21 September 2016
EMA/CVMP/89165/2016
Committee for Medicinal Products for Veterinary Use

European Public MRL Assessment Report (EPMAR)

Hydrocortisone aceponate (all ruminants and *Equidae*)

On 31 August 2016 the European Commission adopted a Regulation[1] establishing maximum residue limits for hydrocortisone aceponate in all ruminants and *Equidae*, 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.

Hydrocortisone aceponate is intended for intramammary use in dairy cattle, in combination with antibiotics, for the treatment of mastitis.

Virbac S.A. submitted to the European Medicines Agency an application for the establishment of maximum residue limits for hydrocortisone aceponate in bovine species on 26 February 2014.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended, on 18 February 2016, the establishment of maximum residue limits for hydrocortisone aceponate in bovine species and the extrapolation of the maximum reside limits to all ruminants and *Equidae*.

Subsequently the Commission recommended, on 28 June 2016, the establishment of maximum residue limits for hydrocortisone aceponate in all ruminants and *Equidae*. This recommendation was confirmed on 19 July 2016 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 31 August 2016.

[1] Commission Implementing Regulation (EU) No 2016/1444, O.J. L235, of 01.09.2016

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Hydrocortisone aceponate
Therapeutic class:	Corticosteroid
Procedure number:	EMEA/V/MRL/002993/FULL/0002
Applicant:	Virbac S.A.
Target species applied for:	Bovine
Intended therapeutic indication:	Treatment of infectious mastitis during the milking period as adjuvant treatment in combination with antibiotic(s)
Route(s) of administration:	Intramammary

1. Introduction

Hydrocortisone aceponate (CAS 74050-20-7) is a di-ester of hydrocortisone with acetic acid at the 21-position and propionic acid at the 17-position.

Hydrocortisone, a naturally occurring corticosteroid (also known as cortisol) produced by the adrenal cortex, is used in veterinary medicine in topical preparations for ocular, auricular and cutaneous administration.

In humans, hydrocortisone is administered as free alcohol, acetate, aceponate, butyrate, cypronate, hemisuccinate, phosphate or valerate. For replacement therapy, in cases of acute or chronic adrenocortical insufficiency, the normal oral dose is 20 mg in the morning and 10 mg in the evening, to mimic the circadian rhythm of the body. Hydrocortisone may also be administered intravenously for emergency treatment of post-adrenalectomy crises or certain allergic emergencies at a dose of 100 to 500 mg, repeated 3 or 4 times every 24 hours. A range of topical preparations is also available.

Hydrocortisone was previously assessed by the CVMP. No ADI was established for the substance, but in view of the nature of the substance and its intended use (topical use only), the CVMP concluded that the establishment of an ADI was not required. Hydrocortisone was included in table 1 of the annex to Regulation (EU) No 37/2010 with a 'No MRL required' classification in all food producing species and a restriction to topical use only.

On 26 February 2014, Virbac submitted an application to the European Medicines Agency for the establishment of maximum residues for hydrocortisone aceponate in cattle. The substance is intended for use in dairy cattle, in combination with antibiotics, for the treatment of mastitis during the lactating period. The proposed recommended dose is 20 mg/quarter up to four times, 12 hours apart, by intramammary infusion.

2. Scientific risk assessment

2.1. Safety assessment

Hydrocortisone aceponate is metabolised to hydrocortisone and hence no hydrocortisone aceponate-specific safety data were provided. This is acceptable as the previous MRL evaluation for hydrocortisone addresses the consumer safety aspects. The pharmacology and toxicology sections of this report are predominantly copied from the CVMP Summary report for hydrocortisone

(EMEA/MRL/377/98-FINAL), with additional information relating to hydrocortisone aceponate added where this is available.

2.1.1. Overview of pharmacological properties

Hydrocortisone influences carbohydrate, protein and lipid metabolism, but its mineralocorticoid action is weak. Its gluconeogenic potency is approximately 2.5% of that of dexamethasone. There were no data to establish a pharmacological NOEL.

In humans the oral bioavailability of hydrocortisone was shown to range from 45 to 80% and was dose-dependent. In fasted adult males, a Cmax value of 199 ng/ml was attained 1 hour after an oral dose of 10 mg. In the same individuals, a Cmax value of 419 ng/ml was attained 1.7 hours after an oral dose of 50 mg. The half-life for plasma elimination was reported to be in the range 80 to 120 minutes. Plasma clearance was dose-dependent and ranged from 300 to 500 ml/min over the dose range 5 to 50 mg. At normal physiological concentrations (400 nmol/l) hydrocortisone was extensively bound to plasma proteins, 89.5% to transcortin and 6.6% to albumin. Endogenous plasma hydrocortisone concentrations showed diurnal variation and plasma clearance was significantly higher in the morning compared with the evening. Following subcutaneous administration of 0.5 mg/kg bw ^{14}C-hydrocortisone to rats, 74 to 89% of the administered dose was recovered within 24 hours, mostly in the faeces. Rapid excretion was also observed in guinea pigs, however in this species, most of the dose was excreted in urine.

In humans, hydrocortisone was shown to be interconvertible with the inactive metabolite cortisone, with the equilibrium favouring hydrocortisone. Cortisone was metabolised further to 20-hydroxycortisone, and then to cortolones and tetrahydrocortisone. A major metabolic pathway involved 5 beta-reduction to tetrahydrocortisol. The major metabolites did not retain any corticosteroid activity.

Pharmacokinetic data for hydrocortisone aceponate and hydrocortisone were compared following topical administration (as an ointment or a cream) to guinea pigs, rabbits and rats. The results showed that hydrocortisone aceponate underwent greater absorption (20 – 40%) than hydrocortisone after cutaneous administration, and that this greater absorption was similar in damaged and intact skin. The terminal elimination half-lives based on renal and faecal elimination following administration of hydrocortisone aceponate (as an ointment or cream) was 1.3 to 2.0 days. Assays in samples from rats given topical hydrocortisone aceponate failed to detect any unmetabolised di-ester in urine or faeces from 0 to 72 hours. Only hydrocortisone and its metabolites (conjugated and transformed substances) were detected during this time confirming that hydrocortisone aceponate is fully and rapidly converted into hydrocortisone *in vivo*. Following subcutaneous administration of hydrocortisone aceponate to rats, the unmetabolised fraction in urine remained between 5 - 8% of the administered dose 0 – 72 hours after administration.

Following topical and subcutaneous administration of ^{3}H-hydrocortisone aceponate to rabbits and rats, the highest concentrations found at 6 and 30 hours after administration, with both routes of administration and in both species were in the gastrointestinal tract, followed by the liver and the kidneys. Total residue levels in rats following subcutaneous administration were 146, 13.7 and 6.1 µg/kg after 6 hours and 335, 10.8 and 4.4 µg/kg after 30 hours in the gastrointestinal tract, liver and kidneys respectively.

2.1.2. Calculation of pharmacological ADI, if relevant

No pharmacological ADI was calculated as the pharmacology studies did not establish NOAELs.

2.1.3. Overview of toxicology

Single dose toxicity studies were carried out in rats and mice. The acute intraperitoneal LD_{50} in rats was reported to be 150 mg/kg bw. The acute subcutaneous LD_{50} in male Sherman rats was greater than 1800 mg/kg bw following a 7-day observation period. However, many rats died in the second week after administration due to infections which may have been related to the immunosuppressive effect of the substance. The effects observed in acute studies in rats and mice included reduced adrenal weights, liver damage, lung consolidation and gastrointestinal effects.

Repeated-dose toxicity studies were carried out in rabbits given intramuscular injections of 10 or 15 mg/animal of hydrocortisone or 25 mg/animal of hydrocortisone acetate per day for up to 8 days. The studies were designed to investigate hepatotoxicity and no other parameters were monitored. Hepatotoxicity was observed in all treated groups with increased liver weight, focal hepatic necrosis and increased glycogen deposition. Liver weights in rabbits which were left untreated for 20 days before necropsy were comparable with the controls. No NOEL was established.

There were no multigeneration studies and no studies concerning the potential effects of hydrocortisone on fertility or peri/post-natal development.

Intramuscular doses of 15 to 50 mg/animal of hydrocortisone to pregnant hamsters induced cleft palate in the foetuses. Ocular administration of 1.2 or 1.8 mg/animal of hydrocortisone was teratogenic in rabbits. In mice, ocular administration of 0.75 and 1.5 mg/animal to dams caused a dose-related incidence of cleft palate in the foetuses but no significant increase was observed following administration of 0.18 mg/animal. Cortisone, which is metabolised to hydrocortisone, also induced foetal cleft palate when administered intramuscularly to pregnant guinea pigs at a dose of 320 mg/kg bw. These studies were designed primarily to investigate the induction of cleft palate and therefore did not follow OECD guidelines and used limited dosing regimens. No conclusions could be drawn regarding NOELs.

Hydrocortisone was not mutagenic in an *in vitro* assay for gene mutation in *Salmonella typhimurium* TA97a, TA98, TA100 or TA1535, in either the presence or absence of metabolic activation. Positive results were obtained in an *in vitro* chromosomal aberration assay in human lymphocytes though there was no dose-response over the concentration range studied (1 to 50 µg/ml). There was a dose-related increase in the number of micronucleated polychromatic erythrocytes in an *in vivo* micronucleus test in which mice were given single intraperitoneal injections of 1, 10 or 100 mg/kg bw hydrocortisone. Positive results were also obtained in an *in vivo* sister chromatid exchange analysis in the bone marrow of mice given single intraperitoneal injections of 0.1, 1 or 10 mg/kg bw hydrocortisone. All of the positive results were reported in a single published report and no information was provided concerning the purity of the material tested. The results conflicted with the negative results of mutagenicity studies carried out with the synthetic corticosteroids dexamethasone, prednisolone and methylprednisolone.

No carcinogenicity studies were provided. Carcinogenicity studies with the synthetic corticosteroid prednisolone, and its metabolite prednisone, gave no indication of carcinogenic potential.

2.1.4. Calculation of the toxicological ADI or alternative limit

No toxicological ADI was calculated as the toxicology studies did not establish NOAELs.

2.1.5. Overview of microbiological properties of residues

No microbiological data were available which is acceptable as hydrocortisone aceponate is not classified as an antimicrobial agent and is not structurally related to antimicrobial agents used in human or veterinary medicine.

2.1.6. Calculation of microbiological ADI

As no microbiological effects are expected a microbiological ADI is not necessary.

2.1.7. Observations in humans

In a cross-over design study, human volunteers were given a single intravenous dose of 100 or 400 mg/person hydrocortisone. Both doses caused transient decreases in lymphocyte and monocyte counts which had reverted to normal values 24 hours after administration.

Adverse reactions following clinical use of hydrocortisone are normally observed only after administration of high doses for a prolonged period and include gastrointestinal haemorrhage and opportunistic infections. Hydrocortisone has fewer side effects and is less likely to cause adrenal insufficiency when administered topically.

2.1.8. Findings of EU or international scientific bodies

No information on evaluations by other EU or international committees was available.

2.1.9. Overall conclusions on the ADI

A microbiological ADI is not considered necessary.

No pharmacology or toxicology studies were submitted for hydrocortisone aceponate. Hydrocortisone aceponate is rapidly hydrolysed to three esters (hydrocortisone propionate, cortisone aceponate, cortisone propionate) that are ultimately transformed into hydrocortisone and subsequent metabolites similar to substances of endogenous origin, and that consequently, the safety assessment of residues can be based on hydrocortisone alone.

No NOELs were established for hydrocortisone in the pharmacology and toxicity studies that could be used as the basis for an ADI calculation. However, hydrocortisone levels in kidney, muscle and fat fall well within the range seen in untreated animals. In addition, treatment related residue levels in the liver were very low and negligible compared to normal physiological human production. Therefore, ADIs for hydrocortisone and hydrocortisone aceponate are not necessary for the safety assessment of residues in tissues. On the other hand, it is considered likely that residues in milk would be increased over the normal physiological levels found in untreated animals; hydrocortisone aceponate and its metabolites are orally bioavailable in humans; these are hormone-type molecules and may therefore elicit changes to normal physiology if ingested in quantities that are higher than would be found in the normal diet. However, the establishment of an ADI is not considered necessary as endogenous levels of hydrocortisone in milk represent an appropriate reference limit to use in establishing MRLs (hydrocortisone levels in milk and tissues from untreated animals are presented in section 2.2.3 Monitoring or exposure data). This can further be compared to the daily production of hydrocortisone in humans (reported to be between 4900 and 29000 µg/person/day).

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

No pharmacokinetic studies in the target species were submitted.

The normal blood concentrations of hydrocortisone were reported to be 130 to 293 µg/l in horses, 61 ± 7 µg/l in cattle, 224 ± 36 µg/l in sheep, 235 ± 29 µg/l in goats and 297 ± 10 µg/l in pigs.

Hydrocortisone levels in milk from untreated cows were reported to be up to 4 µg/kg (as reported in section 2.2.3 Monitoring or exposure data).

2.2.2. Residue depletion studies

Eight Holstein/Friesian lactating cows (in early and late lactation) were administered four consecutive intramammary doses of ^{14}C- hydrocortisone aceponate at a target dose rate of 20 mg hydrocortisone aceponate per infusion 12 hours apart. Only one quarter was treated and the average dose was 20.4 mg hydrocortisone aceponate per quarter. Milk samples were collected from the treated quarter and untreated quarters separately from the first milking following the last infusion (12 hours) until the end of the study (96 hours) at 12-hour intervals. The animals were then slaughtered in two groups of 4 after 72 and 96 hours. Total, hydrocortisone aceponate and hydrocortisone residue levels in milk, liver, kidneys, muscle, peri-renal fat and plasma were measured. The mean total residue level in milk from treated quarters after 12 hours was 37 µg equivalents/kg, which then rapidly decreased to 3.6 µg equivalents/kg at 24 hours. At 96 hours, the mean total residue level in milk was 0.42 µg equivalents/kg. The mean total residue levels found in the pooled untreated quarters after 12 hours was 3.9 µg equivalents/kg and depleted to 0.05 µg equivalents/kg at 96 hours after last treatment. The mean total radioactive residue levels after 72 hours in liver, kidney, fat, muscle and plasma were 5.87, 1.26, 0.37, 0.66 and 0.44 µg equivalents/kg respectively and the values decreased to 3.94, 0.96, 0.33, 0.46 and 0.37 µg equivalents/kg respectively after 96 hours.

Hydrocortisone levels in milk were below the limit of quantification of 5 µg/kg in all samples. In a single sample, taken at 72 hours post last infusion, hydrocortisone levels were greater than 0.8 µg/kg, which was the lowest concentration used in the linearity determination and is considered to represent a level down to which residues can be reliably measured. The measured value in this sample was 1.36 µg/kg. There were two milk samples with hydrocortisone aceponate residues greater than the limit of quantification of 2 µg/kg (2.67 and 2.44 µg/kg, both seen at 12 hours). Residues of hydrocortisone and hydrocortisone aceponate in the untreated quarters remained below 0.8 µg/kg. At the first time point for tissues (72 hours), no residues of hydrocortisone aceponate or hydrocortisone greater than 0.8 µg/kg were detected in any liver samples. There were no hydrocortisone aceponate residues greater than 0.8 µg/kg detected in kidney, but two kidney samples had hydrocortisone residues greater than 0.8 µg/kg but less than the limit of quantification of 50 µg/kg for hydrocortisone in this matrix (1.78 and 1.42 µg/kg, respectively).

While the information reported in the paragraph above indicates that hydrocortisone aceponate and hydrocortisone residues in milk were low at all timepoints (including 12 hours), the information in the residue profiling part of the study suggests that residues in milk may be somewhat higher. Residue profiling indicates that metabolites in milk 12 hours after the last treatment were made up of 3 major compounds: hydrocortisone aceponate, cortisone propionate and hydrocortisone propionate. The results showed that total radioactivity was composed of about 50% of minor substances (including known hydrocortisone metabolites), 30% hydrocortisone aceponate and about 20% hydrocortisone propionate and cortisone propionate. The hydrocortisone aceponate values reported in milk 12 hours after last treatment were: 2.73, 7.10, 23.04, 0.22, 8.35, 10.75, 23.76 and 0.90 µg/kg. However, hydrocortisone aceponate and cortisone aceponate eluted at the same time and it is not clear what proportion of the reported levels were hydrocortisone aceponate. When hydrocortisone aceponate values alone were measured, it is reported that only 2 milk samples contained hydrocortisone aceponate residues above 2 µg/kg (2.67 and 2.44 µg/kg, as described above).

The radioactive profiling study in milk did not determine the actual concentration of hydrocortisone present.

Marker residue

Hydrocortisone levels detected in milk and tissues in the study were almost all below the limit of quantification (5 µg/kg in milk and 50 µg/kg in tissues), whereas detectable levels of hydrocortisone aceponate, cortisone aceponate as well as cortisone and hydrocortisone propionate were reported in milk.

Besides hydrocortisone and its esters, treatment related residues in milk also include cortisone and its esters and the total residue of pharmacological concern is the sum of hydrocortisone and cortisone and theirs esters which would also include the endogenous corticoids (i.e. endogenous hydrocortisone/cortisone and their esters). The marker residue is established as the 'Sum of hydrocortisone and its esters after alkaline hydrolysis, expressed as hydrocortisone'. The marker to total residues ratio can then be used to account for cortisone and its esters.

For tissues, given the low absorption from the udder and the rapid physiological regulation of the corticoid levels it is not necessary to select a marker residue for residue control.

Ratio of marker to total residues

The total treatment related intake of corticoids other than those included in the marker residue could not be precisely determined because not all relevant metabolites could be separated in the metabolic profiling. However, estimates showed that the ratio of marker to total corticoids is in a worst case not larger than 1:5, obtained from the quotient of total corticoid metabolites in milk (at 12 hours) to the concentration of identified hydrocortisone/hydrocortisone esters (i.e. hydrocortisone propionate, as in practice only this ester was present at measurable levels). This assumes that all radiolabelled metabolite fractions, which could not be clearly identified, are active corticoids other than the marker residue (i.e. hydrocortisone), thereby considerably overestimating the ratio.

The tissue ratio of marker to total residue levels is not determined as the proposal is to not establish MRLs for tissues.

2.2.3. Monitoring or exposure data

A study was presented where physiological background levels of hydrocortisone and hydrocortisone aceponate in untreated cows were measured in bovine milk, plasma, liver, kidney, muscle and fat. Milk samples were taken from 8 cows over a period of 3 days prior to administration of hydrocortisone aceponate. Tissues were sourced from other animals. The background levels found were as follows:

Matrix	hydrocortisone concentration range found (µg/kg)	Validated hydrocortisone LOQ (µg/kg)	Hydrocortisone aceponate concentration range found (µg/kg)	Validated hydrocortisone aceponate LOQ (µg/kg)
Liver	ND	3	ND	2
Kidney	7.44 – 27.7	50	ND	2
Muscle	4.81 – 5.98	10	ND	2
Fat	0.854 – 3.74	15	ND	2
Milk	<0.8 – 3.74	5	ND	2
Plasma	ND – 14.3	50	ND	

ND: not detected

In addition, data from the publicly available literature were submitted, which supported the above study in terms of normal physiological levels of hydrocortisone found in milk.

2.2.4. Analytical method for monitoring of residues

Analytical methods for the determination of residues in tissues and milk were provided in an internationally acceptable format and validated in accordance with the requirements set out in Volume 8 of The rules governing medicinal products in the European Union.

The analytical method for determination of hydrocortisone aceponate residues in cattle tissues was provided to allow the evaluation of the residues depletion study; however, since the proposal is for a 'no MRL required' entry in table 1 of 37/2010 for tissues, no details are reported here.

For milk, a validated analytical method was provided that included extraction, hydrolysis and analysis steps.

The analytes were extracted from the milk using acetonitrile, and cleaned up using a dichloromethane/hexane mixture. The acetonitrile layer contained the analytes, and so this was evaporated to dryness and added to methanol.

Sodium hydroxide was added to the methanol solution, in order to hydrolyse the hydrocortisone and cortisone esters to their free alcohols; this mixture was then cleaned up and added to the mobile phase, ready for analysis by LC-MS/MS. The resulting output was that the hydrocortisone esters were converted to hydrocortisone and based on a limited selection of standards cortisone esters were converted to cortisone, but there was virtually no conversion of cortisone to hydrocortisone, or vice versa.

All validation criteria were met and the limit of quantification was 1 µg/kg.

The relevant EU Reference Laboratory has reviewed the analytical method and is in agreement with the above review.

2.2.5. Findings of EU or international scientific bodies

The FDA which sets Tolerance and/or Safe Levels of Animal Drug Residues in Milk in the USA has set a level of 10 µg/kg for hydrocortisone. Health Canada has also established a MRL of 10 µg/kg for hydrocortisone; the marker residue is hydrocortisone.

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 effect on microorganisms used for industrial food processing is expected.

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

Hydrocortisone is endogenously produced in mammals. When considering the establishment of maximum residue limits it is important to ensure that any limits under consideration would not result in noncompliant findings in foodstuffs from untreated animals as a result of detection of endogenous hydrocortisone.

The residue data provided were generated following intramammary administration. The results cannot be extrapolated to other routes of administration and consequently a corresponding restriction is recommended.

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

3.3. Elaboration of MRLs

The consumer should not be exposed to hydrocortisone levels significantly exceeding naturally occurring levels in tissues and milk, given that hydrocortisone, as a glucocorticoid represents a potent hormone and is orally bioavailable. The residue study shows that hydrocortisone aceponate levels and treatment-related total radiolabelled residues in milk 12 hours after the last application are significantly higher than naturally occurring hydrocortisone levels, and nothing is known about the total (endogenous plus exogenous) hydrocortisone levels in milk from treated animals.

Setting an MRL in milk for hydrocortisone aceponate, its ester cleavage products and hydrocortisone is therefore appropriate as a basis for the establishment of adequate withdrawal periods after administration. In addition, the MRL would give a control option to detect non-physiological, treatment related hydrocortisone aceponate/hydrocortisone levels (and compliance with potential withdrawal periods). Furthermore, the CVMP noted that other countries/regions have implemented an MRL for hydrocortisone in milk of 10 µg/kg in their legislation.

Hydrocortisone aceponate is rapidly hydrolysed to three esters (hydrocortisone propionate, cortisone aceponate, cortisone propionate) that are ultimately transformed into hydrocortisone and subsequent metabolites similar to substances of endogenous origin. Therefore, in the absence of an ADI for hydrocortisone aceponate the naturally occurring levels of hydrocortisone in milk and tissues can be used as the quantitative benchmark for a tolerable intake, which can be further compared to the endogenous human production of hydrocortisone. As long as this level is not exceeded significantly after treatment it can be concluded that treatment will have no impact on consumer safety.

In milk, intake based on the proposed marker residue and a MRL of 10 µg/kg milk would lead to intake of 15 µg total hydrocortisone per person per day (based on the consumption figure of 1.5 litres per person per day). Based on the marker to total residues ratio of 1:5, this would lead to a theoretical worst case daily intake of 75 µg corticoids/person based on milk.

As daily production of hydrocortisone in humans is reported to be between 4900 and 29000 µg/person/day, the amount of total corticoids intake via milk would be a maximum of 1.5% of the lower level of endogenous hydrocortisone production in humans.

Based on data available, physiological levels of hydrocortisone in cows' milk are significantly below 10 µg/kg (range of less than 0.8 to 3.74 µg/kg) and a MRL concentration of 10 µg/kg is therefore considered appropriate. At this level risk of false positive findings from natural hydrocortisone can reasonably be ruled out while the resulting intake would be safe for consumers.

For tissues, data from radiolabelled studies show that total radiolabelled corticoid residues in kidney, muscle and fat were far below physiological hydrocortisone levels. Endogenous levels of corticoids in cattle liver could not be detected in the study provided and total radiolabelled residues in liver after treatment were very low (5.87 µg/kg) leading to a worst case intake of 0.6 µg corticoids/person, which is negligible compared to the physiological human production of 4900 and 29000 µg/person/day. These comparisons indicated that intramammary treatment does not lead to a significant systemic absorption and increase in total corticoid levels in tissues. The expected intake of corticoids from tissues would be well within the range of naturally occurring levels of corticoids and, therefore, no MRLs are deemed necessary for the edible tissues (liver, kidney, muscle and fat).

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 its recommendation on maximum residue limits for hydrocortisone aceponate in bovine tissues and milk to other food producing species and commodities.

The data and argumentation are based on intramammary use only and hence extrapolation can only be considered for species for which this route of administration is relevant, i.e. ruminants and horses. Although no data are available in other ruminant species and horses, there is no reason to consider that the pharmacokinetic behaviour of hydrocortisone aceponate following intramammary administration will be significantly different in different ruminant species or in horses. In relation to the analytical method for residue monitoring, although there are no data available to demonstrate that the method proposed for monitoring residues in cows' milk is applicable to milk of other ruminant species or horses there is no reason for believing that it would not be. Consequently the recommendation can be extrapolated to other ruminants and horses, with the same restriction (for intramammary use only).

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

Having considered that:

- although no ADI has been established for hydrocortisone aceponate or hydrocortisone, the need for MRLs and, where necessary, the derivation of numerical MRLs can be undertaken with reference to the levels of hydrocortisone ordinarily present in food of animal origin and with reference to the level of endogenous production of hydrocortisone in humans,
- hydrocortisone aceponate in milk is rapidly hydrolysed,
- the marker residue in milk is established as the sum of hydrocortisone and its esters after alkaline hydrolysis, expressed as hydrocortisone; no marker residue is needed for tissues,
- the ratio of marker to total corticoid residues calculated 12 hours after the end of treatment was 1:5 in milk,
- following intramammary administration of hydrocortisone aceponate, residues of hydrocortisone and its esters in tissues will make a negligible contribution to overall consumer exposure to hydrocortisone and its esters,
- following intramammary administration of hydrocortisone aceponate, treatment related residues of hydrocortisone and its esters in milk were significantly higher than levels seen in untreated animals,
- at the proposed MRL for milk, the worst case intake will represent no more than 1.5% of the lower level of endogenous hydrocortisone production in humans,
- extrapolation of the maximum residue limits recommended for bovine tissues and milk to all ruminants and *Equidae* is considered appropriate,
- a validated analytical method for the monitoring of residues of hydrocortisone aceponate in cattle milk is available,
- although it was not specifically demonstrated, the analytical method for monitoring of residues in bovine milk is expected to be basically applicable for monitoring of residues in milk from other ruminant species and horses;

the CVMP recommends the establishment of maximum residue limits for hydrocortisone aceponate in bovine tissues and milk. Furthermore, and with reference to article 5 of Regulation (EC) No 470/2009, the Committee agreed to extrapolate the conclusions to all ruminants and *Equidae*, in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Hydrocortisone aceponate	Sum of hydrocortisone and its esters after alkaline hydrolysis expressed as hydrocortisone	All ruminants, *Equidae*	10 µg/kg	Milk	For intramammary use only	Corticosteroids
	NOT APPLICABLE	All ruminants, *Equidae*	No MRL required for all tissues except milk	NOT APPLICABLE		

Background information on the procedure

Submission of the dossier	26 February 2014
Steps taken for assessment of the substance	
Application validated:	12 March 2014
Clock started:	13 March 2014
List of questions adopted:	10 July 2014
Consolidated response to list of questions submitted:	12 January 2015
Clock restarted:	12 January 2015
List of outstanding issues adopted:	12 March 2015
Clock restarted:	20 January 2016
CVMP opinion adopted:	18 February 2016