Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal products, animal species, routes of administration, applicant / marketing authorisation holder in the Member States

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
France	Zoetis France 23-25 Avenue du Dr Lannelongue 75014 Paris France	SOLU-MEDROL 120 MG	Methylprednisolone hydrogen succinate	Lyophilisate and diluent for solution for injection	120 mg per bottle	Cattle, cats, dogs	Intramuscular or intravenous
France	Zoetis France 23-25 Avenue du Dr Lannelongue 75014 Paris France	SOLU-MEDROL 500 MG	Methylprednisolone hydrogen succinate	Lyophilisate and diluent for solution for injection	500 mg per bottle	Cattle, cats, dogs	Intramuscular or intravenous
Germany[1]	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 D-31303 Burgdorf Germany	Solupred 125 mg Pulver und Lösungsmittel zur Herstellung einer Injektionslösung	Methylprednisolone hydrogen succinate	Powder and solvent	500 mg per bottle	Cattle, cats, dogs	Intramuscular or intravenous

[1] Marketing authorisation not granted for target species cattle

Annex II

Scientific conclusions and grounds for refusal of the granting of the marketing authorisation for the target species cattle and for the variation of the existing marketing authorisations in order to remove any reference to the target species cattle

Overall summary of the scientific evaluation of veterinary medicinal products containing methylprednisolone hydrogen succinate for use in target species cattle (see Annex I)

1. Introduction

Methylprednisolone hydrogen succinate is an ester of the synthetic glucocorticoid methylprednisolone. Methylprednisolone, a 6α-methyl derivative of prednisolone, is a synthetic corticosteroid, which is used in veterinary medicine as a free alcohol, and as various esters. Veterinary medicinal products containing methylprednisolone hydrogen succinate are used for treatment of inflammatory or allergic conditions and also for treatment and prevention of shock conditions.

Following a marketing authorisation application to the Federal Office of Consumer Protection and Food Safety of Germany, under Article 13(1) of Directive 2001/82/EC, i.e., a generic application, for the veterinary medicinal product Solupred 125 mg (applicant: CP-Pharma), it appeared that no product-specific residue data are available in support of the cattle meat and offal withdrawal periods of 6 days for the reference products Solu-Medrol 120 mg and Solu-Medrol 500 mg which are authorised in France for use in dogs, cats and cattle (marketing authorisation holder: Zoetis).

Using the data available in the CVMP EPMAR for methylprednisolone (EMEA/MRL/798/01-FINAL)[2], Germany considered that residues of methylprednisolone at injection sites may lead to intake of amounts of methylprednisolone significantly above the Acceptable Daily Intake (ADI). Even if formulation differences and differences between the chemical forms of the active substances (methylprednisolone as free alcohol versus methylprednisolone hydrogen succinate) are taken into account, Germany considered that these data strongly indicate that a withdrawal period of 6 days for cattle (meat and offal) treated with methylprednisolone hydrogen succinate containing products might not be sufficient to ensure consumer safety.

Therefore, on 2 May 2016, Germany initiated a procedure under Article 35 of Directive 2001/82/EC, for veterinary medicinal products containing methylprednisolone hydrogen succinate presented as solutions for injection for intramuscular use in cattle. The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to review all available residue depletion data and recommend withdrawal periods for meat and offal derived from treated cattle.

2. Discussion of data available

Residue depletion data in cattle meat and offal

No product specific residue depletion data or any other information concerning residues of veterinary medicinal products containing methylprednisolone hydrogen succinate are available.

No information has been found in open databases (e.g. PubMed, Scopus, VetMed Resource, Web of Science) regarding pharmacokinetic and residue data of methylprednisolone hydrogen succinate in edible tissues and at the injection site of cattle.

The only residue depletion study for methylprednisolone after intramuscular injection in cattle is cited in the CVMP EPMAR for methylprednisolone (EMEA/MRL/798/01-FINAL). The veterinary medicinal product that has been used in the residue depletion study for the establishment of maximum residue limits (MRLs) for methylprednisolone is a combination product containing methylprednisolone (as free

[2] CVMP EPMAR for methylprednisolone (EMEA/MRL/798/01-FINAL) - http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500015081.pdf

alcohol) and two antibiotic substances (neomycin and benzylpenicillin). The residue depletion data concerning methylprednisolone can be summarised as follows:

- After administration of 400 µg/kg bw for 5 consecutive days, residues in injection site muscle ranged from below LOQ (10 µg/kg) to 8393 µg/kg at day 7 after injection and at day 14 from below LOQ to 90 µg/kg. At the injection site, the MRL for muscle was exceeded more than 800 fold at day 7 and still 9 fold at day 14. In addition, the pharmacological ADI was exceeded up to 262 fold at day 7 and up to 2.8 fold at day 14. Twenty-one days after administration residues at injection sites were below the LOQ in all animals. Residues in muscle, liver, kidney and fat were already below LOQ (10 µg/kg) at the earliest slaughter time (day 7).

The residue depletion data do not allow a statistically based determination of a withdrawal period. However, the first time point all data were below the MRL was day 21. Even if formulation differences and differences between the chemical forms of the active substances (methylprednisolone as free alcohol versus methylprednisolone hydrogen succinate) are taken into account, these data strongly indicate that a withdrawal period of 6 days for cattle (meat and offal) treated with methylprednisolone hydrogen succinate-containing products is insufficient to ensure consumer safety.

Taking all the information together, it cannot be confirmed from the available data that the withdrawal period of 6 days for cattle (meat and offal) for the reference product Solu-Medrol is safe for the consumer. This conclusion applies to the administration of the products via the intramuscular route or the intravenous route.

3. Benefit-risk assessment

Introduction

The aim of the referral procedure was to consider all available residue depletion data and recommend withdrawal periods for meat and offal derived from treated cattle.

Benefit assessment

Veterinary medicinal products containing methylprednisolone hydrogen succinate are used for treatment of inflammatory or allergic conditions and also for treatment and prevention of shock conditions. However, the efficacy assessment does not fall within the scope of this referral procedure. These veterinary medicinal products are also authorised for use in dogs and cats, but considering the scope of the referral, these target species were not assessed during this procedure.

Risk assessment

No residue depletion data are available for veterinary medicinal products containing methylprednisolone hydrogen succinate. In the absence of residue depletion data it cannot be ensured that residue levels are below the MRLs in all edible tissues at 6 days post-treatment. This is relevant for administration of the products via the intramuscular route as well as administration via the intravenous route. Furthermore, the data from the MRL file on methylprednisolone support the assumption that the potential consumer exposure from injection site residue will be above the pharmacological ADI, indicating a serious risk for consumer safety.

Risk management or mitigation measures

As no residue depletion data are available for veterinary medicinal products containing methylprednisolone hydrogen succinate, the CVMP is not able to recommend withdrawal periods for meat and offal derived from treated cattle.

Evaluation and conclusions on the benefit-risk balance

In the absence of residue depletion data it cannot be ensured that residue levels are below the MRLs in all edible tissues at 6 days post-treatment. This is relevant for administration of the products via the intramuscular route as well as administration via the intravenous route. Furthermore, the data from the MRL file on methylprednisolone support the assumption that the potential consumer exposure from injection site residue will be above the pharmacological ADI, indicating a serious risk for consumer safety.

Therefore, the Committee considers that the benefit-risk balance for veterinary medicinal products containing methylprednisolone hydrogen succinate presented as solutions for injection for use in target species cattle is not favourable in the absence of adequate residue depletion data to justify a withdrawal period of 6 days for cattle (meat and offal). Consequently, the Committee recommends the refusal of the granting of the marketing authorisation for the target species cattle and the variation of the existing marketing authorisations in order to remove any reference to the target species cattle for veterinary medicinal products containing methylprednisolone hydrogen succinate.

Grounds for refusal of the granting of the marketing authorisation for the target species cattle and for the variation of the existing marketing authorisations in order to remove any reference to the target species cattle

Whereas

- the CVMP considered that in the absence of residue depletion data, it cannot be ensured that residue levels are below the MRLs in all edible tissues at 6 days post-treatment;
- the CVMP considered that the data from the MRL file for methylprednisolone support the assumption that the potential consumer exposure from injection site residue will be above the pharmacological ADI, indicating a serious risk for consumer safety;
- the CVMP considered that a withdrawal period for meat and offal derived from treated cattle cannot be set;

the CVMP has recommended the refusal of the granting of the marketing authorisation for the target species cattle and the variation of the existing marketing authorisations in order to remove any reference to the target species cattle for veterinary medicinal products containing methylprednisolone hydrogen succinate as referred in Annex I.

Annex III

Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

All references to target species cattle should be deleted from the summary of product characteristics, labelling and package leaflet.