14 May 2020
EMA/CVMP/101968/2019
Committee for Medicinal Products for Veterinary Use

# European public MRL assessment report (EPMAR)

## Ciclesonide (*Equidae*)

On 17 January 2020 the European Commission adopted a Regulation[1] establishing maximum residue limits for ciclesonide in *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.

Ciclesonide is intended for use in horses for the treatment of airway diseases.

Boehringer Ingelheim Vetmedica GmbH submitted to the European Medicines Agency an application for the establishment of maximum residue limits on 26 February 2018.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 21 February 2019 the establishment of maximum residue limits for ciclesonide in *Equidae*.

Subsequently the Commission recommended on 12 October 2019 that maximum residue limits in *Equidae* are established. This recommendation was confirmed on 2 November 2019 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 17 January 2020.

[1] Commission Implementing Regulation (EU) No 2020/43, O.J. L 15, of 20 January 2020

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# Summary of the scientific discussion for the establishment of MRLs

| | |
|---|---|
| Substance name: | Ciclesonide |
| Therapeutic class: | Corticosteroid |
| Procedure number: | EMEA/V/MRL/005010/FULL/0001 |
| Applicant: | Boehringer Ingelheim Vetmedica GmbH |
| Target species: | *Equidae* |
| Intended therapeutic indication: | Airway diseases |
| Route(s) of administration: | Inhalation |

# 1. Introduction

Ciclesonide is a glucocorticosteroid and a pro-drug. It is converted in lung tissue into the active metabolite desisobutyryl-ciclesonide (des-CIC), which has an anti-inflammatory effect resulting from its binding to the glucocorticoid receptor.

Ciclesonide is intended for use in horses for the treatment of airway diseases. The substance is to be administered by inhalation at the dose of 2744 µg twice daily for the first 5 days of treatment, and 4116 µg daily for the next 5 days of treatment.

In human medicine ciclesonide is used for the treatment of asthma and allergic rhinitis.

The CVMP provided scientific advice to the applicant in 2016. The advice was largely followed.

# 2. Scientific risk assessment

## *2.1. Safety assessment*

### 2.1.1. Overview of pharmacological properties

**Pharmacodynamic properties including mode of action**

Three pharmacological effects of ciclesonide or ciclesonide metabolites were studied: the antagonistic effects against induced bronchospasms in guinea pigs, the induction of the enzyme tyrosine aminotransferase (TAT) in the liver of ciclesonide exposed rats, and the suppression of circulating corticosterone levels in rats.

In a non-GLP study in guinea pigs, the capability of ciclesonide to prevent acetylcholine-induced bronchospasms was evaluated using single oral doses of 1, 3, 10 and 30 mg ciclesonide/kg bw. Heart rate and blood pressure were not affected at any dose level. Prevention of bronchospasms was observed at doses of 3 mg/kg bw and above, therefore the NOEL in this study was 1 mg/kg bw.

In rats given single oral ciclesonide doses of 0, 0.060, 0.180, 0.540 mg/kg bw, TAT activity in liver samples was increased at the highest dose and corticosterone plasma levels were not affected. The NOEL was 0.180 mg/kg bw.

In a similar test in rats, two ciclesonide metabolites (not being the active metabolite des-CIC) showed a reduced glucocorticoid activity when compared to ciclesonide. The NOELs for changes in TAT activity were 0.540 mg/kg bw and 1.620 mg/kg bw, the highest dose tested.

**Pharmacokinetic properties (mainly in laboratory animals)**

The pharmacokinetics: absorption, distribution, metabolism and excretion of ciclesonide and its primary metabolite des-CIC were investigated in a number laboratory species (rat, mouse, rabbit and dog).

The absorption of ciclesonide was measured after oral administration of [$^{14}$C]-ciclesonide to rats and dogs, and after intratracheal administration to rats. Ciclesonide is moderately absorbed after oral administration. Approximately 24% and 66% of the dose was absorbed in rats and dogs after oral administration, respectively. About 53% was absorbed after intratracheal administration in rats.

The oral bioavailability of ciclesonide measured in dogs was very low and could not be estimated reliably. A similar low bioavailability was found for des-CIC also in dogs (some 0.7%-2%) and in mice (0.6%-0.8%). Both compounds showed an extensive first-pass effect caused by biotransformation in the gut wall and/or the liver.

The tissue distribution of [$^{14}$C]-ciclesonide was investigated in the rat. Following intravenous, oral and intratracheal dosing, radioactivity was distributed widely throughout the body, and the highest tissue concentrations were observed in lungs, thyroid, liver and kidney. The high levels of radioactivity in the gastrointestinal tract showed that the major route of excretion was via the bile/faeces.

The *in vitro* plasma protein binding of ciclesonide and its active metabolite des-CIC was found to be high. In mouse, rat, rabbit and dog, 93-99% of both compounds was bound to plasma proteins.

The *in vitro* metabolism of ciclesonide in the presence of rat, dog, and human liver microsomes showed no gross interspecies differences regarding the formation of the major metabolites, the major one (des-CIC) being formed by enzymatic de-esterification of ciclesonide.

Des-CIC formation was found to occur in homogenates of various tissues of rats and dogs. In these tissues, des-CIC is then further metabolised through hydroxylation into a large number hydroxyl and dihydroxy derivates. In lung tissue, esterification of des-CIC with fatty acids was observed to be a major metabolic pathway.

A total of 12 groups of metabolites derived from des-CIC were characterized and identified between mouse, rats, rabbits, dogs and humans, but not all metabolites were present in all species.

The apparent terminal plasma half-life of ciclesonide appeared to be very short and was not determinable in all species; the apparent terminal half-life of the active metabolite des-CIC was longer and ranged from 2.4 to 6.9 hours in the 4 species (rat, dog, mouse, and rabbit).

In dogs, faecal excretion measured as total radioactivity of ciclesonide, dominated and accounted for 86% of the total dose after intravenous dosing, and 81% of the total dose after oral dosing while only a minor part of the dose: 6% and 8% was eliminated via urine, indicating that biliary excretion and/or gastrointestinal secretion was the major elimination route for ciclesonide-derived radioactivity. Studies in the rat showed similar results.

## 2.1.2. Calculation of pharmacological ADI, if relevant

Given that the exposure to the active metabolite is higher following oral administration of ciclesonide than after oral administration of the active metabolite itself, the use of the parent substance for pharmacology testing was accepted.

The tyrosine aminotransferase (TAT) activity, and the corticosterone plasma levels in rats were used as markers for pharmacological activity.

The rat showed a low sensitivity for TAT induction and cortisone depression by ciclesonide and therefore these studies are not the best models for studying the most sensitive pharmacological endpoint in the most sensitive animal species. However, it is acknowledged that the main effects reported in the repeated dose toxicity studies were consistent with the glucocorticoid activity, and that therefore the toxicological studies would sufficiently cover the pharmacological effects. This approach is further justified by the observation that ciclesonide-induced pharmacological effect levels are driven by the exposure duration.

Because the pharmacological effects are adequately covered in the toxicity studies, it is considered unnecessary to establish a separate pharmacological ADI. In the case of ciclesonide, the toxicological ADI is considered to be also protective for pharmacological effects.

## 2.1.3. Overview of toxicology

A battery of toxicological studies was provided in which ciclesonide was orally administered to various species of laboratory animals, including mice, rats, rabbits, and dogs.

**Single dose toxicity**

Single dose toxicity studies were not provided but are not considered necessary for the establishment of an ADI and the derivation of MRLs.

**Repeated dose toxicity**

Short term toxicity studies were conducted in rats (4 weeks and 6 months duration) and dogs (4 weeks duration). Although these studies were not 90-days studies as required by Commission Regulation 2018/782 and VICH guidelines, they were suitable for selecting the most sensitive laboratory animal species for chronic toxicity testing, because the difference in sensitivity was very obvious, i.e. the dog was approximately 10 times more sensitive than the rat. This may be explained (at least in part) by the higher body burden of des-CIC in dogs, compared to rats, after an oral dose of ciclesonide. Chronic toxicity was studied in a 1-year oral toxicity study in dogs. Because chronic toxicity was tested in dogs, and because dogs are much more sensitive than rats, the conduct of further 90-days studies is not expected to provide additional information that would be relevant in the establishment of the overall NOAEL from repeated dose toxicity studies.

In the 4-week oral toxicity study in rats with oral gavage doses of 0, 0.1, 0.45, or 2.0 mg/kg bw per day body weights, adrenal weights and thymus weights were reduced at 0.45 and 2.0 mg/kg bw per day. At 2.0 mg/kg bw per day, thymus and adrenal atrophy was observed. The NOEL in this study was 0.1 mg/kg bw per day.

In the second oral toxicity study, rats were given ciclesonide by gavage at doses of 0, 0.08, 0.36, or 1.6 mg/kg bw per day for 6 months. The NOEL was 0.08 mg/kg bw per day, based on changes in bodyweights, adrenal weights, thymus weights and spleen weights observed at 0.36 mg/kg bw per day, the next highest dose level.

In an oral toxicity study, dogs were given ciclesonide in gelatine capsules at doses of 0, 0.01, 0.04, or 0.4 mg/kg bw per day for four weeks. Decreased body weights and adrenal weights, decreased levels of serum cortisol, and histopathological changes in the adrenals and the thymus were observed at the highest dose. The NOEL in this study was 0.04 mg/kg bw per day.

In the chronic oral toxicity study, dogs were given ciclesonide in gelatine capsules at doses of 0, 0.005, 0.03, 0.2 mg/kg bw per day for one year. Also in this study, decreased serum cortisol levels, decreased body weights, and decreased weights of the adrenals and thymus caused by atrophy, were observed. Dose related thymus atrophy, spermatogenic disturbance and oligospermia were seen

already at the lowest dose tested. Therefore, no NOEL could be established. The LOEL in this study was 0.005 mg/kg bw per day.

**Reproductive toxicity, including developmental toxicity**

In rats, reproductive toxicity, developmental toxicity, and postnatal toxicity were studied in segment I, II, and III studies, in accordance with ICH guidelines for human medicines. The dose levels in these studies were 0, 0.1, 0.3, and 0.9 mg/kg bw per day, given by oral gavage. Decreased bodyweights of the parent(s) was observed at 0.3 and 0.9 mg/kg bw per day. No effects on reproduction or embryo-/foetotoxicity, or pup toxicity were observed.

Further studies on developmental toxicity were carried out in rabbits. In the dose range-finding study, rabbits were given 0, 0.3, 1.0, and 5.0 mg/kg bw per day, and in the final study 0, 0.1, 0.3, and 2.0 mg/kg bw per day. For the two studies combined, the NOEL for maternal toxicity was 1.0 mg/kg bw per day, based on decreased body weights at 2.0 and 5.0 mg/kg bw per day. The NOEL for embryo-/foetotoxicity was 0.3 mg/kg bw per day, based on reduced foetal weight and post implantation/litter losses at 1.0, 2.0 and 5.0 mg/kg bw per day. In the first study, teratogenicity was observed at 1.0 and 5.0 mg/kg bw per day, although no teratogenic effects were seen in the second study up to 2.0 mg/kg bw per day. It was concluded that ciclesonide is teratogenic with a NOEL of 0.3 mg/kg bw per day.

**Genotoxicity**

In an adequate battery of *in vitro* and *in vivo* genotoxicity studies covering the requirements of VICH guidelines 23, ciclesonide did not induce gene mutations in prokaryotic and eukaryotic test systems *in vitro*. Ciclesonide was also negative in *in vitro* micronucleus and chromosomal aberration tests. However, ciclesonide was associated with dose-related increases of micronuclei in bone marrow of mice following oral treatment. The induction of micronuclei is common for this class of substances and is considered to be secondary to the pharmacological action of glucocorticoids, and mediated by binding to the glucocorticoid receptor rather than by direct DNA interaction. It is therefore concluded that ciclesonide is not a DNA-reactive genotoxic substance.

**Carcinogenicity**

In a carcinogenicity test, mice were given ciclesonide by oral gavage at doses of 0, 0.150, 0.450, or 0.900 mg/kg bw per day for two years. Statistically significant increases in incidence and degree of osteosclerosis of the femur and/or tibia were seen in female mice (but not in males) of the 0.450 and 0.900 mg/kg bw per day groups. Adenomas, hyperplasia and metaplasia were found in the antrum of the stomach at the two highest dose levels, with adenomas in females reaching statistical significance at 0.900 mg/kg bw per day by trend analysis but not by pair-wise analysis. The NOEL in this study was 0.150 mg/kg bw per day. A treatment related effect on the formation of adenomas can therefore not be excluded.

In a rat inhalation carcinogenicity study there was no evidence of a carcinogenic potential of ciclesonide. Systemic exposure could be confirmed at a higher level than in the mouse study.

The low incidence of (benign) adenomas was observed in one organ of one species only. The exact mechanism is not clear, however considering the location of the adenomas, the method of administration, being daily intubation of ciclesonide dissolved in polyethylene glycol (rather than in-feed administration), may have played a role. Overall as ciclesonide is not considered to be a direct acting genotoxin and as adenomas were observed in one species only and may have resulted from the route of administration, ciclesonide is not considered to represent a cancer risk for consumers.

## 2.1.4. Calculation of the toxicological ADI or alternative limit

An overall NOEL from the toxicology studies could not be set, because adverse effects were observed at 0.005 mg/kg bw per day, the lowest dose tested in the 1-year oral toxicity study in dogs, the most sensitive species. The incidences of the findings at this LOEL were relatively low, therefore it would be possible to use this LOEL as a point of departure for the establishment of a toxicological ADI, using an additional Safety Factor of 2.

The overall safety factor to be applied to the LOEL of 0.005 mg/kg bw per day is 200. The toxicological ADI is therefore calculated as follows:

$$\frac{5\ (\mu g/kg\ \ bw\ per\ day)}{200} = 0.025\ (\mu g/kg\ bw)$$

Using a standard bodyweight of 60 kg, this ADI corresponds to a daily intake of 1.5 µg per person.

It is noted that the margins between this ADI and the NOELs for teratogenicity and adenomas are 12000 and 18000, respectively, which gives the assurance that the ADI is sufficiently protective for these effects.

## 2.1.5. Overview of microbiological properties of residues

No microbiological data were provided, which is acceptable as no microbiological effects are expected for ciclesonide.

## 2.1.6. Calculation of microbiological ADI

As no microbiological effects are expected, the establishment of a microbiological ADI is not considered necessary.

## 2.1.7. Observations in humans

Whereas ciclesonide is used in human medicine, oral studies in humans were not available. From inhalation studies it appears that ciclesonide is well tolerated at the treatment dose.

## 2.1.8. Findings of EU or international scientific bodies

Ciclesonide has been notified as "suspected of damaging fertility or the unborn child" and "may cause damage to organs through prolonged or repeated exposure", within the context of the Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008 (ECHA). Ciclesonide has not been evaluated by EFSA or JECFA.

## 2.1.9. Overall conclusions on the ADI

The toxicological ADI of 0.025 µg/kg bw (1.5 µg per person) is the overall ADI.

## *2.2. Residues assessment*

### 2.2.1. Pharmacokinetics in target species

Two studies in horses were performed to determine the plasma kinetics and urinary excretion of ciclesonide and its active metabolite des-CIC.

In a pilot study in horses and ponies, plasma and urine concentrations of ciclesonide and des-CIC were measured after a single administration via inhalation of 2700 and 4050 µg ciclesonide/animal, and a single intravenous administration at 0.1 mg/kg bw of ciclesonide. Ciclesonide was rapidly absorbed after the inhalation administrations with conversion to its active metabolite des-CIC. The absolute systemic bioavailability of ciclesonide was low, and not higher than 5% for the dose of 2700 µg ciclesonide/animal, and not higher than 17% for the dose of 4050 µg ciclesonide/animal. The apparent systemic bioavailability of the active metabolite des-CIC following administration of ciclesonide was 33.8% and 59.0% at 2700 µg and 4050 µg ciclesonide/animal, respectively. The kinetic profiles and pharmacokinetic parameters for ciclesonide and its active metabolite des-CIC were similar between the subgroups, sex and body weight classes/species (i.e. ponies versus horses). In urine samples, the concentrations of ciclesonide and its active metabolite des-CIC were below the lowest limit of quantification (LLOQ) (20 and 50 pg/ml, respectively), for all sampling times.

After inhalation, the plasma exposure for ciclesonide and des-CIC increased with the dose, but this increase was not proportional between the 2700 µg and 4050 µg doses. A trend for an increase of ciclesonide and des-CIC plasma exposure greater than dose proportionality was observed. The elimination phase was similar for ciclesonide and des-CIC, with a harmonic mean terminal plasma half-life of 11 hours for both ciclesonide and des-CIC after intravenous administration.

After inhalation the mean terminal plasma half-life of ciclesonide was very short, approximately 1.4 hours and 2.6 hours following 2700 µg and 4050 µg, respectively. Des-CIC had a slightly longer mean terminal plasma half-life, ranging from 1.92 hours to 3.18 hours following 2700 µg and 4050 µg, respectively.

In the pivotal study two groups of horses (n=6; 3 males + 3 females) weighing respectively 509-611 kg and 282-381 kg, were used. The study consisted of 4 test periods, with different dosing schedules of ciclesonide via inhalation:

- single dose of 4116 µg ciclesonide/horse
- single dose of 5488 µg ciclesonide/horse
- 2744 µg ciclesonide/horse twice a day for 4 consecutive days, followed by one last dose of 2744 µg ciclesonide/horse on day 5
- 2744 µg ciclesonide/horse twice a day for 5 consecutive days, followed by doses of 4116 µg ciclesonide/horse once daily for 5 consecutive days.

In urine, the concentrations of ciclesonide and des-CIC were below the LLOQ (20 and 50 pg/ml, respectively) 24 hours and 48 hours after repeated daily dosing at 2744 µg twice a day for five days, followed by repeated daily dosing at 4116 µg once a day for five days.

The mean apparent harmonic terminal half-life after single administration by inhalation was approximately 3-5 hours for ciclesonide and approximately 4-5 hours for des-CIC.

In the animals with a lower bodyweight (282-381kg) an increase in mean terminal plasma half-life was observed for ciclesonide after repeated dose administration compared to after a single dose. However, in the animals weighing 500-700 kg, the elimination phase was similar for all days.

The same trend was observed for des-CIC. In conclusion, this study demonstrated that ciclesonide was rapidly converted to the active metabolite des-CIC following inhalation administration. A statistically significant body weight class effect was observed for des-CIC regarding $C_{max}$ (increasing $C_{max}$ with decreasing body weight).

In an *in vitro* metabolism study the metabolic profile of [$^{14}$C]-ciclesonide in horse hepatocytes was studied. Thirty three different metabolites were detected, three of them representing more than 10% of the total peak area each. The three major metabolites identified in horse hepatocytes were des-CIC and two isomers of hydroxycyclohexane des-CIC (referred to as M3-2 and M3-4). The three minor metabolites identified in horse hepatocytes were dihydroxycyclohexane des-CIC, another isomer of hydroxycyclohexane des-CIC and hydroxysteroid des-CIC. Other metabolites, including reduction derivates and glucuronide conjugates were not found in horse hepatocytes.

The amount of metabolites formed by rat and dog liver microsomes was comparable to the amount of metabolites formed by horse liver microsomes. It could be shown that the major metabolites found in horse hepatocyte incubations were also produced by both rat and dog liver microsomes. As the rat and the dog are the standard toxicology species and also used for the toxicological characterization of ciclesonide, all major metabolites found in horse can be considered toxicologically qualified.

### 2.2.2. Residue depletion studies

In the pivotal residue depletion study, residues were studied in horses (body weight 335 and 500 kg) following the intended inhalation administration for the maximum intended duration (i.e. initial treatment with 2744 µg ciclesonide) of 5 days twice daily followed by administration of 4116 µg ciclesonide for an additional 5 days once daily. Two validated analytical methods were used to measure des-CIC levels (an analytical method for the analysis of liver, kidney, muscle, and lung tissues and a separate analytical method for the analysis of fat). The analysis of des-CIC included the residues of parent ciclesonide, converted to des-CIC. The depletion of ciclesonide and metabolites (i.e. des-CIC, M3-2, and M3-4) in the edible tissues (muscle, liver, kidney, and fat) and the lung was determined at 12 hours, 3 days, 6 days or 9 days after the last administration. At 12 hours, des-CIC concentrations were 0.35-0.77 µg/kg in kidney, <0.3-0.76 µg/kg in muscle, 6.0-33.3 µg/kg in fat, and undetectable in liver. At 3 days, the residue concentrations of des-CIC were below the LOQ in liver and kidney, <0.3-0.38 µg/kg in muscle, and 1.3-7.3 in fat. At the two later time points, des-CIC was only detected in fat: 0.3-3.2 µg/kg at 6 days, and 0.47-2.9 µg/kg at 9 days. It was found that the major metabolites referred to as M3-2, and M3-4 that were identified in vitro could hardly be detected at all in vivo.

A second tissue residue study was performed aimed at establishing the marker to total ratio in equine tissue samples. This was a non-radiolabel study with semi-quantitative analysis of a selection of metabolites. The results are therefore considered indicative only, and therefore the presence of further metabolites cannot be excluded. One animal per time point was slaughtered at 1, 3, and 6 days after the last dose. The metabolite profiles were qualitatively similar in all selected tissues: only very low levels of des-CIC and ciclesonide were detected in most cases. No fatty ester of des-CIC was detected except des-CIC oleate at very low level in lung. Very low levels of metabolites referred to M3 metabolites (including M3-1, M3-2, M3-3 and M3-4) were detected in fat tissue only. In general, fat had the highest level of residues among all tissues. Ciclesonide was the major component detected in fat. The results of this study and the pivotal study both show that the major metabolite of ciclesonide *in vivo* is des-CIC. Although M3-2 and M3-4 were considered major metabolites based on the results of the *in vitro* studies, this was not observed *in vivo* and these metabolites were below the limit of quantification or detection in plasma and in all tissues except for some of the fat samples in the study aimed at establishing the marker to total ratios.

**Selection of marker residue and ratio of marker to total residues**

Des-CIC (including ciclesonide hydrolytically transformed to des-CIC) is the major component in edible tissues as it was the only quantifiable residue above the LLOQ in muscle, kidney, and lung 12 hours after the last dose and in fat 12 hours, 3, 6 and 9 days after the last dose. The sum of ciclesonide and des-CIC measured as des-CIC after hydrolysis is therefore taken as the marker residue.

The total residues were determined in non-radiolabel studies and estimated on the basis of the sum of measured parent and metabolites. Considering the uncertainties in this estimation due to the limited number of metabolites measured, and the relatively high LOQ of the analytical method, a conservative approach was used to establish the ratio of marker to total residues. The ratio of marker to total residues was set to 0.5 for muscle and fat, 0.15 for liver, and 0.25 for kidney based on mean residue levels seen across the first three time points.

### 2.2.3. Monitoring or exposure data

No relevant monitoring or exposure data other than that described elsewhere in this report were available.

### 2.2.4. Analytical methods used in the residue studies

Two methods were used for the determination of the marker residue in horse tissues. One method was used for the determination in muscle, liver, and kidney, and another method was used for the determination in fat. The methods were described in an internationally recognised format and validated in accordance with VICH Guideline 49. The limit of quantification for the marker residue was 0.3 µg/kg in all edible tissues.

The relevant European Reference Laboratory (EURL) has reviewed the analytical method and is in agreement with the above assessment.

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

Ciclesonide has not been evaluated by EU or international scientific bodies.

# 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 effects on microorganisms used for industrial food processing are expected.

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

Horses are considered a minor species and therefore the guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005) and 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) were taken into account for the evaluation.

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

## *3.3. Elaboration of MRLs*

Based on the residue depletion seen in tissues and taking the limit of quantification of the analytical method into consideration the following MRLs could be derived for *Equidae* tissues:

- 0.6 µg/kg for muscle, liver and kidney, i.e. twice the limit of quantification of the analytical method
- 4 µg/kg for fat

In the calculation of the consumer intake (below), a factor of 1.15 was used to convert the amount of desisobutyryl-ciclesonide to molar equivalents of ciclesonide. This factor was based on the difference in molar weight (470.6 g/mol for desisobutyryl-ciclesonide and 540.7 g/mol for ciclesonide). This conversion is needed for the comparison of the consumer intake with the ADI; the latter is expressed as µg ciclesonide per kg bw, or µg ciclesonide per person.

**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 (µg)** |
|---|---|---|---|---|
| Muscle | 0.30 | 0.6 | 0.5 | 0.41 |
| Fat | 0.05 | 4 | 0.5 | 0.46 |
| Liver | 0.10 | 0.6 | 0.15 | 0.46 |
| Kidney | 0.05 | 0.6 | 0.25 | 0.14 |

The intake calculation results in a theoretical maximum intake of 1.47 µg per person, which represents 98% of the ADI. It is noted that the theoretical maximum intake leaves no room for other future uses for which other food matrices need to be considered (i.e. milk, eggs, honey). However, given the nature of the substance and its historical use in humans, it is considered unlikely that any future uses of the substance would require consideration of other food matrices, and therefore it is deemed justified, in this particular case, to use (nearly) the full ADI.

## *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 the maximum residue limits recommended for *Equidae* to other food producing species and commodities, taking into account the provisions laid down in Commission Regulation (EU) 2017/880.

The marker residue is the sum of ciclesonide and desisobutyryl-ciclesonide, measured as desisobutyryl-ciclesonide after hydrolysis of ciclesonide to desisobutyryl-ciclesonide.

For ciclesonide, metabolism data are available in mice, rats, rabbits, dogs, horses, and humans. Most data were derived by *in vitro* studies using hepatocytes. The metabolism was roughly the same across animal species, although the formation rate of the various metabolites differed.

The MRLs cannot be extrapolated to other species in absence of information on residues, in particular on the expected ratios of marker to total residues. Because nearly the full ADI was used for the MRLs for *Equidae*, small differences in the M/T ratio may result in maximum consumer intakes above the ADI. Moreover, for horses, a minor species, a full data set was not available, which would be needed for extrapolation.

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

Having considered that:

- a separate pharmacological ADI is not needed because the pharmacological effects are adequately covered by the toxicological ADI,
- an overall (toxicological) ADI of 0.025 µg/kg bw (i.e. 1.5 µg per person) was established,
- the marker residue is the sum of ciclesonide and desisobutyryl-ciclesonide, measured as desisobutyryl-ciclesonide after hydrolysis of ciclesonide to desisobutyryl-ciclesonide,
- the marker residue to total residue ratios were set at 0.5 for muscle and fat, at 0.15 for liver and 0.25 for kidney,
- a validated analytical method was available indicating that residues in edible tissues can be adequately monitored,

the Committee recommends the establishment of maximum residue limits for ciclesonide in *Equidae*, in accordance with the following table:

| **Pharmaco-logically active substance** | **Marker residue** | **Animal species** | **MRLs** | **Target tissues** | **Other provisions** | **Therapeutic classification** |
|---|---|---|---|---|---|---|
| Ciclesonide | The sum of ciclesonide and desisobutyryl-ciclesonide, measured as desisobutyryl-ciclesonide after hydrolysis of ciclesonide to desisobutyryl-ciclesonide | *Equidae* | 0.6 µg/kg<br>4 µg/kg<br>0.6 µg/kg<br>0.6 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney | Not for use in animals from which milk is produced for human consumption | Corticoides / Glucocorticoides |

The maximum consumer intake calculated from these MRLs represents 98% of the ADI.

# 4. Background information on the procedure

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|---|---|
| Submission of the dossier: | 26 February 2018 |
| Steps taken for assessment of the substance | |
| Application validated: | 21 March 2018 |
| Clock started: | 22 March 2018 |
| List of questions adopted: | 19 July 2018 |
| Consolidated response to list of questions submitted: | 28 September 2018 |
| Clock restarted: | 8 October 2018 |
| List of outstanding issues adopted: | 6 December 2018 |
| Response to list of outstanding issues submitted: | 22 January 2019 |
| Clock restarted: | 23 January 2019 |
| CVMP opinion adopted: | 21 February 2019 |