[Version 8.10/2012]

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ACEGON 50 micrograms/ml solution for injection for cattle.

In Portugal: GONESTIN 50 micrograms/ml solution for injection for cattle.
In Norway and Denmark: ACEGON Vet 50 micrograms/ml solution for injection for cattle.
In Italy: 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 $F_{2\alpha}$ ($PGF_{2\alpha}$) with or without progesterone as part of Fixed Time Artificial Insemination (FTAI) protocols:
-In cycling cows. To be used in combination with $PGF_{2\alpha}$ or analogue.
-In cycling and non-cycling cows and heifers. To be used in combination with $PGF_{2\alpha}$ or analogue and progesterone releasing device.

4.3 Contraindications

Do not use in animals with known hypersensitivity to gonadorelin and to any excipient.
Do not use for shortening of oestrus during infectious diseases and other relevant disorders.

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 $PGF_{2\alpha}$ 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.
Care should be taken to avoid skin and eye contact. In case of skin contact, rinse immediately and thoroughly with water as GnRH analogues can be absorbed through the skin. In case of accidental contact with eyes, rinse thoroughly with plenty of water.

The effects of accidental exposure 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, should avoid contact with the veterinary medicinal product.

4.6 Adverse reactions (frequency and seriousness)

None

4.7 Use during pregnancy, lactation or lay

<u>Pregnancy</u>

Not applicable

<u>Lactation</u>
Can be used during lactation

4.8 Interaction with other medicinal products and other forms of interaction

A synergistic effect occurs in case of combined administration of FSH.

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 isrecommended.
  - 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 $F_{2\alpha}$ (PGF2*α*) 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 $PGF_{2\alpha}$ 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 $PGF_{2\alpha}$ 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 $PGF_{2\alpha}$ 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

<u>Absorption</u>
After intramuscular administration in cows, gonadorelin is rapidly absorbed from the injection site, with a plasma half-life of approximately 20 minutes.
<u>Distribution</u>
An increase in the level of LH is detected thirty minutes after the administration, demonstrating fast distribution to the adenohypophysis.
<u>Metabolism</u>
The compound is rapidly metabolized into smaller inactive peptides and aminoacids.
<u>Elimination</u>
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 hydrogen phosphate
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal 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 ºC.

6.5 Nature and composition of immediate packaging

Material of the primary container
Type II colourless glass vials (6, 10, 20, 50 and 100 ml).
Type I bromobutyl stoppers.

Pack sizes
Cardboard box containing 1 glass vial of 6, 10, 20, 50 or 100 ml with a rubber stopper and aluminium cap.
Cardboard box with 10 glass vials of 6 ml with a rubber stopper and aluminium cap.

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.U.
Avda. Párroco Pablo Díez 49-57
24010 León - Spain

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be supplied only on veterinary prescription.

For animal treatment only.

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

{cardboard box}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Acegon 50 micrograms/ml solution for injection for cattle.
In Portugal: Gonestin 50 micrograms/ml solution for injection for cattle.
In Norway and Denmark: ACEGON Vet 50 micrograms/ml solution for injection for cattle.
In Italy: RELOSYL 50 micrograms/ml solution for injection for cattle

Gonadorelin (as gonadorelin acetate)

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

50 micrograms /ml Gonadorelin (as gonadorelin acetate).
Benzyl alcohol (E 1519).

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

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

5. TARGET SPECIES

Cattle: Cows and heifers

6. INDICATION(S)

Read the package leaflet before use

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

8. WITHDRAWAL PERIOD

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 ºC.

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

Disposal: read 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 REACH AND SIGHT OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratorios SYVA S.A.U.
Avda. Párroco Pablo Díez, 49-57
24010 León (Spain)

16. MARKETING AUTHORISATION NUMBER(S)

[To be completed in accordance with national requirements after conclusion of the MR phase]

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

<PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE>

{50 ml/100 ml vials**}**

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Acegon 50 micrograms/ml solution for injection for cattle.
In Portugal: Gonestin 50 micrograms/ml solution for injection for cattle.
In Norway and Denmark: ACEGON Vet 50 micrograms/ml solution for injection for cattle.
In Italy: RELOSYL 50 micrograms/ml solution for injection for cattle
Gonadorelin (as gonadorelin acetate)

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

50 micrograms/ml gonadorelin (as gonadorelin acetate)
Benzyl alcohol (E 1519).

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml/100 ml

5. TARGET SPECIES

Cattle

6. INDICATION(S)

Read the package leaflet before use

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use

8. WITHDRAWAL PERIOD

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 ºC.

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

Disposal: read 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 REACH AND SIGHT OF CHILDREN"

Keep out of the sight and reach of children

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratorios SYVA, S.A.U.
Avda. Párroco Pablo Díez, 49-57
24010 León (Spain)

16. MARKETING AUTHORISATION NUMBER(S)

[To be completed in accordance with national requirements after conclusion of the MR phase]

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{6 ml/10 ml/20 ml**}**

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Acegon 50 micrograms/ml solution for injection for cattle.
In Portugal: Gonestin 50 micrograms/ml solution for injection for cattle.
In Norway and Denmark: ACEGON Vet 50 micrograms/ml solution for injection for cattle.
In Italy: RELOSYL 50 micrograms/ml solution for injection for cattle

Gonadorelin (as gonadorelin acetate)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

50 micrograms/ml gonadorelin (as gonadorelin acetate)

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

6 ml/10 ml/20 ml

4. ROUTE(S) OF ADMINISTRATION

Intramuscular use

5. WITHDRAWAL PERIOD

Meat and offal: zero days.
Milk: zero hours

6. BATCH NUMBER

Batch {number}

7. EXPIRY DATE

EXP {month/year}
Once broached, use by_____

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Acegon 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 and manufacturer responsible for batch release: Laboratorios SYVA S.A.U., Avda. Párroco Pablo Díez 49-57, 24010 Leon, Spain

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Acegon 50 micrograms/ml solution for injection for cattle.

In Portugal: Gonestin 50 micrograms/ml solution for injection for cattle.

In Norway and Denmark: ACEGON Vet 50 micrograms/ml solution for injection for cattle.

In Italy: RELOSYL 50 micrograms/ml solution for injection for cattle.

Gonadorelin (as gonadorelin 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. INDICATIONS

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 $F_{2\alpha}$ ($PGF_{2\alpha}$) with or without progesterone as part of Fixed Time Artificial Insemination (FTAI) protocols:
- In cycling cows: To be used in combination with $PGF_{2\alpha}$ or analogue.
- In cycling and non-cycling cows and heifers: To be used in combination with $PGF_{2\alpha}$ or analogue and progesterone releasing device.

5. CONTRAINDICATIONS

Do not use in animals with known hypersensitivity to gonadorelin and to any excipient.
Do not use for shortening of oestrus during infectious diseases and other relevant disorders.

6. ADVERSE REACTIONS

If you notice any serious effects or other effects not mentioned in this leaflet, 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 $F_{2\alpha}$ ($PGF_{2\alpha}$) 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 $PGF_{2\alpha}$ 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 $PGF_{2\alpha}$ 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 $PGF_{2\alpha}$ 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 PERIOD

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 ºC.

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 WARNINGS

Special warnings for 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 $PGF_{2\alpha}$ 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.

Use during pregnancy and lactation

Pregnancy

Not applicable

Lactation
Can be used during lactation

Special precautions to be taken by the person administering the medicinal products 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.
Care should be taken to avoid skin and eye contact. In case of skin contact, rinse immediately and thoroughly with water as GnRH analogues can be absorbed through the skin. In case of accidental contact with eyes, rinse thoroughly with plenty of water.

The effects of accidental exposure 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, should avoid contact with the veterinary medicinal product.

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

Overdose
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 are observed.

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

15. OTHER INFORMATION

Package sizes: Cardboard box containing 1 glass vial of 6, 10, 20, 50 or 100 ml. Cardboard box containing 10 glass 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.