3 September 2010
EMA/CVMP/339442/2009
Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Methylprednisolone (bovine milk)

On 25 August 2010 the European Commission adopted a Regulation[1] establishing a provisional maximum residue limit for methylprednisolone in bovine milk, valid throughout the European Union. This maximum residue limit was 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.

Methylprednisolone had maximum residue limits already established for bovine species.

Mérial SAS submitted the application for the extension of maximum residue limits to the European Medicines Agency (the Agency), on 2 April 2009.

Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use concluded that the substance should be included in Table 1 of Commission Regulation (EU) 37/2010. Subsequently the Commission recommended on 2 July 2010 that maximum residue limit in bovine milk is established. This recommendation was confirmed on 23 July 2010 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 25 August 2010.

Explanatory Note

The European Public MRL Assessment Report is a public document giving the overview of the assessment carried out by the Committee for Medicinal Products for Veterinary Use (CVMP) of an application submitted for the establishment of maximum residue limits (MRLs). The document is based on the CVMP assessment report of the application from which confidential information has been deleted.

Keywords: Methylprednisolone, bovine

[1] Commission Regulation (EU) No 761/2010, O.J. L224, of 26.08.2010

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Summary of the scientific discussion for the establishment of MRLs

Substance name:	Methylprednisolone
Procedure number:	EU/09/167/MER
Applicant:	Mérial SAS
Target species:	Bovine
Intended therapeutic indication:	Treatment of respiratory disease and urogenital infections in cattle
Route of administration:	Intramuscular injection.

2. 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 a combination product with antibiotics for the treatment of respiratory disease and urogenital infections in cattle by intramuscular injection. 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 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 established in a study investigating tyrosine aminotransferase activity in rats.

Currently, methylprednisolone is included in Commission Regulation (EU) No 37/2010 of 22 December 2009 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 10 µg/kg 10 µg/kg 10 µg/kg	Muscle Fat Liver Kidney	Not for use in animals for which milk is produced for human consumption	Corticoides/ Glucocorticoides

An application has now been submitted for the extension of the MRLs for methylprednisolone to bovine milk. The proposed major indication is for the treatment of bovine respiratory disease (BRD) and urogenital infections in cattle in combination with antibiotics. The proposed dose regimen is a single dose of 400 µg/kg bw/day by intramuscular injection.

3. Scientific risk assessment

3.1. Safety assessment

As the CVMP previously performed a safety assessment for establishing MRLs for bovine tissues (not milk) for methylprednisolone therefore no further assessment regarding the establishment of the ADI of the substance is required for the purpose of this extension application.

3.2. Residues assessment

3.2.1. 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.

3.2.2. 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.

3.2.3. 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 limit of quantification was 0.5 µg/kg for bovine milk. The method was not satisfactorily validated concerning accuracy and precision and there was no information on specificity concerning the susceptibility of interference from residues of other corticosteroids.

3.2.4. Findings of EU or international scientific bodies

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

4. Risk management considerations

4.1. 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.

Other relevant risk management considerations for the establishment of maximum residue limits

No data were provided but none are expected for this type of substance.

4.2. 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- table to be included, if applicable

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.

Based on 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.

4.3. Considerations on possible extrapolation of MRLs

In line with the CVMP Note for Guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-Final) the MRL for bovine milk could be extrapolated to milk from ovine and caprine species provided that it can be confirmed that the proposed analytical method would be applicable and the marker residue is confirmed.

However, it is not considered appropriate to extrapolate MRLs for milk if MRLs cannot also be established for tissues in the relevant species. In this case, no MRLs have been established for ovine or caprine tissues.

In relation to caprine species, extrapolation of the approved MRLs for bovine tissues could be accepted if applicability of the analytical method can be shown, in line with the above mentioned CVMP note for guidance.

On the other hand, the approved MRLs for bovine tissues may not be extrapolated to ovine tissues as ovine is considered a major species and consequently species specific data would be required. As tissue MRLs cannot be recommended for ovine species extrapolation of the MRL for milk cannot be considered for this species.

Further consideration on the extrapolation to caprine tissues and milk will be considered in the context of the establishment of final MRLs for bovine milk, provided that data is made available to demonstrate the applicability of the relevant analytical methods in tissues and milk from caprine species.

4.4. 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 and the ratio of marker to total residues set at 1,
- the current tissue MRLs account for 52% of the ADI,
- an analytical method was available for monitoring of residues although it is not validated in accordance with the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Union;

the Committee recommends the establishment of a provisional maximum residue limit for methylprednisolone in bovine milk 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	2 µg/kg	Milk	Provisional MRL expires on 01.07.2011	Corticoides/ Glucocorticoides

The Committee further recommends the modification of the "Other provisions" for the existing MRLs for methylprednisolone in order to remove the provision "Not for use in animals from which milk is produced for human consumption", 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 10 µg/kg 10 µg/kg 10 µg/kg	Muscle Fat Liver Kidney		Corticoides / Glucocorticoides

Before the Committee can consider the establishment of a final MRL for milk the first question in the list of questions must be satisfactorily addressed.

Consideration of the possibility to extrapolate the bovine MRLs to caprine species is also requested.

5. List of questions

1. The proposed routine analytical method should be fully validated in accordance with Volume 8 of the Rules Governing Medicinal Products in the European Union.
   - Specificity in the presence of analogous substances should be demonstrated and an adequate number of samples used in the accuracy and precision determinations.
   - Relevant concentrations (0.5 µg/kg or ½MRL; plus 1 x MRL and 2 x MRL) should be used and 6 replicates should be analysed at each concentration.
2. The Applicant is requested to consider the applicability of the established routine analytical method for bovine edible tissues and the proposed routine analytical method for bovine milk with regard to possible extrapolation of established MRL to caprine species, in line with to the CVMP Note for Guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-Final).

6. Background information on the procedure

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: 15 July 2009