[Version 8.1, 01/2017]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Hypophysin LA 70 µg/ml solution for injection for cattle and pigs
Depotocin 70 µg/ml solution for injection for cattle and pigs (AT/DE)
Hypophysin LA 70 microgram/ml solution for injection for cattle and pigs (IE/UK)
Hypophysin 70 µg/ml solution for injection for cattle and pigs (EE)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substance:
Carbetocin 70.00 µg

Excipients:
Chlorocresol 1.00 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle, pigs

4.2 Indications for use, specifying the target species

Cows:
- Uterine atony during the puerperal period
- Placental retention as a consequence of uterine atony
- Initiation of milk ejection in stress-induced agalactia or in conditions requiring udder emptying

Sows:
- Acceleration or restart of parturition after disruption of uterine contractions (uterine atony or inertia) following the expulsion of at least one piglet
- Supportive therapy of mastitis-metritis-agalactia (MMA-) syndrome
- Initiation of milk ejection
- Shortening of total parturition duration as a component of synchronisation of parturition in sows The product may be applied to sows which have previously been administered an appropriate $PGF_{2\alpha}$ or $PGF_{2\alpha}$ analogue (e.g. cloprostenol) not prior to day 114 of pregnancy and have not started farrowing within 24 hours after the $PGF_{2\alpha}$ or $PGF_{2\alpha}$ analogue injection (day 1 of pregnancy is the last day of insemination)

4.3 Contraindications

Do not administer to accelerate parturition if cervix is not opened or if there is a mechanical cause for the delayed parturition such as physical obstruction, positional and postural abnormalities, convulsive labour, threatened rupture of uterus, uterine torsion, relative foetal oversize or deformities of the birth canal.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

The responsiveness to carbetocin of the myometrium is likely to be close to zero from the 5th to the 11th day post-partum. Therefore, the administration of the veterinary medicinal product during this period is likely to be inefficient and should be avoided.

If treatment with carbetocin should fail, then it is advisable to reconsider the aetiology of the condition, specifically if hypocalcaemia could be a complicating factor.

In case of severe septic metritis, appropriate concomitant therapy should be instigated when administering the veterinary medicinal product.

4.5 Special precautions for use

Special precautions for use in animals

None.

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

In case of accidental self-injection uterine contractions could be induced in pregnant women.
Pregnant women, women post-partum and breast-feeding women should not administer this product, in order to avoid an accidental exposure.
In case of an accidental self-injection of the veterinary medicinal product in non-pregnant women the following effects may occur: facial flushing and warmth, lower abdominal pain. These effects usually disappear within a short span of time.

In the case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
Personal protective equipment consisting of disposable gloves should be worn when handling the veterinary medicinal product.
Carbetocin may be absorbed through the skin. In case of accidental contact with the skin, the corresponding area should be thoroughly cleaned with soap and water.
In case of contact with the eyes, they should be thoroughly rinsed with water.
People with known hypersensitivity to carbetocin or any of the excipients should avoid contact with the veterinary medicinal product.
Women of childbearing age should administer the product with special caution.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases carbetocin may have a uterotonic effect in the late pregnancy.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The veterinary medicinal product is indicated to induce milk ejection.
See also 4.3 Contraindications.

4.8 Interaction with other medicinal products and other forms of interaction

The administration of oxytocin after the administration of the veterinary medicinal product is unnecessary. Due to a possible intensification of the effect of oxytocin, undesirable uterine spasms may be induced.

4.9 Amounts to be administered and administration route

For intramuscular or intravenous use.

Cows
For all indications:
3.0 – 5.0 ml/animal, corresponding to 210 – 350 µg carbetocin/animal
Sows
For shortening of total parturition duration as a part of the synchronisation of parturition:
0.5 ml/animal, corresponding to 35 µg carbetocin/animal
For acceleration or restart of parturition after disruption of uterine contractions (uterine atony or inertia) following the expulsion of at least one piglet:
0.5 -1.0 ml/animal, corresponding to 35 - 70 µg carbetocin/animal
For MMA and milk ejection:
1.5 – 3.0 ml/animal, corresponding to 105 – 210 µg carbetocin/animal

The dosage requirements can be variable within the indicated limits based on the assessment of the veterinarian.

In case of treatment for milk ejection in the cow and sow or supportive therapy in MMA-syndrome in sow, a repeated administration is possible after 1 to 2 days. The interval between two injections should not be shorter than 24 hours.
For all other indications stated in section 4.2 [indications] the product should be administered once.

The rubber stopper of the vial may be safely punctured up to 25 times. Otherwise, automatic syringe equipment, or a suitable draw-off needle, should be used for the 20 and 50 ml vials to avoid excessive puncturing of the closure.

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

An overdosing of more than 400 µg of carbetocin/animal could increase the stillbirth rate in older sows if administered during prolonged parturition.

An overdosing of 600 µg of carbetocin/animal may induce profuse lactation in sows that may result in diarrhoea, reduced weight gain and increased mortality in their piglets.
Carbetocin is considered as moderately irritant. At the injection sites of treated animals, focal lymphocytic infiltration was observed at higher doses (1000 µg of carbetocin/animal).

4.11 Withdrawal periods

Cattle, pigs	Meat and offal:	Zero days
Cattle	Milk:	Zero hours

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Systemic hormonal preparations, excl. sex hormones and insulin
ATCvet code: QH01BB03

5.1 Pharmacodynamic properties
Carbetocin is a synthetic analogue of the posterior pituitary lobe hormone oxytocin and has its physiological and pharmacological main effects at the smooth muscle (induction and increase of contractions) of reproductive organs.
Carbetocin has the same effect as natural oxytocin: at the oestrogen stimulated uterus it causes a change from weak, spontaneous and irregular to synchronised, regular, increased and directed contractions. Moreover, in the mammary gland it produces physiological contractions of the myoepithelial cells in the alveolae and small lactiferous ducts as well as a simultaneous relaxation of the teat sphincter.
The action of carbetocin is prolonged and it causes an intensification of the physiological effect.

5.2 Pharmacokinetic particulars
Carbetocin is, due to its strongly developed peptidase-resistance, much more slowly degraded in vivo and distinguishes itself by a prolonged efficacy. Carbetocin is much more lipophilic than exogenously applied oxytocin and therefore, a better distribution and a longer effect on the receptors occur. Beside the stability against proteases, this may also contribute to the prolonged increase of uterine tone activity. After administration of 600 µg of carbetocin, in sows a bicompartimental kinetic was observed. The elimination half-life is approximately 85 - 100 min. There are no essential differences between intramuscular and intravenous administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Chlorocresol
Acetic acid (glacial)
Sodium acetate trihydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Major 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:
3 years

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

6.4. Special precautions for storage
Store in a refrigerator (2 - 8 °C). Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging
Colourless glass injection vial, type I, containing 10 ml, 20 ml or 50 ml, respectively, solution for injection closed with a fluorinated bromobutyl rubber stopper and sealed with an aluminium cap.
1 x 10 ml, 1 x 20 ml or 1 x 50 ml solution for injection, packaged in an outer cardboard box.

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Veyx-Pharma GmbH
Söhreweg 6
34639 Schwarzenborn
Germany

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

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

for 10 ml / 20 ml / 50 ml vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Hypophysin LA 70 µg/ml solution for injection for cattle and pigs
Depotocin 70 µg/ml solution for injection for cattle and pigs (AT/DE)
Hypophysin LA 70 microgram/ml solution for injection for cattle and pigs (IE/UK)
Hypophysin 70 µg/ml solution for injection for cattle and pigs (EE)
Carbetocin

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml solution for injection contains:
Active substance:
Carbetocin 70.00 µg
Excipients:
Chlorocresol 1.00 mg

3. PHARMACEUTICAL FORM

Solution for injection.

4. PACKAGE SIZE

1 x 10 ml
1 x 20 ml
1 x 50 ml

5. TARGET SPECIES

Cattle, pigs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For intramuscular or intravenous use. Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period

Cattle, pigs	Meat and offal:	Zero days
Cattle	Milk:	Zero hours

9. SPECIAL WARNING(S), IF NECESSARY

Pregnant and breast feeding women should avoid handling this product.
Read the package leaflet before use.

10. EXPIRY DATE

Expiry date: month/year
Once broached, use by:
Shelf life after first broaching the vial: 28 days

11. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 - 8 °C). Keep the vial in the outer carton in order to protect from light.

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 SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Veyx-Pharma GmbH
Söhreweg 6
34639 Schwarzenborn
Germany

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch number:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

20 ml / 50 ml vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Hypophysin LA 70 µg/ml solution for injection for cattle and pigs
Depotocin 70 µg/ml solution for injection for cattle and pigs (AT/DE)
Hypophysin LA 70 microgram/ml solution for injection for cattle and pigs (IE/UK)
Hypophysin 70 µg/ml solution for injection for cattle and pigs (EE)
Carbetocin

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml solution for injection contains:
Active substance:
Carbetocin 70.00 µg
Excipients:
Chlorocresol 1.00 mg

3. PHARMACEUTICAL FORM

4. PACKAGE SIZE

20 ml
50 ml

5. TARGET SPECIES

Cattle, pigs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For intramuscular or intravenous use. Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period

Cattle, pigs	Meat and offal:	Zero days
Cattle	Milk:	Zero hours

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

Expiry date: month/year
Once broached, use by:
Shelf life after first broaching the vial: 28 days

11. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 - 8 °C). Keep the vial in the outer carton in order to protect from light.

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

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

Veyx-Pharma GmbH
Söhreweg 6
34639 Schwarzenborn
Germany

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch number:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10 ml vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Hypophysin LA 70 µg/ml solution for injection for cattle and pigs
Depotocin 70 µg/ml solution for injection for cattle and pigs (AT/DE)
Hypophysin LA 70 microgram/ml solution for injection for cattle and pigs (IE/UK)
Hypophysin 70 µg/ml solution for injection for cattle and pigs (EE)
Carbetocin

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

70 µg/ml

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

10 ml

4. ROUTE(S) OF ADMINISTRATION

For intramuscular or intravenous use.

5. WITHDRAWAL PERIOD

Withdrawal period

Cattle, pigs	Meat and offal:	Zero days
Cattle	Milk:	Zero hours

6. BATCH NUMBER

Batch number:

7. EXPIRY DATE

Expiry date: month/year
Once broached, use by:

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:

Hypophysin LA 70 µg/ml solution for injection for cattle and pigs
Depotocin 70 µg/ml solution for injection for cattle and pigs (AT/DE)
Hypophysin LA 70 microgram/ml solution for injection for cattle and pigs (IE/UK)
Hypophysin 70 µg/ml solution for injection for cattle and pigs (EE)

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

Marketing authorization holder and manufacturer responsible for batch release:
Veyx-Pharma GmbH
Söhreweg 6
34639 Schwarzenborn
Germany

Manufacturer responsible for batch release:
Veyx Pharma BV
Forellenweg 16
NL-4941 SJ Raamsdonksveer
The Netherlands

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Hypophysin LA 70 µg/ml solution for injection for cattle and pigs
Carbetocin

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS

Hypophysin LA is a clear colourless solution for injection containing:
Active substance:
Carbetocin 70.00 µg/ml
Excipients:
Chlorocresol 1.00 mg/ml

4. INDICATION(S)

Cows:
- Uterine atony during the puerperal period
- Placental retention as a consequence of uterine atony
- Initiation of milk ejection in stress-induced agalactia or in conditions requiring udder emptying

Sows:
- Acceleration or restart of parturition after disruption of uterine contractions (uterine atony or inertia) following the expulsion of at least one piglet
- Supportive therapy of mastitis-metritis-agalactia (MMA-) syndrome
- Initiation of milk ejection
- Shortening of total parturition duration as a component of synchronisation of parturition in sows The product may be applied to sows which have previously been administered an appropriate $PGF_{2\alpha}$ or $PGF_{2\alpha}$ analogue (e.g. cloprostenol) not prior to day 114 of pregnancy and have not started farrowing within 24 hours after the $PGF_{2\alpha}$ or $PGF_{2\alpha}$ analogue injection (day 1 of pregnancy is the last day of insemination)

5. CONTRAINDICATIONS

Do not administer to accelerate parturition if cervix is not opened or if there is a mechanical cause for the delayed parturition such as physical obstruction, positional and postural abnormalities, convulsive labour, threatened rupture of uterus, uterine torsion, relative foetal oversize or deformities of the birth canal.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

In very rare cases carbetocin may have a uterotonic effect in the late pregnancy.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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, pigs

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

For intramuscular or intravenous use.

Cows
For all indications:
3.0 – 5.0 ml/animal, corresponding to 210 – 350 µg carbetocin/animal
Sows
For shortening of total parturition duration as a part of the synchronisation of parturition:
0.5 ml/animal, corresponding to 35 µg carbetocin/animal
For acceleration or restart of parturition after disruption of uterine contractions (uterine atony or inertia) following the expulsion of at least one piglet:
0.5 -1.0 ml/animal, corresponding to 35 - 70 µg carbetocin/animal
For MMA and milk ejection:
1.5 – 3.0 ml/animal, corresponding to 105 – 210 µg carbetocin/animal

The dosage requirements can be variable within the indicated limits based on the assessment of the veterinarian.

In case of treatment for milk ejection in the cow and sow or supportive therapy in MMA-syndrome in sow, a repeated administration is possible after 1 to 2 days. The interval between two injections should not be shorter than 24 hours.
For all other indications stated in section 4 [indications] the product should be administered once.

The rubber stopper of the vial may be safely punctured up to 25 times. Otherwise, automatic syringe equipment, or a suitable draw-off needle, should be used for the 20 and 50 ml vials to avoid excessive puncturing of the closure.

9. ADVICE ON CORRECT ADMINISTRATION

None.

10. WITHDRAWAL PERIOD

Cattle, pigs	Meat and offal:	Zero days
Cattle	Milk:	Zero hours

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Store in a refrigerator (2 - 8 °C).
Keep the vial in the outer carton in order to protect from light.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and vial label after "EXP". The expiry date refers to the last day of that month. Shelf life after first opening the immediate packaging: 28 days
When the container is broached (opened) for the first time, using the in-use shelf-life which is specified on this package insert, the date on which any product remaining in the vial should be discarded should be worked out. This discard date should be written in the space provided on the label.

12. SPECIAL WARNING(S)

Special warnings for each target species:
The responsiveness to carbetocin of the myometrium is likely to be close to zero from the 5th to the 11th day post-partum. Therefore, the administration of the veterinary medicinal product during this period is likely to be inefficient and should be avoided.

If treatment with carbetocin should fail, then it is advisable to reconsider the aetiology of the condition, specifically if hypocalcaemia could be a complicating factor.

In case of severe septic metritis, appropriate concomitant therapy should be instigated when administering the veterinary medicinal product.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
In case of accidental self-injection uterine contractions could be induced in pregnant women.
Pregnant women, women post-partum and breast-feeding women should not administer this product, in order to avoid an accidental exposure.
In case of an accidental self-injection of the veterinary medicinal product in non-pregnant women the following effects may occur: facial flushing and warmth, lower abdominal pain. These effects usually disappear within a short span of time.

In the case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
Personal protective equipment consisting of disposable gloves should be worn when handling the veterinary medicinal product.
Carbetocin may be absorbed through the skin. In case of accidental contact with the skin, the corresponding area should be thoroughly cleaned with soap and water.
In case of contact with the eyes, they should be thoroughly rinsed with water.
People with known hypersensitivity to carbetocin or any of the excipients should avoid contact with the veterinary medicinal product.
Women of childbearing age should administer the product with special caution.

Use during pregnancy, lactation or lay:
The veterinary medicinal product is indicated to induce milk ejection.
See also 5. Contraindications.

Interaction with other medicinal products and other forms of interaction:

The administration of oxytocin after the administration of the veterinary medicinal product is unnecessary. Due to a possible intensification of the effect of oxytocin, undesirable uterine spasms may be induced.

Overdose (symptoms, emergency procedures, antidotes):
An overdosing of more than 400 µg of carbetocin/animal could increase the stillbirth rate in older sows if administered during prolonged parturition.

An overdosing of 600 µg of carbetocin/animal may induce profuse lactation in sows that may result in diarrhoea, reduced weight gain and increased mortality in their piglets.
Carbetocin is considered as moderately irritant. At the injection sites of treated animals, focal lymphocytic infiltration was observed at higher doses (1000 µg of carbetocin/animal).

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. Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.
Any unused veterinary medicinal product or waste materials 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

1 vial (10 ml) in a cardboard box
1 vial (20 ml) in a cardboard box
1 vial (50 ml) in a cardboard box

Not all pack sizes may be marketed.