

2. STATEMENT OF ACTIVE SUBSTANCE

Each ml contains:

Active substance:

Gonadorelin (as gonadorelin acetate).....50 µg

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

6 ml/

20 ml, 50 ml, 100 ml, 10 x 6 ml

5. TARGET SPECIES

Cattle: Cows and heifers.

6. INDICATION(S)

7. METHOD AND ROUTE OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

8. WITHDRAWAL PERIODS

Withdrawal periods:

Meat and offal: zero days.

Milk: zero hours.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

Once broached, use by:

Shelf life after first opening the immediate packaging: 28 days.

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

Keep the vial in the outer carton.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read the package leaflet

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

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

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratorios SYVA, S.A.
Calle Marqués de la Ensenada, 16
28004 Madrid
Spain

16. MARKETING AUTHORISATION NUMBER(S)**17. MANUFACTURER'S BATCH NUMBER**

Batch {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{ Vials 6 ml/ 20 ml }

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

RELOSYL 50 micrograms/ml solution for injection for cattle.

Gonadorelin (as acetate)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Gonadorelin (as gonadorelin acetate)50 µg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

6 ml/20 ml

4. ROUTE OF ADMINISTRATION

Intramuscular use

5. WITHDRAWAL PERIODS

Withdrawal periods:

Meat and offal: zero days

Milk: zero hours

6. BATCH NUMBER

Batch {number}

7. EXPIRY DATE

EXP {month/year}

Once opened, use by:

Shelf life after first opening the immediate packaging: 28 days.

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET
RELOSYL 50 micrograms/ml solution for injection for cattle

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:

Laboratorios SYVA S.A.
Calle Marqués de la Ensenada, 16
28004 Madrid
Spain

Manufacturer responsible for batch release:

Laboratorios SYVA S.A.
Avenida del Párroco Pablo Díez, 49-57
San Andrés del Rabanedo
24010 León
Spain

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

RELOSYL 50 micrograms/ml solution for injection for cattle.
Gonadorelin (as acetate)

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each ml contains:

Active substance:

Gonadorelin (as gonadorelin acetate) 50 µg

Excipients:

Benzyl alcohol (E1519) 9 mg

Clear, colourless or almost colourless solution free from visible particles.

4. INDICATION(S)

In cattle (cows and heifers):

Treatment of ovarian follicular cysts.

In association with artificial insemination to optimise the time of ovulation.

Induction and synchronisation of oestrus and ovulation in combination with prostaglandin F_{2α} (PGF_{2α}) with or without progesterone as part of Fixed Time Artificial Insemination (FTAI) protocols:

-In cycling cows: To be used in combination with PGF_{2α} or analogue.

-In cycling and non-cycling cows and heifers: To be used in combination with PGF_{2α} or analogue and progesterone releasing device.

5. CONTRAINDICATIONS

Do not use in animals with known hypersensitivity to gonadorelin or to any of the excipients.

6. ADVERSE REACTIONS

None.

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 inform your veterinary surgeon.

7. TARGET SPECIES

Cattle: cows and heifers.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Intramuscular use.

- **Treatment of ovarian follicular cysts:** 100-150 micrograms of gonadorelin (as acetate) per animal (i.e. 2- 3 ml of the product per animal). If necessary, treatment can be repeated at intervals of 1-2 weeks.
- **In association with artificial insemination to optimise the time of ovulation,** improving the chances that the treated cow will become fertile: 100 micrograms of gonadorelin (as acetate) per animal (i.e. 2 ml of the product per animal). It must be administered at the same time as artificial insemination and/or 12 days after this.

The following timing of injection and insemination should be followed:

- Injection should be performed between 4 and 10 hours after oestrus detection.
- An interval of at least 2 hours between the injection of GnRH and artificial insemination is recommended.
- Artificial insemination should be carried out in accordance with the usual field recommendations, i.e., 12 to 24 hours after oestrus detection.

- **Induction and synchronisation of oestrus and ovulation in combination with prostaglandin F_{2α} (PGF_{2α}) with or without progesterone as part of Fixed Time Artificial Insemination (FTAI) protocols:**

The following FTAI protocols have been commonly reported in the literature:

In cycling cows:

- Day 0 Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product)
- Day 7 Inject PGF_{2α} or analogue (luteolytic dose)
- Day 9 Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product)
- Artificial insemination 16–20 hours later, or at observed oestrus if sooner.

Alternatively:

- Day 0 Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product)
- Day 7 Inject PGF_{2α} or analogue (luteolytic dose)
- Artificial insemination and injection of 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product) 60–72 hours later, or at observed oestrus if sooner.

In cycling and non-cycling cows and heifers:

- Insert intravaginal progesterone releasing device for 7-8 days.
- Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product) at progesterone device insertion.
- Inject a luteolytic dose of PGF_{2α} or analogue 24 hours prior to device removal.
- FTAI 56 hours after removal of the device, or
- Inject 100 micrograms of gonadorelin (as acetate) per animal (2 ml of the product) 36 hours after progesterone releasing device removal and FTAI 16 to 20 hours later.

9. ADVICE ON CORRECT ADMINISTRATION

10. WITHDRAWAL PERIODS

Meat and offal: zero days.

Milk: zero hours.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Do not store above 25 °C.

Keep the vial in the outer carton.

Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after “EXP”. The expiry date refers to the last day of that month.

Shelf-life after first opening the container: 28 days.

12. SPECIAL WARNING(S)

Special warnings for each target species:

Cystic ovaries: In the treatment of cystic ovaries, the condition of ovarian follicular cysts should be diagnosed by rectal palpation revealing the presence of persisting follicular structures with a diameter over 2.5 cm and should be confirmed by the use of plasma or milk progesterone assay.

Product should be administered at least 14 days after calving due to the absence of receptivity of the hypophysis before that time.

For induction and synchronisation of oestrus and ovulation in Fixed Time Artificial Insemination (FTAI) protocols, the product should be administered at least 35 days after calving. The response of cows and heifers to synchronisation protocols is influenced by the physiological state at the time of treatment. Responses to treatment can vary either across herds or across cows within herds. However, the percentage of cows displaying oestrus within a given period is usually greater than in untreated cows and the subsequent luteal phase is of normal duration.

For protocol that only includes PGF_{2α} recommended for cycling cows: To maximise conception rates of cows to be treated, the ovarian status should be determined and regular cyclic ovarian activity confirmed. Optimal results will be achieved in healthy normally-cycling cows.

Animals in poor condition, whether from illness, inadequate nutrition, or other factors, may respond poorly to treatment.

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

Care should be taken when handling the product to avoid self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Accidental spillage on the skin or eyes should be washed off with plenty of water.

Gonadorelin is a Gonadotropin Releasing Hormone (GnRH) analogue which stimulates the re-lease of sex hormones. The effects of accidental exposure to GnRH analogues in pregnant women or in women with normal reproductive cycles are unknown; therefore it is recommended that pregnant women should not administer the product, and that women of child-bearing age should administer the product with caution.

People with known hypersensitivity to GnRH analogues and benzyl alcohol, should avoid contact with the veterinary medicinal product.

Pregnancy and lactation:

Not indicated for use during pregnancy.
No contraindications have been described during lactation.

Overdose (symptoms, emergency procedures, antidotes):

Up to 5 times the recommended dose and in a regimen extended from one to three daily administrations, no measurable signs of either local or general clinical intolerance were observed.

Incompatibilities:

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste. Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

{Month YYYY}

15. OTHER INFORMATION

Package sizes:

Cardboard box with 1 vial of 6 ml
Cardboard box with 1 vial of 20 ml
Cardboard box with 1 vial of 50 ml
Cardboard box with 1 vial of 100 ml
Cardboard box with 10 vials of 6 ml.

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.