01 July 2020
EMA/CVMP/94885/2020
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Ketoprofen (Bovine, Porcine and *Equidae*)

Ketoprofen is intended for treatment of inflammatory and painful conditions of the bones, joints and muscular-skeletal systems in cattle, horses, dogs and cats, for alleviation of pain associated with colic in horses and cattle, for reducing pyrexia and respiratory rate in case of respiratory infections in pigs and as supportive treatment of mastitis-metritis-agalactia syndrome in the sow. The dose in food producing species is 2 to 3 mg/kg bw by intravenous or intramuscular route.

Ketoprofen was previously assessed by the CVMP and is included in Table 1 of the Annex to Commission Regulation (EU) No. 37/2010 with a no MRL required classification for bovine, porcine and *Equidae*.

Zoetis Belgium SA submitted to the European Medicines Agency an application for the review of maximum residue limits on 1 February 2019.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 18 March 2020 that the entry for ketoprofen in Table 1 of the Annex to Regulation (EU) No. 37/2010 should remain unaltered.

Subsequently the Commission confirmed that no change is to be made to the entry for ketoprofen in the Annex to Regulation (EU) No. 37/2010.

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Ketoprofen
Therapeutic class:	Nonsteroidal anti-inflammatory agents
Procedure number:	EMEA/V/MRL/003652/MODF/0003
Applicant:	Zoetis Belgium SA
Target species:	Bovine
Intended therapeutic indication:	Treatment of inflammatory and painful conditions, reduction of pyrexia associated with bacterial infections
Route(s) of administration:	Intramuscular, intravenous

1. Introduction

Ketoprofen is a non-steroidal anti-inflammatory drug belonging to the arylpropionic acid group. It is used in human and veterinary medicine for its anti-inflammatory, analgesic and antipyretic activities. It is indicated for inflammatory and painful conditions of the bones, joints and muscular-skeletal systems in cattle, horses, dogs and cats, for alleviation of pain associated with colic in horses and cattle, for reducing pyrexia and respiratory rate in case of respiratory infections in pigs and as supportive treatment of mastitis-metritis-agalactia syndrome in the sow. The dose in food producing species is 2 to 3 mg/kg bw by intravenous or intramuscular route.

Ketoprofen was previously assessed by the CVMP and a pharmacological ADI of 5 µg/kg bw, i.e 0.3 mg/person was established.

Currently ketoprofen is included in Table 1 of the Annex to 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**
Ketoprofen	NOT APPLICABLE	Bovine, porcine, *Equidae*	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

On 1 February 2019 Zoetis Belgium SA submitted to the European Medicines Agency a request under Article 11 of Regulation (EC) No 470/2009 to issue a new opinion on ketoprofen taking into account additional data relating to the safety of the substance.

2. Scientific risk assessment

The consumer safety of ketoprofen was originally assessed by the CVMP in 1995 and 1996 (see published summary reports EMEA/MRL/020/95 and EMEA/MRL/076/96-FINAL). The information presented in those reports is detailed below along with additional information provided for the current review and consisting of new safety data.

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of ketoprofen and established an ADI of 5 µg/kg bw, i.e 0.3 mg/person, based on an estimated pharmacological NOEL in humans of 3 mg/person and applying an uncertainty factor of 10.

In addition to the previously existing data, new toxicity studies have been provided.

Pharmacodynamic properties including mode of action

Ketoprofen inhibits the activity of cyclooxygenase enzymes, which are involved in the synthesis of prostaglandins. Prostaglandins are involved in pain and inflammation.

A single dose, double-blind study was reported to determine the relative analgesic efficacy of low dose ketoprofen (6.25 mg, 12.5 mg, and 25 mg) compared with ibuprofen (200 mg) and placebo in 175 patients with moderate to severe postoperative pain secondary to extraction of impacted third molars. In this study, ketoprofen at dose levels of 6.25 mg, 12.5 mg, and 25 mg, and ibuprofen at a dose of 200 mg were found to be effective analgesics (significantly superior to placebo). A dose-response relationship was seen for the 6.25 mg dose and the two higher doses of ketoprofen. However, there was a plateau effect between the 12.5 mg and 25 mg dose levels. The dose of 6.25 mg per person is therefore regarded as a LOAEL and corresponds to 0.1 mg/kg bw.

Pharmacokinetic properties (mainly in laboratory animals)

Ketoprofen is well absorbed after oral administration in all species studied (rats, dogs, rabbits, non-human primates, and humans). Studies in rats demonstrated significant entero-hepatic cycling. Nearly all absorbed ketoprofen is glucuronidated and the glucuronide conjugates are mainly excreted in urine. In rats, females had a higher systemic exposure than males, which may be explained by a lower metabolic clearance in females. These sex differences were however not observed in any other animal species, including humans, and are therefore of limited importance for the human risk assessment, although they may become of relevance in the interpretation of results obtained in rats. The metabolite RP 69400 (2-(phenyl 3-alpha-hydroxybenzoyl) propionic acid) was found in significant amounts in plasma of all species except the rat where only trace levels were detected.

2.1.1. Calculation of pharmacological ADI, if relevant

The previously estimated pharmacological NOEL of 3 mg/person (based on slight analgesic effects in humans at a dose of 6.25 mg/person) is supported by a larger, double-blinded human study. This study would therefore support the previously established ADI. However, a large amount of human pharmacokinetic data is available to estimate the variation in AUCs between humans, which allows adjusting the standard uncertainty factor of 10 that was previously used by the CVMP. This factor of 10 for intraspecies variation can be divided into 2 subfactors of 3.16 each, one for variation in pharmacokinetics and one for pharmacodynamics. Based on 17 published studies including healthy adults, as well as elderly patients, young and aged arthritis patients, cholecystectomy patients, and end-stage renal disease patients, the subfactor for pharmacokinetics can be adjusted to 2.4. It was noted that the database used did not include data on children, however separate published studies indicated that the pharmacokinetics of total racemic ketoprofen was similar in children (older than 6 months) and adults. The total intraspecies uncertainty factor would therefore be 2.4x3.16=7.58. Applying this factor to the pharmacological NOAEL of 3 mg/person results in a pharmacological ADI of 0.007 mg/kg bw, *i.e.* 0.42 mg/person.

2.1.2. Overview of toxicology

Toxicity studies in mice, rats, rabbits, dogs, and non-human primates have been provided. The main effects noted in these studies were stomach ulceration/haemorrhages/perforation, papillary necrosis of the kidneys, and delayed/incomplete parturition. These three toxicological effects are all related to the mechanism of action involving the decreased synthesis of prostaglandins and are consistent with the effects known for other NSAIDs.

Single-dose toxicity, where appropriate

Single dose toxicity studies were conducted using oral and parenteral routes. In mice, rabbits and dogs, the LD50 by all routes (oral, subcutaneous, intraperitoneal) was approximately 500 mg/kg bw. In rats, results were more variable from 30 to 480 mg/kg bw. Clinical signs reported were those usually observed with other NSAIDs.

Repeated dose toxicity

From four oral repeated dose toxicity studies in rats, covering exposure of 13 to 104 weeks, the overall NOAEL was 0.1 mg/kg bw/day, based on histopathological changes in the stomach and kidneys at 0.5 mg/kg bw/day.

A 13-week oral repeated dose toxicity study in dogs revealed a LOAEL of 3 mg/kg bw/day, based on gastric ulceration at the lowest dose tested.

Studies in cynomolgus monkeys and baboons, covering exposure of 13 to 52 weeks, revealed an overall NOAEL of 3 mg/kg bw/day, based on an increased incidence of vomiting and emesis.

The previous CVMP Summary Report stated the following additional NOELs: 2 mg/kg bw/day in dogs, but only 2 animals were used in this study, and 4.5 mg/kg bw/day in a 6-month oral study carried out in baboons. The summary Report did not state the effects observed in these studies. It is noted that a longer (1 year) oral repeated dose toxicity study in baboons had a NOAEL of 9 mg/kg bw/day.

Reproductive toxicity, including developmental toxicity

The CVMP reported previously that in fertility studies, in rats, effects of ketoprofen on male and female reproduction functions were observed with a NOEL of 3 mg/kg bw/day.

In a new oral 2-generation reproductive toxicity study, rats were given ketoprofen at doses of 0, 0.1, 0.3, 1.0, and 3.0 mg/kg bw/day. The F0 and F1 parents showed stomach and kidney lesions at all dose levels. A BMDL5 of 0.04 mg/kg bw/day for kidney lesions was derived. The NOAEL for effects on reproduction was 0.3 mg/kg bw/day, based on an increased gestation length. This study used a dosing holiday during the last part of pregnancy, including delivery, in view of treatment-related delayed or incomplete parturition observed in an earlier study that was terminated. Two additional parturition studies confirmed that the NOAEL of 0.3 mg/kg bw/day observed in the reproductive toxicity study is also protective for effects on parturition. No neonatal toxicity was observed in the pups.

In relation to developmental toxicity, the CVMP reported previously that after oral administration, no embryotoxic or teratogenic effects could be seen in rats and mice. However, in rats, ketoprofen was maternotoxic at 9 mg/kg bw/day. In rabbits, ketoprofen was maternotoxic at doses higher than 2 mg/kg bw/day after oral administration. The NOEL for embryotoxicity was 2 mg/kg bw/day.

In a new oral developmental toxicity study, rats were given ketoprofen doses of 0, 0.3, 1, 4, 12 mg/kg bw/day. The NOAEL for both maternal and developmental toxicity was 4 mg/kg bw/day, based on

extreme maternal toxicity at 12 mg/kg bw/day. A further oral developmental toxicity study in rabbits was available. The test substance was ketoprofen methyl ester (KME), a prodrug of ketoprofen; a comparative pharmacokinetic study in rabbits showed that dosing with KME resulted in a similar ketoprofen plasma AUC but a lower ketoprofen Cmax as compared to dosing with ketoprofen. This study revealed a NOAEL of 4 mg KME/kg bw/day for maternal toxicity based on weight loss and decreased food consumption, and a BMDL5 of 2.6 mg KME/kg bw/day for developmental toxicity based on increased post-implantation losses, a reduced mean number of viable foetuses and reduced foetal weights. Teratogenic effects were not observed in these studies. Corrected for differences in Cmax, the NOAEL and BMDL5 for KME corresponded to values for ketoprofen of 3.0 and 2.0 mg/kg bw/day, respectively.

Genotoxicity

The CVMP reported previously that in a set of mutagenic tests (Ames, CHO/HGPRT test, chromosome aberration test in CHO, and micronucleus test) ketoprofen and its metabolite RP 69400 (Ames, micronucleus test) did not show mutagenic activity.

Genotoxicity studies provided with this modification application included studies with ketoprofen, with ketoprofen metabolite RP69400, and with the pro-drug ketoprofen methyl ester (KME).

Ketoprofen was tested *in vitro* in the Ames test and in a chromosomal aberration assay in CHO cells, and *in vivo* in two micronucleus assays in rat peripheral blood reticulocytes and rat bone marrow. These tests gave negative results.

Metabolite RP69400 was tested *in vitro* in the Ames test and the micronucleus test. Both studies gave negative results.

KME was tested *in vitro* in the Ames test and in a chromosomal aberration assay in CHO cells and *in vivo* in a micronucleus test in rat bone marrow and in a comet assay in rat liver cells. The Ames test was negative, but the chromosomal aberration test was positive, however only with metabolic activation and in the absence of serum. The two *in vivo* studies with KME gave negative results.

Overall, it was concluded that ketoprofen is not genotoxic.

Carcinogenicity

The CVMP previously reported that two carcinogenicity studies carried out in mice (4, 8, 16 or 32 mg of ketoprofen for 105 consecutive weeks) and in rats (3, 4.5 and 7 mg of ketoprofen for 91 weeks followed by a 13-week observation period) showed no treatment-related effects on the incidence or distribution of spontaneous tumour profile of the strain of animals used.

A further combined repeated dose oral toxicity and carcinogenicity study in rats with oral doses of 0, 1.5, 3, 6 mg/kg bw/day also showed no increased incidences of tumours.

2.1.3. Calculation of the toxicological ADI or alternative limit

Rats are the most sensitive species tested. The lowest BMDL5 in rats was 0.04 mg/kg bw/day, based on kidney lesions observed in the new 2-generation reproductive toxicity study. A dose level of 3 mg/kg bw/day was the LOAEL for repeated dose toxicity in dogs and the NOAEL for repeated dose toxicity in monkeys. The NOAEL for reproductive toxicity in rats was 0.3 mg/kg bw/day.

The toxicological ADI can be based on a Point of Departure of 0.04 mg/kg bw/day and an uncertainty factor.

In view of the availability of sufficient pharmacokinetic data in rats and humans, chemical specific adjustment factors can be used to replace the default uncertainty factor of 100 (10x10 for intraspecies and interspecies variation). The factor for interspecies variation is composed of subfactors of 4 and 2.5 for pharmacokinetic and pharmacodynamic variation. The interspecies pharmacokinetic subfactor can be reduced to 0.4 on the basis of the difference in the oral dose for rats and humans needed to achieve the same AUC of S(+)-ketoprofen in plasma. This difference of doses is explained by a higher exposure to S(+)-ketoprofen in the rat than in the human, due to a high chiral inversion to the active S(+)-enantiomer and enterohepatic cycling in rats. The factor for intraspecies variation is composed of subfactors of 3.16 and 3.16 for pharmacokinetic and pharmacodynamic variation. The intraspecies pharmacokinetic subfactor could be reduced to 2.4 on the basis of the observed variation in AUCs in humans. The resulting overall uncertainty factor is therefore 0.4x2.5x2.4x3.16=7.6.

The toxicological ADI is 0.005 mg/kg bw, based on the BMDL5 of 0.04 mg/kg bw/day and an uncertainty factor of 7.6.

2.1.4. Overview of microbiological properties of residues

Ketoprofen is not classified as an antimicrobial agent and is not structurally related to antimicrobial agents used in human or animal medicine. Data on microbiological properties are therefore not considered necessary.

2.1.5. Observations in humans

See pharmacodynamics.

2.1.6. Findings of EU or international scientific bodies

With the exception of the previous evaluations undertaken by the CVMP ketoprofen has not been evaluated for this purpose by EU or international scientific bodies.

2.1.7. Overall conclusions on the ADI

The previously established pharmacological ADI of 0.005 mg/kg bw/day (0.3 mg/person) is increased to 0.007 mg/kg bw/day (0.42 mg/person), because of the use of chemical specific adjustment factors to replace the standard uncertainty factor.

The toxicological ADI is 0.005 mg/kg bw/day (0.3 mg/person), based on the BMDL5 of 0.04 mg/kg bw/day and an uncertainty factor of 7.6.

The toxicological ADI is lower than the (increased) pharmacological ADI, but equal to the pharmacological ADI previously established by the CVMP.

2.2. Residues assessment

No new pharmacokinetic or residue data in target animal species have been submitted with the modification application. Because the value of the currently established ADI is equal to the value of the pharmacological ADI previously established by the CVMP, there is no need to revise the risk assessment, and therefore further residue data are not deemed necessary.

2.2.1. Pharmacokinetics in target species

The CVMP previously reported the following pharmacokinetic data in target animals.

Ketoprofen is converted into a carbonyl-reduced derivative, the RP 69400 (2-(phenyl 3-alpha-hydroxybenzoyl) propionic acid).

Ketoprofen is strongly bound to proteins (97% in cattle). After single intramuscular administration of 3 mg of ketoprofen/kg bw supplemented with ^{14}C ketoprofen, plasma data showed a good relationship between total radioactivity and the sum of ketoprofen and RP 69400.

Ketoprofen represents about 50% of total activity from 4 to 8 hours post treatment.

In cattle after intramuscular administration, ketoprofen is rapidly absorbed ($t_{1/2}$ ka = 0.15-0.25 h). Bioavailability ranged from 85% to 100%. After a single intramuscular administration of 3 mg of ketoprofen/kg bw (with ^{14}C methyl-ketoprofen), 90% of the radioactivity was recovered in the urine within 96 hours: 90-93% of the radioactivity was due to the metabolite RP 69400, whereas ketoprofen only represented 1%. The hydroxyl derivatives in position 3 and 4 represented only 0.5 to 2.7% of the urine metabolites. About 6% of the administered dose was recovered in the faeces.

After a single intramuscular administration of 3 mg/kg bw of ^{14}C -ketoprofen to calves, the ratio ketoprofen/total residue could be evaluated: 56% for muscle, 35% for fat, 2% for liver and 56% for kidney. At the injection site, the ratio was close to 85%.

In horses, after intravenous administration of 2.2 mg of ketoprofen/kg bw/day, ketoprofen and RP 69400 were no longer detected in plasma three hours after injection. In urine, concentrations of metabolite RP 69400 (free and conjugated forms) were lower than those of ketoprofen. Metabolites 3- and 4- hydroxy-ketoprofen could not be detected either in plasma or in urine.

The reduction of ketoprofen into metabolite RP 69400 was demonstrated in an in vitro metabolism study of ^{14}C-ketoprofen by the microsomal and cytosol fractions of pig liver. However, this reduction is about two-fold lower than that in bovine species.

In pigs, after a single intravenous administration of 3 mg/kg bw, ketoprofen is poorly distributed, the steady-state volume of distribution (Vdss) being low (= 0.17 $\pm$ 0.02 l/kg). The mean residence time (MRT) was 2.32 $\pm$ 0.41 h.

Thirty minutes after a single intramuscular injection of 3 mg/kg bw of ^{14}C-ketoprofen to pigs, a peak mean plasma concentration of 12.74 ± 2.50 mg equivalents ^{14}C-ketoprofen/l was observed. The concentrations decreased rapidly to reach 0.07 ± 0.01 mg equivalents ^{14}C-ketoprofen/l twenty-four hours later. For later collecting points, ^{14}C-Ketoprofen was detected as traces.

It was shown that about 84% of the plasma radioactivity in pigs was due to the parent compound, and 7% to RP 69400. The remaining radioactivity was due to unidentified polar materials accounting for about 8% of radioactivity.

In pigs, a balance study after a single intramuscular injection of 3 mg/kg bw of ^{14}C-ketoprofen showed that 72% of the total radioactivity administered was excreted via urine within 96 hours, a majority being excreted within 24 hours. Only 20% were recovered in faeces.

In pig urine, about 30% of the radioactivity was due to RP 69400, 12% to the parent compound, and approximately 45% to polar components.

The concentrations of metabolite RP 69400 were below the limit of quantification of 0.1 mg/kg in all tissues, at all times and in all animals.

Due to very fast elimination of the radioactivity, the ratio of ketoprofen/total residues and RP 69400/total residues could only be evaluated in samples collected 3 hours after a single intramuscular administration of 3 mg/kg bw of ^{14}C-ketoprofen to pigs.

The percentage of ketoprofen residues with respect to total residues were as follows: 31.5% for kidney, 0.3% for liver, 72% for fat, 94% at the injection site.

For RP 69400, the figures were respectively: 29% for kidney, 78% for liver, 10% for fat, and 3% at the injection site.

2.2.2. Residue depletion studies

The CVMP previously reported the following residues depletion data in target animals.

In cattle, after a single intramuscular administration of 3 mg/kg bw with ^{14}C ketoprofen, only trace levels were detected at the injection sites, 96 hours after treatment. After repeated administrations of 3 mg/kg bw/day for 3 days, ketoprofen and RP 69400 could only be measured in kidneys, 24 hours after the third injection: 0.19 ± 0.14 µg/g for ketoprofen and 0.24 ± 0.17 µ/g for RP 69400. In other tissues, they were either non detectable (<0.025 µg/g for ketoprofen and 0.05 µg/g for metabolite RP 69400) or lower than the quantification limit (0.05 µg/g for ketoprofen, 0.1 µg/g for RP 69400). At the injection site, corresponding to the 3rd injection, only ketoprofen was detectable, the mean concentration being 1.51 ± 1.68 µg/g.

Ketoprofen and its metabolite RP 69400 could not be detected (<0.025 µg/ml) in the milk at any milking both during and after treatment by ketoprofen at the recommended dosage.

No residue depletion study was carried out in the horse. However, from the comparison of basic pharmacokinetic parameters obtained for cattle and horses, it can be concluded that tissue depletion of ketoprofen in horse will be faster than in cattle.

A radiometric depletion study was carried out in pigs with ^{14}C-ketoprofen at the recommended intramuscular dosage of 3 mg/kg bw:

- Three hours post injection, the concentrations were the following: kidney (11.63 mg equivalents-ketoprofen/kg), liver (3.02 mg equivalents ketoprofen/kg), at the injection site (12.40 mg equivalents ketoprofen/kg). In the samples of skin plus fat and in muscle, the amounts were close to 1 and 0.5 mg equivalents ketoprofen/kg;
- Twenty four hours post dose, the radioactivity levels had already decreased to 2.07 mg equivalents ketoprofen/kg in kidney and to 0.24 mg equivalents ketoprofen/kg in liver. In other edible tissues, the concentrations were close to the limit of quantification (0.03 and 0.09 mg equivalents ketoprofen/kg for muscle and skin plus fat respectively;
- Ninety six hours post dose, ^{14}C-ketoprofen could only be measured in kidney (0.82 mg equivalents ketoprofen/kg) and in liver (0.07 mg equivalents ketoprofen/kg).

In a non-radiometric study in pigs carried out with 3 x 3 mg/kg bw at 12 hours apart, the concentrations of ketoprofen in the liver, muscle and skin-fat, were below the limits of quantification (0.050 mg/kg) in all animals except one in which the levels in the skin-fat and muscle were 0.058 and 0.060 mg/kg respectively, twenty-four hours after the end of the treatment. In kidney, the levels ranged from 0.067 to 0.097 mg/kg in 3 pigs and for the 4th animal, the concentration was below the limit of quantification (0.050 mg/kg). Twenty-four hours post dosing, the ketoprofen levels at the injection sites ranged from 20.80 to 0.40 mg/kg. Four and ten days after the final injection, the concentrations of ketoprofen were

below the limits of quantification of the method (0.050 mg/kg) for all the tissues, the injection site included.

Selection of marker residue and ratio of marker to total residues

Currently, ketoprofen has a "No MRL Required" status. Therefore, selection of a marker residue and determination of ratios of marker to total residues is not necessary.

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 method for monitoring of residues

The CVMP previously reported that there is an adequate and transferable analytical HPLC method with UV detection technique to ensure the monitoring of ketoprofen residues in the various tissues of cattle and in muscle of horses. The limits of detection and of quantification of this method are 25 and 50 µg/kg respectively.

The CVMP also previously reported that an analytical method for residues detection in skin plus fat, liver and kidney of pigs has been validated according to the recommendations of Volume VI of The rules governing medicinal products in the European Union (which has now been superseded by Regulation (EU) 2018/782) and described according to the format ISO 78/2. The limits of quantification for ketoprofen and RP 69400 were 0.050 and 0.100 mg/kg respectively. The limits of detection ranged between 0.017 to 0.031 mg/kg for ketoprofen and from 0.027 to 0.066 mg/kg for RP69400.

2.2.5. 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.

2.2.6. Findings of EU or international scientific bodies

With the exception of the previous evaluations undertaken by the CVMP ketoprofen has not been evaluated for this purpose by EU or international scientific bodies.

3. Risk management recommendations

The intention of this modification application is only to review the ADI. Because the value of the ADI established as part of this review is equal to the value of the ADI previously established by the CVMP, there is no need to revise the risk management recommendations. This includes the previous recommendation of the Committee for a withdrawal period of 4 days for edible tissues to ensure adequate depletion of residues at the injection site.

3.1. Availability of alternative medicines and other legitimate factors

Various non-steroidal anti-inflammatory drugs (NSAIDs) are available for food producing species in the EU.

3.2. Elaboration of MRLs

Ketoprofen is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009, with no MRLs required for bovine species, porcine species, and *Equidae*. Because the current assessment resulted in the same numerical value for the ADI, there is no need to amend the MRL entry.

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 "No MRL Required status" recommended for ketoprofen in cattle, pigs and *Equidae* to other food producing species and commodities, taking into account the provisions laid down in Regulation (EU) 2017/880. The regulation indicates that, as an identical MRL status has been established in a major ruminant and a major monogastric species extrapolation to all mammals can be considered. However, pharmacokinetic and/or residue data were only available in cattle, pigs and *Equidae* and the similarity of the metabolic profiles in other species is not known. In view of these uncertainties extrapolation is not recommended.

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

Having considered that:

- a pharmacological ADI of 0.007 mg/kg bw (0.42 mg/person) was established,
- a toxicological ADI of 0.005 mg/kg bw (0.3 mg/person) was established,
- the overall ADI of 0.005 mg/kg bw is equal to the ADI previously established by the CVMP;

the CVMP recommends that the entry for ketoprofen in Table 1 of the Annex to Regulation (EU) No. 37/2010 should remain unaltered in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Ketoprofen	NOT APPLICABLE	Bovine, porcine, *Equidae*	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

In the original CVMP assessment for ketoprofen a withdrawal period of 4 days was recommended to allow residues at the injection site to deplete. As the current evaluation did not re-examine the residues file this recommendation is considered to remain appropriate.

6. Background information on the procedure

Submission of the dossier	01 February 2019
Steps taken for assessment of the substance	
Application validated:	20 February 2019
Clock started:	21 February 2019
List of questions adopted:	20 June 2019
Consolidated response to list of questions submitted:	18 December 2019
Clock restarted:	23 December 2019
Opinion adopted:	18 March 2020