Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURES

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Depotocin 35 µg/ml
Depotocin 70 µg/ml

Date: 22 July 2014

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0156/001-002/DC
Name, strength and pharmaceutical form	Depotocin 35 µg/ml, Solution for injection Depotocin 70 µg/ml, Solution for injection
Applicant	Veyx-Pharma GmbH Söhreweg 6 34639 Schwarzenborn GERMANY
Active substance(s)	Carbetocin
ATC Vetcode	QH01BB03
Target species	Cattle, Pig
Indication for use	Cow: - 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 Sow: - Acceleration or restart of parturition after disruption of uterine contractions (uterine atony or inertia) following the expulsion of at least 1 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

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

	appropriate $PGF_{2\alpha}$ (e.g. cloprostenol) not prior to day 114 of pregnancy and have not started farrowing within 24 hours after the $PGF_{2\alpha}$ injection (day 1 of pregnancy is the last day of insemination)

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid applications in accordance with Article 13(3) of Directive 2001/82/EC as amended
Date of completion of the original Decentralised procedure	23 April 2014
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	AT, BE, BG, CZ, EE, ES, FR, HU, IE, IT, LT, LU, LV, NL, PL, PT, RO, SI, SK, UK

I. SCIENTIFIC OVERVIEW

Depotocin 35µg/ml and Depotocin 70µg/ml solutions are hybrid applications for injection containing the active ingredient carbetocin for use in cows and sows. The reference product is LongActon, authorised in Germany in 2000.

The products in question are produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the products can be safely used for the following indications:
Cow:
- 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

Sow:
- Acceleration or restart of parturition after disruption of uterine contractions (uterine atony or inertia)

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

following the expulsion of at least 1 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 $PGF_{2\alpha}$ (e.g. cloprostenol) not prior to day 114 of pregnancy and have not started farrowing within 24 hours after the $PGF_{2\alpha}$ injection (day 1 of pregnancy is the last day of insemination)

The safety and efficacy aspects of these products are identical to the reference product.
The products are safe for the end user, the consumer of foodstuffs from treated animals and for the environment when used as recommended. Suitable warnings and precautions are indicated in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The products contain 35µg/ml resp. 70 µg/ml of Carbetocin and the excipients chlorocresol, sodium acetate trihydrate, acetic acid, glacial, sodium hydroxide and water for injections.

The container/closure system consists of colourless type I glass injection vials with fluorinated bromobutyl rubber stoppers and aluminium caps.

The choice of the formulation and the presence of the preservative are justified.

The products have an established pharmaceutical form and their development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The products are manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

C. Control of Starting Materials

The active substance is carbetocin, an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on intermediate products

There are no intermediate products.

E. Control Tests on the Finished Product

The finished product specifications control the relevant parameters for the pharmaceutical form. The tests in the specifications, and their limits, have been justified and are considered appropriate to adequately control the quality of the products.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specifications.

F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished products have been provided in accordance with applicable European guidelines, demonstrating the stability of the products throughout their shelf lifes when stored under the approved conditions.

The claim of 28 days stability after broaching is based on the demonstration of stability for a batch broached and stored at 5 °C ± 3 °C through 4 weeks for the 10 ml and 100 ml vials.

G. Other Information

Not applicable.

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

See Part IV A

Toxicological Studies

These are hybrid applications according to Article 13(3) of Directive 2001/82/EC as amended based on the essential similarity of the reference product LongActon, another carbetocin-containing injection solution for use in cattle and pig.
So the applicant is not required to submit data from toxicological studies.

Warnings and precautions as listed on the product literature go in part beyond those set out for the reference product and are adequate to ensure safety of the products to users.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the products.

Environmental Risk Assessment

Phase I

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. Both medicinal products are for single intramuscular or intravenous injection for individual animals only and are intensively metabolised in the animal.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the products are used as directed.

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

Conclusion

Based on the data provided, the ERA can stop at Phase I. The products are not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues documentation

Residue Studies

As hybrid applications according to Article 13 have been made for Depotocin 35µg/ml and Depotocin 70µg/ml solutions for injection, and bioequivalence with a reference product is assumed based on the composition of the products, residue depletion studies were not required.
Products are aqueous solutions, the composition is similar to the reference product and the maximum intended dose is not higher than for the reference product. Residue depletion studies are considered as not necessary.

MRLs

Carbetocin

Carbetocin is listed in Table 1 of Commission Regulation (EU) No 37/2010 for all mammalian food producing species. In accordance with Council Regulation (EC) No 470/2009 no MRL is required.

Pharmacologically active substance(s)	Animal species	Other provisions
Carbetocin	All mammalian food-producing species	

Chlorocresol

Maximum residues limits (MRL) for chlorocresol are published in Table 1 of Commission Regulation (EU) No 37/2010. In accordance with Council Regulation (EC) No 470/2009 no MRL is required.

Pharmacologically active substance(s)	Animal species	Other provisions
Chlorocresol	All food-producing species	

Withdrawal Periods

Based on the data provided above, the following withdrawal periods are justified:

Cattle:	Meat and offal	0 days
	Milk:	0 days
Pigs:	Meat and offal	0 days

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

IV. CLINICAL ASSESSMENT (EFFICACY)

As a hybrid application according to Article 13 (3) has been made for Depotocin 35µg/ml and Depotocin 70µg/ml solutions for injection, and bioequivalence with a reference product is assumed based on the composition of the products, efficacy studies were principally not required. However, as the efficacy claims for Depotocin differ in some aspects from those of the reference product, a hybrid application was mandatory and deviations from the reference product have been supported by specific data.

IV.A Pre-Clinical Studies

Pharmacology

The active ingredient of Depotocin 35µg/ml and Depotocin 70µg/ml is carbetocin, a synthetic oxytocin-analogue. Due to its chemical structure it is suggested to be more stable to enzymatic degradation than natural oxytocin.

The primary pharmacodynamic effect of carbetocin is comparable to that of oxytocin, but is prolonged. It is directed to the smooth muscles of the reproductive organs. At the estrogen stimulated uterus carbetocin like oxytocin causes synchronised, regular, increased and directed contractions. In the mammary gland it induces contraction of the myoepithelium of the basket cells in the alveola and of the lactiferous ducts and causes relaxation of the teat sphincter.

The therapeutic indications of Depotocin 35µg/ml and Depotocin 70µg/ml in cows and sows are based on these effects.

Both products can be administered intravenously or intramuscularly. The pharmacokinetic properties of carbetocin are largely similar at both injection routes.

Tolerance in the Target Species of Animals

Because Depotocin 35µg/ml and 70µg/ml are hybrid-generics to an authorised reference product, the same safety information has been given with the product literature by and large as approved for the latter. It has been completed by some additional warnings in order to improve the safe and effective use of the products.

As an additional support for the safety of carbetocin, two Periodic Safety Update Reports (PSURs) related to another product of the same applicant have been submitted, that is composed like Depotocin 70µg/ml and has been authorised in Germany in 2004.

These reports covered the period from December 2003 to September 2012. In this period a large number of pigs and cows have been treated with the product in EU-

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

countries and non EU-countries. No adverse event reports had been received in this period.

IV.B Clinical Studies

Based on the oxytocin-like properties of the active ingredient carbetocin, Depotocin 35µg/ml and Depotocin 70µg/ml are indicated in cows to stimulate uterine motility during the puerperal period, to treat placenta retention and to initiate milk ejection in case of stress-induced agalactia and when udder emptying is required.
In sows the products are indicated for the stimulation of uterine motility at farrowing, as a component of a parturition synchronisation regime and for the treatment of mastitis-metritis-agalactia syndrome.

Laboratory and Field Trials

The applicant has conducted laboratory and field studies which show that the treatment dose in sows can be reduced in comparison to the doses authorised for the reference product in indications related to parturition.

In other indications for cows and sows the doses approved for the authorised reference product have been adopted.

V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the products are used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the products for humans and the environment is acceptable.

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal products. The current SPC is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."