14 February 2012
EMA/CVMP/664126/2010
Committee for Medicinal Products for Veterinary Use

# European public MRL assessment report (EPMAR)

## Methylprednisolone (bovine milk after provisional MRLs)

On 13 February 2012 the European Commission adopted a Regulation[1] establishing maximum residue limits for methylprednisolone in bovine milk, 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.

Methylprednisolone is intended for use in bovine species for the treatment of respiratory disease and urogenital infections in cattle by intramuscular injection in combination with antibiotics. The recommended dose is equivalent to 400 µg/kg bw/day of methylprednisolone for 4 to 5 days.

MERIAL S.A.S. submitted the application for the extension of maximum residue limits to the European Medicines Agency, on 2 April 2009.

Methylprednisolone had maximum residue limits already established[2] for bovine species and provisional maximum residue limits already established[3] for bovine milk.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 5 May 2011 the establishment of maximum residue limits for methylprednisolone in bovine milk.

Subsequently the Commission recommended on 21 December 2011 that maximum residue limits in bovine milk are established. This recommendation was confirmed on 11 January 2012 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 13 February 2012.

[1] Commission Implementing Regulation (EU) No 122/2012,O.J. L 40, of 14.02.2012
[2] Commission Regulation (EC) No 77/2002, O.J. L 16, of 18.01.2002
[3] Commission Regulation (EU) No 761/2010, O.J. L 224 of 26.08.2010

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# Summary of the scientific discussion for the establishment of MRLs

| | |
|---|---|
| Substance name: | Methylprednisolone |
| Therapeutic class: | Corticoides/Glucocorticoides |
| Procedure number: | EU/09/167/MER |
| Applicant: | Merial S.A.S. |
| Target species: | Bovine |
| Intended therapeutic indication: | Treatment of bovine respiratory disease (BRD) and urogenital infections |
| Route (s) of administration: | Intramuscular |

## 1. Introduction

Methylprednisolone is a synthetic corticosteroid, which is used in veterinary medicine as the free alcohol, and as various esters. It is the 6α-methyl derivative of prednisolone. Methylprednisolone is used in the treatment of respiratory disease and urogenital infections in cattle by intramuscular injection in combination with antibiotics. The recommended dose is equivalent to 400 µg/kg bw/day of methylprednisolone for 4 to 5 days.

Methylprednisolone is also used in human medicine, as the free alcohol, as the acetate, the aceponate and as the sodium succinate.

Methylprednisolone is included in Commission Regulation (EU) No 37/2010 of 22 December 2009, as amended, in accordance with the following table:

| Pharmaco-logically active substance | Marker residue | Animal species | MRLs | Target tissues | Other provisions | Therapeutic classification |
|---|---|---|---|---|---|---|
| Methyl-prednisolone | Methyl-prednisolone | Bovine | 10 µg/kg<br>10 µg/kg<br>10 µg/kg<br>10 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney | | Corticoids / Glucocorticoids |
| | | | 2 µg/kg | Milk | Provisional MRL expires on 01.07.2011 | |

Following the establishment of a provisional MRL, additional data concerning the validation of the analytical method for the monitoring of residues in milk were submitted to allow for the establishment of a final maximum residue limit for bovine milk.

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# 2. Scientific risk assessment

## *2.1. Safety assessment*

Methylprednisolone was previously assessed by the CVMP and a pharmacological ADI of 0.16 µg/kg bw (i.e. 9.6 µg/person) was established by applying a safety factor of 100 to the NOEL of 16 µg/kg bw/day which was established in a study investigating tyrosine aminotransferase activity in rats. Therefore no further assessment regarding the establishment of the ADI of the substance is required.

## *2.2. Residues assessment*

### 2.2.1. Pharmacokinetics in target species

Pharmacokinetic data had previously been assessed by the CVMP when establishing MRLs for bovine tissues (but not milk) and the conclusions of the assessment are summarised in the paragraphs below. No additional pharmacokinetic studies are available.

Pharmacokinetic studies in humans, laboratory animals, cattle and horses showed that the esters of methylprednisolone such as the acetate, sodium succinate, the hemisuccinate and the phosphate, were rapidly converted *in vivo* to methylprednisolone and that methylprednisolone was responsible for the pharmacological activity. The plasma half-life of the esters was generally less than 10 minutes.

In humans, the oral bioavailability was generally high (80 to 99%) but depended on the dosage form. Methylprednisolone was widely distributed to the tissues, crossed the blood-brain barrier and was secreted in breast milk. After oral administration of about 1 mg/kg bw, the half-life of elimination in humans was in the range 1 to 3 hours; the volume of distribution was in the range 1 to 1.5 l/kg. The time to peak plasma concentration was 1 to 2 hours. Over the dose range 10 to 3000 mg, the plasma clearance was around 6.5 ml/min/kg. Plasma protein binding was approximately 77%.

In humans and laboratory and farm animals, methylprednisolone is reversibly metabolised to methylprednisone, which is pharmacologically inactive and formed by oxidation of the $C_{11}$ hydroxyl group to the ketone. In humans the plasma concentration of methylprednisone is around 10% that of the parent methylprednisolone. The metabolism of methylprednisolone followed similar pathways to those of prednisolone, except for the inability of methylprednisolone to undergo hydroxylation at the $C_6$ position. In both humans and dogs, methylprednisolone, like prednisolone was metabolised to plasma and urinary metabolites which lacked corticosteroid activity.

### 2.2.2. Residue depletion studies

Cattle were given daily intramuscular injections of a proprietary product containing methylprednisolone, together with the antibiotics neomycin and benzylpenicillin, for 5 consecutive days. The dose of methylprednisolone corresponded to 400 µg/kg bw/day. All 24 cows were milked twice daily for 13 days after the first administration. Residues of methylprednisolone in milk were determined using the proposed routine analytical method based on HPLC with MS/MS detection. The limit of quantification was 0.5 µg/kg. At the first milking after the last administration, residues of methylprednisolone in milk ranged from 3.32 µg/kg to 12.9 µg/kg. At the 11$^{th}$ milking (6 days) after last administration, residues of methylprednisolone in milk ranged from below 0.5 µg/kg to 1.01 µg/kg and at the 12$^{th}$ milking nearly half of the samples were below the limit of quantification.

**Selection of marker residue and target tissues**

In the previous evaluation of methylprednisolone the CVMP assessed data from humans, laboratory animals, horses and cattle, which showed that there was an interconversion of methylprednisolone and the biologically inert metabolite methylprednisone. In humans and dogs, both substances were further metabolised to a number of other metabolites; on structural grounds these were not expected to possess corticosteroid activity. The evidence suggested that like dexamethasone and prednisolone, methylprednisolone was metabolised in both humans and animals to substances with no pharmacological activity. Therefore no radiometric studies were required. As the overall ADI was set based on pharmacological effects and the only component with pharmacological effect was the parent compound, methylprednisolone was retained as an appropriate marker residue and the ratio of marker to total residues was thus set at 1.

### 2.2.3. Analytical method for monitoring of residues

The proposed routine analytical method was based on HPLC with MS/MS detection and was described in an internationally recognised format (ISO 78/2). The limit of detection was 0.1 µg/kg and the limit of quantification was 0.5 µg/kg for bovine milk. The method has now been satisfactorily validated in accordance with the requirements of Volume 8 of The Rules Governing Medicinal Products in the EU.

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

No MRLs for methylprednisolone have been established by JECFA/Codex Alimentarius.

## 3. Risk management considerations

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

No data were provided, but as microbiological effects are not expected for this type of substance such data are not required.

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

None.

### *3.3. Elaboration of MRLs*

In the absence of a radiometric study, the MRL has been calculated in relation to the previously unused portion of the ADI (daily intake of residues from edible tissues in cattle is considered to use up to 52% of the ADI leaving 48% available). The maximum MRL value that could be set for milk in order not to exceed the ADI would be 3.1 µg/kg. Having also considered the requirement to set a practicable milk withdrawal period and to retain flexibility to set possible higher MRLs for other species or food commodities in the future, it was concluded that a bovine milk MRL should be set at 2 µg/kg.

**Calculation of theoretical daily intake of residues.**

Detailed calculation of theoretical daily intake of residues.

| Edible tissue or products | Daily consumption (kg) | MRL proposal (µg/kg) | Ratio of the marker/total residue | Amount per edible tissue or product |
|---|---|---|---|---|
| Muscle | 0.3 | 10 | 1 | 3.0 |
| Fat | 0.05 | 10 | 1 | 0.5 |
| Liver | 0.1 | 10 | 1 | 1 |
| Kidney | 0.05 | 10 | 1 | 0.5 |
| Milk | 1.5 | 2 | 1 | 0.5 |
| Total daily intake of residues (µg) | | | | 8.0 |
| TMDI as % of pharmacological ADI (9.6 µg/person) used | | | | 83.3% |

Based on the MRL of 2 µg/kg, the theoretical daily residue intake from milk is 3 µg which is equivalent to 31.3 % of the ADI and taking into account the MRLs already set for the other bovine edible tissues and the proposed MRLs for milk, the theoretical maximum daily intake was calculated to be 83.3% of the ADI.

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

In line with the provisions of Article 5 of Regulation (EU) No 470/09, the Committee considered the possibility of extrapolating the MRL recommended for bovine milk to other food-producing species with a view to ensuring availability of veterinary medicinal products for conditions affecting food producing animals while ensuring a high level of protection of human health.

Extrapolation of MRLs is based on the fact that animal species of the same class exhibit similar patterns of metabolism and residues. When contemplating extrapolating MRLs the CVMP must consider whether the metabolism of the substance in the species/tissue to which extrapolation is proposed is similar to that in the original species/tissue, and in particular whether the established marker residue is produced in the species/tissue to be extrapolated to. In addition the CVMP must consider the consumer exposure to residues that may occur as a result of consumption of the food commodity to which an MRL has been extrapolated. The ratio of marker to total residues is the tool that enables potential total residue levels in a food commodity to be derived from the MRL. As a result of pharmacokinetic differences between species and between tissues/food commodities within species this ratio should ideally be known for each tissue/food commodity of each species in order to allow establishment of MRLs while ensuring consumer safety. However, for minor species it can be considered that limitations due to lack of species specific data will be compensated for by the fact that the exposure of the consumer to residues in minor species is in general limited. At the present time no scientific rationale has been developed that would allow the establishment of safe MRLs in major species without provision of species specific data.

These principles form the basis for the approach described in the Notice to applicants and Guideline - Veterinary medicinal products - Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin (Volume 8 of the Rules governing medicinal products in the European Union), which states that "*Considering the knowledge on the variation of residue depletion within classes of animals and therefore on the exposure assessment, the risk characterisation should also not differ substantially within an animal class*" and further detailed in the Note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL).

While the Note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin allows, in principle, extrapolation of MRLs to minor species it does specify that

there needs to be confirmation that the marker residue occurs in the minor species and demonstration of the applicability of the analytical method proposed for residue control.

No data were made available to confirm the marker residue or to demonstrate the applicability of the relevant analytical methods in tissues and milk in other species. The CVMP considered that without supporting data, extrapolation to other species would not be supported by scientific evidence and thus the possibility that consumers might be at risk of ingestion of residues above safe levels could not be excluded based on the current scientific knowledge. Therefore the CVMP concluded that extrapolation of existing MRLs could not be recommended.

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

Having considered that:

- a pharmacological ADI of 0.16 µg/kg bw (i.e. 9.6 µg/person) was previously established for methylprednisolone,
- methylprednisolone has been retained as the marker residue in milk from bovines and the ratio of marker to total residues set at 1,
- an analytical method is available for monitoring of residues and was validated in accordance with the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Union,

the Committee, further to the establishment of a provisional MRL for bovine milk recommends the establishment of a maximum residue limit for methylprednisolone in bovine milk and the modification of the current entry for methylprednisolne in table 1 of the Annex of Commission Regulation (EU) No 37/2010 of 22 December in accordance with the following table:

| Pharmaco-logically active substance | Marker residue | Animal species | MRLs | Target tissues | Other provisions | Therapeutic classification |
|---|---|---|---|---|---|---|
| Methyl-prednisolone | Methyl-prednisolone | Bovine | 10 µg/kg<br>10 µg/kg<br>10 µg/kg<br>10 µg/kg<br>2 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney<br>Milk | | Corticoides/ Glucocorticoides |

# 4. Background information on the procedure

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| Submission of the dossier | 2 April 2009 |
| Steps taken for assessment of the substance | |
| Application validated: | 16 April 2009 |
| Clock started: | 17 April 2009 |
| CVMP opinion adopted (provisional MRL): | 15 July 2009 |
| Submission of the response on outstanding issues | 14 October 2010 |
| Steps taken for assessment of the response after provisional MRL for milk | |
| Clock started: | 15 October 2010 |
| CVMP opinion adopted: | 12 January 2011 |
| Request from Commission for reconsideration | 22 March 2011 |
| CVMP revised opinion adopted | 5 May 2011 |