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EMA/CVMP/165950/2012
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Diclazuril (extension to poultry)

On 8 February 2013 the European Commission adopted a Regulation[1] establishing maximum residue limits for diclazuril in poultry, 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.

Maximum residue limits had previously been established for diclazuril in porcine species and for all ruminants with a 'No MRL required' entry with a restriction 'For oral use only'. Huvepharma NV submitted to the European Medicines Agency an application for the extension of maximum residue limits for diclazuril to poultry, on 27 October 2011.

Diclazuril is intended for use in poultry (chicken and pheasants) for the treatment of coccidiosis to be administered orally at a dose rate of up to 0.3 mg/kg bw/day for 3 days in chicken and a dose of up to 0.4 mg/kg for 28 days in pheasants.

Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 13 April 2012 the establishment of maximum residue limits for diclazuril in poultry.

Subsequently the Commission recommended on 27 November 2012 that maximum residue limits in poultry are established. This recommendation was confirmed on 18 December 2012 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 8 February 2013.

[1] Commission Implementing Regulation (EU) No 115/2013, O.J. L38, of 09.02.2013

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Diclazuril
Therapeutic class:	Antiparasitic agents/Agents acting against protozoa/ benzeneacetonitrile derivative
Procedure number:	EU/11/198/HUV
Applicant:	Huvepharma NV
Target species:	Poultry
Intended therapeutic indication:	Control of coccidiosis in chickens and pheasants.
Route(s) of administration:	Orally

1. Introduction

Diclazuril is (2,6-Dichloro-α-(4-chlorophenyl)-4-(4,5- dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-benzeneacetonitrile) a benzeneacetonitrile derivative used for the control of coccidiosis in calves, piglets and lambs. In calves and piglets the recommended dose regimen is 5 mg/kg bw as a single oral administration. In lambs the therapeutic dosage is either a single administration of 1 mg diclazuril/kg bw (most commonly at about 6-8 weeks of age) or two administrations (the first at 3 to 4 weeks of age and the second about 3 weeks later).

Diclazuril is intended for use in poultry (chicken and pheasants) for coccidiosis to be administered orally at a dose of up to 0.3 mg/kg bw for 3 days in chicken and a dose of up to 0.4 mg/kg for 28 days in pheasants.

Diclazuril is also authorised in the EU as feed additive used to control coccidiosis in poultry.

Diclazuril was previously assessed by the CVMP and toxicological acceptable daily intake (ADI) of 0.030 mg/kg bw (*i.e.* 1.8 mg/person) was established.

Currently, diclazuril 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
Diclazuril	NOT APPLICABLE	All ruminants, porcine	No MRL required	NOT APPLICABLE	For oral use only	NO ENTRY

Huvepharma NV submitted the application for the extension of maximum residue limits to poultry to the European Medicines Agency, on 27 October 2011.

2. Scientific risk assessment

Diclazuril was previously assessed by the CVMP and a toxicological acceptable daily intake (ADI) of 0.03 mg/kg bw (i.e. 1.8 mg/person), was established based on a NOEL of 3 mg/kg bw/day retained from the 2-year chronic toxicity/carcinogenicity study in mice applying a safety factor of 100.

Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application.

The same ADI value of 0.03 mg/kg bw was established by EFSA and the Joint WHO/FAO Expert Committee on Food Additives (JECFA) at its 50th meeting in 1998.

2.1. Residues assessment

2.1.1. Pharmacokinetics in target species

No pharmacokinetic data were provided.

The published pharmacokinetic studies summarised in the JECFA reports indicate that biotransformation of diclazuril in chicken and turkey is low and the major compound found in plasma, tissues, urine and faeces is the parent substance. It was also concluded that although poorly absorbed, diclazuril is detectable in plasma soon after administration with a t_{max} of about 6 hours.

The CVMP has previously assessed diclazuril and based on an *in vitro* comparison of the metabolism of diclazuril in primary cell cultures and in suspension culture of hepatocytes of rats, rabbits, chickens, turkeys, sheep, goats and cattle concluded that the pharmacokinetic profile and metabolism of diclazuril was similar in all these species. The parent compound represented more than 90% of the radioactivity in suspension cell culture of all species.

2.1.2. Residue depletion studies

Two diclazuril residue depletion studies were submitted, one in edible chicken tissue and another one in edible pheasant tissue.

A tissue residue depletion study following oral administration of diclazuril was performed in chicken. The birds were given oral doses of 0.3 mg diclazuril/kg bw/day for 3 consecutive days in feed. The study was non-radiometric depletion study and was conducted in accordance with Good Laboratory

Practice (GLP). Diclazuril residues were the highest in liver followed by kidney. The mean residue levels in chicken depleted from 1443 ± 119 µg/kg in liver, 1208 ± 118 µg/kg in kidney, 522 ± 43 µg/kg in skin+fat and 209 ± 20 µg/kg in muscle after last administration (0 hour) to 565 ± 128 µg/kg in liver, 446 ± 119 µg/kg in kidney, 199 ± 53 µg/kg in skin+fat and 101 ± 19 µg/kg in muscle after 48 hours.

A tissue residue depletion study following oral administration of diclazuril was also performed in pheasants. The birds were given oral doses of 0.4 mg diclazuril/kg bw/day for 28 consecutivie days in feed. The study was non-radiometric depletion study and was conducted in accordance with GLP. Diclazuril residues were the highest in liver followed by kidney. The mean residue levels in pheasants depleted from 1862 ± 186 µg/kg in liver, 1480 ± 194 µg/kg in kidney, 701 ± 41 µg/kg in skin+fat and 207 ± 31 µg/kg in muscle after last administration (0 hour) to 560 ± 97 µg/kg in liver, 524 ± 66 µg/kg in kidney, 229 ± 46 µg/kg in skin+fat and 63 ± 6 µg/kg in muscle after 48 hours.

Moreover, from EFSA and JECFA reports several studies on tissue depletion of diclazuril in chicken and turkey are published. Studies were performed with ^{14}C-diclazuril. From these studies the ratio marker to total residue were between 70 to 90% at 24 hours after the last administration of feed in chicken (85% in liver, 87% in muscle and 78% in fat). In turkey a ratio of 70% was observed in liver 24 hours after the end of feed administration.

The highest residue levels were observed in the submitted studies. From the two depletion studies submitted and the information published in EFSA and JECFA reports, it can be concluded that:

- Residues subsequently deplete rapidly;
- Highest concentrations are found in liver and to a lesser extent, kidney;
- Lower concentrations are found in muscle.

Diclazuril is detected in eggs.

From the residue data submitted, which did not include a radiolabelled study, the ratio of marker to total residues could not be determined. However, in reviewing the reports from EFSA on the evaluation of the substance the CVMP agreed that the conclusion of EFSA could be retained, i.e. a ratio of marker to total residue of 0.7. This value represents the worst case from all available information.

2.1.3. Monitoring or exposure data

No data on monitoring or exposure data were available.

2.1.4. Analytical method for monitoring of residues

The same analytical method, based on LC/MS-MS detection was proposed to assay diclazuril in edible chicken and pheasant tissues. The analytical method was validated according to the Volume 8 of the Rules Governing Veterinary Medicinal Products in the EU for chicken edible tissue. The limit of quantification is 50 µg/kg for all chicken tissues.

With regard to pheasants only the lower limit of quantification and the stability were tested, this was considered adequate in line with the requirements for minor species.

The analytical method was reviewed by the relevant European Reference Laboratory, which confirmed the suitability of the method for monitoring of residues in poultry.

2.1.5. Findings of EU or international scientific bodies

EFSA established MRL values for diclazuril for chicken and turkey tissues concerning the use of the substance as feed additive, as follows:

- Muscle: 500 µg/kg
- Fat and skin: 500 µg/kg
- Liver:1500 µg/kg
- Kidney: 1000 µg/kg

In 1999 Codex Alimentarius established the following MRLs for diclazuril poultry as follows:

- Muscle: 500 µg/kg
- Fat and skin 1000 µg/kg
- Liver: 3000 µg/kg
- Kidney: 2000 µg/kg

3. Risk management considerations

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

In view of the nature of the substance no data were considered necessary in the context of this evaluation.

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

MRLs for diclazuril are established in the EU for its use as a feed additive in poultry. With a view to ensuring a consistent approach with regard to consumer safety and the feasibility of the monitoring of residues, the Committee took into account these MRLs when making its recommendation.

3.3. Elaboration of MRLs

From the tissue residue depletion studies available in chicken and pheasants, the highest levels of residues were observed in liver immediately following treatment (zero hours).

Using the data submitted together with all the other publically available information, the theoretical maximum daily intake was found not to exceed 30% of the ADI immediately after last treatment. Therefore, in line with the current entry for all ruminants and porcine species, a no MRL required recommendation was considered by the Committee. However, in order to ensure consistency in approach in the EU, the CVMP agreed to recommend the same MRLs as the ones established for the use of diclazuril as a feed additive in poultry i.e.:

- Muscle: 500 µg/kg
- Fat and skin: 500 µg/kg
- Liver: 1500 µg/kg
- Kidney: 1000 µg/kg

No sufficient data were provided to recommend an MRL for eggs.

The CVMP notes that these MRLs are different to the ones established by Codex, however, in view of the fact that MRLs for diclazuril are established in the EU in poultry for its use as a feed additive, further considerations on the possibility of harmonising the MRLs with Codex were not pursued.

Calculation of the theoretical maximum daily intake (TMDI) 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 (µg)
Muscle	0.30	500	0.7	214
Skin and fat in natural proportions	0.09	500	0.7	64
Liver	0.10	1500	0.7	214
Kidney	0.01	1000	0.7	14
			Total intake (µg)=	506
			% of ADI=	28%

These MRLs represent 28% of the ADI.

No residue data in eggs were provided; therefore the use should be restricted to animals from which eggs are not produced for human consumption.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the recommended maximum residue limits established for diclazuril to other food producing species and food commodities. A "no MRL required" status has been established for oral use for all ruminants and porcine species.

Taking into account the current scientific knowledge the recommendations on extrapolation of the recommended MRLs for chicken and pheasants are justified as follows:

Animal species/ food commodities	Extrapolation possible (YES/NO)	Justification
Poultry (tissues)	Yes	Existing data indicate that the pattern of metabolism seen in chicken and turkey is similar. Based on this existing inter-species metabolism data, the assumption was made that the parent compound will be the predominant residue in other poultry species. From specific pharmacokinetic and residue data available for chicken and pheasant the recommendation about MRLs as recommended for

		chicken and pheasant can also be recommended in poultry without compromising the safety of the consumer.
Poultry eggs	No	No data are available that would allow conclusions to be drawn on the appropriate marker residue or marker to total residues ratio to use in eggs. No analytical method for monitoring of residues in eggs was available for evaluation.
Horses	No	Existing data indicate that the pattern of metabolites seen in rats, rabbits, chickens, turkeys, sheep, goats and cattle is similar and it can be expected that the parent compound would be a suitable marker residue in horses. However, no data are available to demonstrate that the analytical method used for monitoring of residues in chicken and pheasants is applicable for monitoring of residues in horse tissues.
Rabbits	No	Existing data indicate that the pattern of metabolites seen in rats, rabbits, chickens, turkeys, sheep, goats and cattle is similar and it can be expected that the parent compound would be a suitable marker residue in rabbits. However, no data are available to demonstrate that the analytical method used for monitoring of residues in chicken and pheasants is applicable for monitoring of residues in rabbit tissues.
Fin fish	No	Metabolism is generally less complicated in fish than in mammalian species or birds. Consequently, if the marker residue is the parent compound in chicken and pheasants it can be assumed that the parent compound would also be a suitable marker residue in fin fish meat. However, no analytical method for monitoring of residues in fin fish meat was available for evaluation.
Honey	No	Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data in other food products cannot be extrapolated to honey. Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in honey. No data are available to demonstrate that the analytical method used for monitoring of residues in cattle and pig tissues is applicable for monitoring of residues in honey.

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

Having considered that:

- The toxicological ADI of 0.030 mg/kg bw (i.e. 1.80 mg/day per 60 kg/bw person) was previously established as the overall ADI for diclazuril;
- Diclazuril was retained as the marker residue in chicken and pheasant tissues;

- The ratio of marker to total residue was considered to be 0.7 for edible tissues in chicken and pheasants;
- A validated analytical method for the monitoring of residues of diclazuril in chicken and pheasant tissues (muscle, liver, kidney and skin and fat) is available;
- Similar metabolism was observed in chicken, turkeys and pheasants and therefore an extrapolation to all poultry species is acceptable.

The Committee recommends the establishment of maximum residue limits for diclazuril in poultry and the amendment of 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
Diclazuril	Diclazuril	Poultry	500 µg/kg 500 µg/kg 1500 µg/kg 1000 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney	Not for use in animals from which eggs are produced for human consumption	Antiparasitic agents/Agents acting against protozoa

Based on the recommended MRLs, the theoretical daily intake of residues from poultry represent 28% of the ADI.

4. Background information on the procedure

Submission of the dossier	27 October 2011
Steps taken for assessment of the substance	
Application validated:	9 November 2011
Clock started:	10 November 2011
CVMP opinion adopted:	13 April 2012