27 July 2018
EMA/CVMP/405782/2018
Committee for Medicinal Products for Veterinary Use

# European public MRL assessment report (EPMAR)

## Porcine prolactin (porcine species)

On 16 May 2018 the European Commission adopted a Regulation[1] establishing maximum residue limits for porcine prolactin in porcine species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Porcine prolactin is intended for use in sows for the treatment and prevention of primary agalactia and mastitis-metritis-agalactia syndrome and in suckling piglets for reducing mortality and stimulating the immune system.

Biochefa Pharmaceutical Research and Production Plant submitted to the European Medicines Agency an application for the establishment of maximum residue limits on 4 September 2015.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 9 November 2017 the establishment of maximum residue limits for porcine prolactin in porcine species.

Subsequently the Commission recommended on 29 March 2018 maximum residue limits in porcine species are established. This recommendation was confirmed on 19 April 2018 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 16 May 2018.

[1] Commission Implementing Regulation (EU) No 2018/721 , O.J. L 122 , of 17 May 2018

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# Summary of the scientific discussion for the establishment of MRLs

| | |
|---|---|
| Substance name: | Porcine prolactin |
| Therapeutic class: | Agents acting on the reproductive system |
| Procedure number: | EMEA/V/MRL/004113/FULL/0001 |
| Applicant: | Ryszka Florian "Biochefa" Pharmaceutical Research and Production Plant |
| Target species: | Porcine |
| Intended therapeutic indication: | Primary agalactia and mastitis-metritis-agalactia syndrome |
| Route(s) of administration: | Intramuscular, oral |

## 1. Introduction

Porcine prolactin is a peptide hormone secreted by the pituitary of the pig. Prolactin stimulates the production of milk by the mammary gland.

It is intended for use in sows (weighing 130-160 kg) in the treatment and prevention of primary agalactia and mastitis-metritis-agalactia syndrome as one or two doses of 2 mg (100 IU) per animal by the intramuscular route, and in suckling piglets for reducing mortality and stimulating the immune system, as a single dose of 0.2-0.5 mg/animal (10–25 IU) (weighing 0.9-1.4 kg) by the oral route.

## 2. Scientific risk assessment

### *2.1. Safety assessment*

Literature data have been provided to cover the pharmacodynamics, pharmacokinetic and toxicological properties of prolactin.

#### 2.1.1. Overview of pharmacological properties

Literature data have been provided to illustrate the pharmacodynamic properties of prolactin, with an emphasis on its intended use in piglets and sows. Prolactin is important for mammogenesis and has several modulating effects on a number of tissues (e.g. decidua, brain, endothelial cells and immune cells), where it acts more like a cytokine than a hormone.

The effect of exogenous prolactin on suckling pigs and lactating sows are described. Higher prolactin levels at birth are correlated with a higher survival rate in piglets and prolactin is the main factor affecting the development of the mammary gland during pregnancy. Hyperprolactinemia as well as hypoprolactinemia may lead to impairment of mainly the reproductive system.

Prophylactic administration of 5 mg exogenous prolactin to sows is associated with a lesser number of sows developing mastitis-metritis-agalactia, a higher body weight of the piglets and a larger litter size. Oral administration of exogenous prolactin (0.1 mg/kg bw, 0.5 mg/kg bw, 1 mg/kg bw) to piglets in the first hour after farrowing reduces the number of piglet deaths in the period after birth and before weaning and results in a higher daily weight gain. Positive effects have been shown after oral application of prolactin to newborn piglets and indicates therefore a good oral bioavailability of prolactin in newborn piglets.

Release of prolactin from the pituitary gland is highly dependent on the oestrus cycle. Thus, release is highest immediately before parturition and decreases gradually during lactation: from 4.4 to 13.0 ng/ml (early pregnancy) to 124.2 ng/ml to 147.3 ng/ml during labour and about 40 ng/ml on the fifth day of lactation.

A bioavailability study in Wistar rats after intramuscular, intraperitoneal or intranasal administration of prolactin shows that the bioavailability of prolactin is highest after intramuscular administration, but also after intranasal application its bioavailability is more than 80%.

Pharmacokinetic data after oral treatment of piglets suggested oral bioavailability in newborns. Data on oral bioavailabilty in older piglets or adults or in humans are not available.

A distribution study in Wistar rats after subcutaneous application of prolactin demonstrates that prolactin is distributed in various organs with emphasis on the mammary gland, blood and pituitary gland.

A study in rabbits demonstrates that prolactin is metabolised in kidneys and liver, kidneys being the main and most effective route. Approximately 90% of prolactin is eliminated from blood after 12 hours (depending on the administration route). No information is available regarding the other possible elimination routes.

### 2.1.2. Calculation of pharmacological ADI, if relevant

Data to allow the derivation of a pharmacological ADI have not been provided.

However, a pharmacological ADI or equivalent limit is considered not necessary in light of the intended dose and use of the substance, since it was satisfactorily demonstrated that prolactin levels were within the physiological range in piglets after the intended oral dose of 0.2 mg/animal and within 13 hours after intramuscular administration of 5 mg/animal in sows.

### 2.1.3. Overview of toxicology

Data from standard toxicological studies necessary for the establishment of a toxicological ADI are not available. Instead, publicly available studies regarding efficacy of prolactin in the target species were submitted. The data were considered not relevant in respect to toxicity, but gave some information on the natural range of plasma prolactin in sows during different life stages (prepubertal, pregnancy, parturition and lactation).

However, data on toxicology are not considered necessary in light of the intended doses and the use of the substance since it was satisfactorily demonstrated that prolactin levels were within the physiological range in piglets after administration of the intended oral dose of 0.2 mg/animal and within 13 hours after intramuscular administration of 5 mg/animal in sows.

### 2.1.4. Calculation of the toxicological ADI or alternative limit

No toxicological ADI could be derived from the submitted data. However, no toxicological ADI or equivalent limit is considered necessary in light of the proposed use and the intended doses of the substance since it was satisfactorily demonstrated that the prolactin levels were within the physiological range in piglets after administration of the intended oral dose of 0.2 mg/animal and within 13 hours after intramuscular administration of 5 mg/animal in sows.

### 2.1.5. Overview of microbiological properties of residues

No microbiological data were provided, which is acceptable as no microbiological effects are expected for a substance of this type.

### 2.1.6. Calculation of microbiological ADI

As no microbiological effects are expected, the establishment of a microbiological ADI is not considered necessary.

### 2.1.7. Observations in humans

Physiological levels of prolactin in (non-pregnant) women and men are over 10-fold less than the levels seen in pregnant women close to term and newborns (up to 500 ng/ml). A high inter- and intra-individual variability and a diurnal cycle with highest prolactin levels during the late sleeping phase is known. Hyperprolactinemia is defined at levels over 25 µg/l in women and 20 µg/l in men and is associated with several clinical signs.

### 2.1.8. Findings of EU or international scientific bodies

No relevant evaluations by EU or international scientific bodies were identified.

### 2.1.9. Overall conclusions on the ADI

The establishment of a pharmacological ADI and a toxicological ADI (or of equivalent limits), and therefore an overall ADI are considered not necessary in light of the intended doses and use of the substance since it was satisfactorily demonstrated that prolactin levels were within the physiological range in piglets after the intended oral dose of 0.2 mg/animal and within 13 hours after intramuscular administration of 5 mg/animal in sows.

A microbiological ADI is not considered necessary for this substance as no microbiological effects are expected for a substance of this type.

## *2.2. Residues assessment*

Literature data, as well as an original study in piglets, were provided to cover the metabolism and residue kinetics of prolactin.

### 2.2.1. Pharmacokinetics in target species

Regarding absorption, limited data after oral application of prolactin in piglets and after subcutaneous and intramuscular administration of prolactin in sows are available. In piglets, prolactin serum levels were increased one hour after oral administration, showing a fast absorption of prolactin in newborn piglets. After intramuscular injection of 5 mg prolactin to gilts, highest prolactin levels in plasma were measured after approximately 2.5 hours (approximately 20 ng/ml). After subcutaneous administration of 15 mg prolactin to sows three times daily for 21 days (day 2 to day 23 of lactation) an increase in prolactin serum levels was observed at day 7, 14 and 21 of lactation, demonstrating resorption of prolactin after subcutaneous administration; however, the time of $C_{max}$ was not reported.

Concerning elimination, limited data were available from two studies. One study conducted in three sows (130-135 kg bw) reports plasma concentrations only. It is shown that after a single intravenous injection of porcine prolactin (5 mg) mean prolactin concentration increased from 0.2 ng/ml to more than 20 ng/ml

plasma. Concentrations decreased until 1.5 hours after injection and then increased again and reached the maximum of 24 ng/ml three hours after treatment. Thirteen hours after administration of prolactin, the prolactin concentration reached basal levels. In another study in 22 prepubertal gilts, plasma concentrations after intramuscular prolactin injection decreased to basal levels 12 hours after administration.

No data on distribution and metabolism in the target animals are available.

No information concerning elimination routes (e.g. urine, faeces, bile) was provided.

### 2.2.2. Residue depletion studies

A residue depletion study with the purpose to assess the levels of prolactin in piglets' plasma immediately after treatment was available. Five animals were treated immediately after birth with 0.2 mg porcine prolactin in saline solution (0.2 ml), using the oral route of administration. Additionally, 5 animals acted as controls and received saline only. Plasma levels of prolactin were measured at 1, 24 and 48 hours after treatment. There were differences between treated and control groups at the 1 hour timepoint (higher levels in the treated group), but at 24 and 48 hours there was no difference between the two groups. Levels of prolactin were assayed using ELISA kits; no analytical method validation data were provided. However, comparison with literature data indicate that prolactin plasma levels in treated newborn piglets are comparable to physiological levels in untreated piglets.

As part of this study, the pigs were slaughtered at 150 days post treatment and edible tissues (liver, kidneys, heart, fat and muscle) were analysed for prolactin. Treatment and control groups did not differ significantly. The study was not performed to GLP and did not follow standard guidelines on residues studies. Since the tissue data are not considered to be pivotal, this is acceptable.

No data were provided for the second target population, peri-parturient sows.

**Selection of marker residue and ratio of marker to total residues**

No marker residue or ratio of marker to total residues is proposed as a "No MRL required" classification is recommended.

### 2.2.3. Monitoring or exposure data

Provided literature data show a wide range of prolactin levels in milk, for example, for cow milk levels of 120 ng/ml (in colostrum) to 15 ng/ml (in the fourth week of lactation) were reported. Data from goat and sheep milk indicate prolactin levels of 63 and 175 ng/ml.

### 2.2.4. Analytical method for monitoring of residues

A "No MRL required" status has been proposed and, in line with this, no analytical method validated according to the requirements laid down in Volume 8 has been presented.

### 2.2.5. Findings of EU or international scientific bodies

No relevant evaluations by EU or international scientific bodies were identified.

# 3. Risk management considerations

## *3.1. Potential effects on the microorganisms used for industrial food processing*

As the substance is not expected to possess antimicrobial activity no effects on microorganisms used for industrial food processing are expected.

## *3.2. Other relevant risk management considerations for the establishment of maximum residue limits*

As prolactin is endogenously produced in mammals, establishing numerical MRLs would result in difficulties for residue monitoring authorities as it would not be possible to discriminate between residues of administered prolactin and residues of endogenously produced prolactin. However, there is a need to ensure that prolactin-containing products will not be used in a way that would lead to residues at levels above those that occur naturally. A restriction to oral use and a maximum dose of 0.2 mg/animal is therefore proposed for use in piglets, and a restriction to a maximum dose of 5 mg/animal is proposed for use in sows. These restrictions correspond to the conditions used in the studies in piglets and sows for which limited residue data are available.

No other relevant factors were identified for consideration of the risk management recommendations.

## *3.3. Elaboration of MRLs*

Prolactin is a natural substance that is produced endogenously in mammals, including humans. Therefore, the ADI concept is not suitable to address the safety of residues as a result of the therapeutic treatment of pigs with prolactin. The CVMP considers that consumer safety is ensured when residues of administered porcine prolactin to pigs is maintained within the range of naturally occurring levels. The available data demonstrate that the use of porcine prolactin in piglets at the oral dose of 0.2 mg/animal does not lead to residues above naturally occurring levels. Data in sows show a rapid decline to basal levels after single intramuscular injection of 5 mg/animal. A “No MRL required” classification is therefore recommended in piglets and sows, with a restriction on the dose and route of administration.

## *3.4. Considerations on possible extrapolation of MRLs*

In line with Article 5 of Regulation (EC) No 470/2009, the CVMP considered the possibility of extrapolating the maximum residue limits recommended for porcine species to other food-producing species and food commodities, taking into account the provisions laid down in Regulation (EU) 2017/880. However, the recommendation for the “No MRL required” status is based on the fact that in piglets and sows prolactin plasma concentrations after treatment are within the physiological range. Such data are not available for other species. Therefore, extrapolation of the proposed MRL classification is not recommended.

## *3.5. Conclusions and recommendation for the establishment of maximum residue limits*

Having considered that:

- porcine prolactin is a peptide hormone naturally occurring in pigs,
- prolactin is endogenously produced in humans,
- prolactin is a natural component of the human diet,

- serum concentrations of porcine prolactin in treated gilts and sows were within physiological levels by 13 hours following treatment,
- prolactin levels in treated newborn piglets were within physiological levels,
- a limit on the route of administration and dose in piglets and on the dose in sows is necessary in order to ensure that prolactin levels remain within physiological levels in treated animals,
- although the intended dose in piglets was between 0.2 and 0.5 mg/animal, based on the available residue data the maximum accepted dose in these animals is 0.2 mg/animal,

the Committee concludes that the establishment of maximum residue limits for porcine prolactin is not necessary for the protection of human health, and therefore recommends the inclusion of porcine prolactin in table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

| **Pharmaco -logically active substance** | **Marker residue** | **Animal species** | **MRLs** | **Target tissues** | **Other provisions** | **Therapeutic classification** |
|---|---|---|---|---|---|---|
| Porcine prolactin | NOT APPLICABLE | Porcine | No MRL required | NOT APPLICABLE | For oral use in newborn piglets at a dose of up to 0.2 mg /animal.<br>For use in sows at a total dose of up to 5 mg /animal. | Agents acting on the reproductive system |

# 4. Background information on the procedure

Submission of the dossier: 4 September 2015

Steps taken for assessment of the substance

Application validated: 23 September 2015

Clock started: 24 September 2015

List of questions adopted: 21 January 2016

Response to list of questions submitted: 10 May 2017

Clock restarted: 15 May 2017

List of outstanding issues adopted: 13 July 2017

Response to list of outstanding issues submitted: 11 October 2017

Clock restarted 11 October 2017

CVMP opinion adopted: 9 November 2017