



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CVMP/239233/2014
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR) Clodronic acid (in the form of disodium salt) (*Equidae*)

On 3 July 2015 the European Commission adopted a Regulation¹ establishing maximum residue limits for clodronic acid (in the form of disodium salt) 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.

Clodronic acid (in the form of disodium salt) is intended for use intramuscularly in horses for the treatment of navicular syndrome.

Dechra Limited submitted the application for the establishment of maximum residue limits to the European Medicines Agency, on 26 November 2013.

Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 8 May 2014 the establishment of maximum residue limits for clodronic acid (in the form of disodium salt) in *Equidae*.

Subsequently the Commission recommended on 23 May 2015 that maximum residue limits in *Equidae* are established. This recommendation was confirmed on 13 June 2015 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 3 July 2015.

¹ Commission Implementing Regulation (EU) No 2015/1078, O.J. L 175, of 03 July 2015



Summary of the scientific discussion for the establishment of MRLs

Substance name:	Clodronic acid (in form of disodium salt), also referred to as clodronate disodium
Therapeutic class:	Bisphosphonates
Procedure number:	EU/10/171/DEC
Applicant:	Dechra Limited
Target species:	<i>Equidae</i>
Intended therapeutic indication:	Treatment of navicular syndrome
Route(s) of administration:	Intramuscular injection

1. Introduction

Clodronate, the active part of clodronate disodium, belongs to the bisphosphonate group of substances which are synthetic analogues of naturally occurring pyrophosphate. Clodronate, like other bisphosphonates, is an inhibitor of osteoclast-mediated bone resorption.

Clodronate disodium is intended for use in horses for the treatment of navicular syndrome at a dose of 1.8 mg/kg (maximum dose of 900 mg/ horse) intramuscularly. The dose can be repeated after 6 months if there is a recurrence of clinical signs.

Clodronate is used in human medicine as an adjunct to the treatment of severe hypercalcaemia, especially when associated with malignancy. It is also used in the treatment of osteolytic bone metastases. It is administered orally at a dose of 1.6 g daily up to 3.2 g for six months or longer.

2. Scientific risk assessment

2.1. Safety assessment

2.1.1. Overview of pharmacological properties

Pharmacodynamic properties including mode of action

Due to their affinity for hydroxyapatite, bisphosphonates accumulate in the skeleton and act primarily on calcified tissues. Clodronate increases bone mass by inhibiting bone resorption and retarding bone turnover. Bound to bone matrix, it enters resorbing osteoclasts, alters their morphology and reduces the number of active osteoclasts. The primary target of its pharmacological action is considered to be the osteoclasts.

The effect of clodronate on bone mineral density, histology, bone strength, bone geometry, bone loss, osteopenia and biochemical markers of bone turnover has been investigated in *in vivo* studies including numerous studies with ovariectomised rats and with osteopenia-induced rats. In the studies with ovariectomised rats, the doses ranged from 5 to 500 mg/kg bw (oral route) and 4 to 25 mg/kg bw (administration via subcutaneous or intraperitoneal injection); clodronate was administered repeatedly during a period varying from 3 days up to 12 weeks. In the studies with osteopenia-induced rats, the

doses ranged from 1.5 to 25 mg/kg bw and clodronate was administered subcutaneously once a week during a period of 3 or 6 months. From the studies in ovariectomised and osteopenia-induced rats, it can be concluded that clodronate decreased the loss of total and trabecular bone mineral density, prevented the weakening of bone strength and suppressed, but not completely reversed, osteopenia in oestrogen-deficient rats.

In rat studies investigating effects on the skeleton of healthy animals subcutaneous injections of clodronate (2 to 12 mg/kg bw, once or twice per week, 50 mg/kg bw once per four weeks) administered for approximately 6 months increased bone mass, trabecular bone area and maximum load in a compression test, while longitudinal bone growth appeared to be decreased at relatively high doses. In these studies osteocalcin concentrations, calcium, hydroxylysylpyridinoline and hydroxyproline excretion were decreased. Studies in animals with bone fractures indicate that treatment with clodronate at daily subcutaneous doses of 3 to 30 mg/kg bw or weekly doses of 50 mg/kg bw for 8 to 22 weeks may retard remodelling of the fracture. In rat arthritis models subcutaneous clodronate treatment (5 to 25 mg/kg bw, administered daily or every second day) for 2 to 4 weeks appeared to suppress the intensity of the inflammation and secondary articular and bone lesions. Clodronate (subcutaneous administration at 10 mg/kg bw/day for 21 days) prevented decrease in bone mass due to immobilization.

Studies in mice indicate that intravenously or intracerebroventricularly administered clodronate may exert an antinociceptive effect. Oral treatment of ovariectomized beagles (40 mg/kg bw/day for 8 months) increased bone mineral density and treatment of ovariectomized cynomolgus monkeys (60 mg/kg bw/day for 16 months) prevented bone loss. Doses of 1000 mg/kg bw, orally, and 30 mg/kg bw, intravenously, did not affect behaviour of mice. An intravenous dose of 100 mg/kg bw in mice induced transient changes in behaviour. In anaesthetised dogs, mortality was observed after 30 and 100 mg/kg bw, but not after 10 mg/kg bw. At 30 mg/kg bw, transient cardiovascular and respiratory effects were noted. In rats clodronate at intravenous doses of 30 mg/kg bw and above induced decreases in urinary volume and excretion of electrolytes.

A dose-effect study on the efficacy of clodronate on tumour-induced osteolysis in human patients was available. In this study a NOAEL of 400 mg/day (equivalent to 6.7 mg/kg bw/day for a person weighing 60 kg) was derived, based on inhibition of bone resorption at 1600 and 3200 mg. In additional human studies observations show the occurrence of side effects after oral exposure to dose levels in the range of 13.3 and 17.3 mg/kg bw/day. In the latter studies no dose without an effect was reported and the studied parameters were limited to some clinical effects.

Pharmacokinetic properties (mainly in laboratory animals)

Pharmacokinetic parameters of clodronate have been determined in mice, rats, rabbits, minipigs, horses and humans. Original study reports and public literature were provided.

Clodronate is poorly absorbed following oral administration, with a very low bioavailability (less than 5%) in rats and humans. In contrast, the absorption is extensive following intramuscular and subcutaneous administration and the bioavailability is much higher (105% and 89%, respectively). Peak clodronate concentrations in rat plasma were reached within 5 minutes, regardless of the administration route (intravenous, intramuscular or subcutaneous). At the recommended dose of 900 mg administered by the intended route (intramuscular) in horses, the maximum plasma concentration of 7.5 µg/ml of clodronate was reached by approximately 35 minutes after administration.

In a study conducted in rats and minipigs no metabolites of clodronate could be detected, indicating that clodronate is not metabolised.

Distribution studies in rats and mice showed rapid and high distribution of ¹⁴C-clodronate to the target tissue bone, with relatively high levels even 12 months after administration. It is indicated that incorporation of clodronate in bones was more extensive in the areas with the highest remodelling rate. The route of administration (intravenous, intraperitoneal or subcutaneous) had no effect on the deposition of clodronate in bone in mice. In mice radioactivity was seen to persist in the bone, spleen, thymus and small intestine for up to one year but was much less persistent in liver and kidney. In rats radioactivity persisted in bone and spleen for up to 1 year, in liver for up to 90 days and in kidney for up to 21 days.

Following oral administration, clodronate was mainly excreted via faeces (supporting the low oral bioavailability) in rats, minipigs and humans. Following intravenous, intramuscular or subcutaneous administration, clodronate was eliminated predominantly via urine with a plasma half-life of between 1 and 2 hours regardless of the administration route in rats. In horses, the elimination plasma half-life was 5.6 hours.

In general, the pharmacokinetic data on clodronate is comparable between the species examined. However, some interspecies and sex differences are observed:

- After repeated intravenous administration in rats, the area under the curve (AUC) is higher in males than in females. In addition, the clearance was higher in females (1.02 l/h*kg) compared to males (0.75 l/h*g);
- After single intramuscular administration in horses, females have a higher AUC, C_{max}, half-life and T_{max} compared to males.
- Following oral administration, significantly higher levels were measured in the faeces of female rats compared to males, which supports the finding that a lower bioavailability was observed in females (4.0%) than in males (10.2%);
- The distribution to bone is comparable between mice and rats, however, the distribution to thymus and small intestine is only observed in mice. In addition, accumulation in the spleen was higher in mice compared to rats;
- The elimination plasma half-life of clodronate appears to be slightly slower in the horse and minipig than that reported for the rat.

2.1.2. Calculation of pharmacological ADI

A pharmacological ADI of 0.13 mg/kg bw was derived. This was based on the NOAEL of 6.7 mg/kg bw/day for inhibition of bone resorption in a study with human patients, and using a total safety factor of 50. The safety factor of 50 was comprised of a factor of 10 for intraspecies variability and an additional factor of 5 in view of the limited data base and the small margin between the NOAEL of 6.7 mg/kg bw/day and the LOAELs of 13.3 and 17.3 mg/kg bw/day based on side effects observed in human studies with sometimes small numbers of patients.

2.1.3. Overview of toxicology

Single-dose toxicity

Acute oral toxicity was investigated in rats, mice, and minipigs. In addition data after intravenous exposure were available.

Acute oral toxicity was considered to be low. No difference in sensitivity was observed between males and females. Rats appeared to be more sensitive than mice as observed in both intravenous and oral studies.

Target organs frequently affected appeared to be the liver and kidney. Distension of the gastrointestinal tract might be related to irritation after oral exposure, as these effects were not mentioned after intravenous administration.

Repeated dose toxicity

Oral and intravenous repeated dose toxicity studies in rats and minipigs were available.

In two oral (gavage) toxicity studies in rats, one where rats were exposed to concentrations ranging from 100 to 600 mg/kg bw/day for 3 months (15 animals/sex/dose) and one where rats were exposed to 100 to 400 mg/kg bw/day for 12 months (44 animals/sex/dose) the liver and bone appeared to be the major targets for toxicity. At 100 mg/kg bw/day (lowest dose tested), increases in alanine transaminase and aspartate transaminase levels, reductions in absolute and relative liver weights and the extension of the metaphyseal trabeculae in bones were found. In addition in the 3-month study reduced levels of inorganic phosphorus and calcium were found at this dose and higher doses. In a 6-month oral toxicity study in minipigs (5 animals/sex/dose) exposed to concentrations ranging from 100 to 1000 mg/kg bw/day, doses of 100 mg/kg bw/day and higher caused increased alanine transaminase levels in males, rapid and marked reduction in erythropoiesis in bone marrow smears, reduction in marrow cellularity and myelopoiesis, and zones with closely arranged longitudinal trabeculae in the spongy substances of long bones. In a 12-month study in minipigs (1 to 2 animals/sex/dose) exposed to concentrations ranging from 150 to 600 mg/kg bw/day inhibition of bone resorption (bone turnover) was found at oral doses of 150 mg/kg bw/day and higher. An additional report describing other effects in this 12-month study in minipigs was not available for evaluation.

Effects in rats and minipigs were observed at oral doses of 100 mg/kg bw/day and higher. A NOAEL for oral toxicity could not be established as effects were observed at all dose levels.

In intravenous studies in rats and minipigs the observed effects were qualitatively similar to those observed after oral treatment. The critical effects appeared to be bone structure, bone marrow, the haematopoietic system, and the liver. Effects in rats and minipigs were observed at intravenous doses of 1 mg/kg bw/day and higher. A NOAEL could not be established.

Reproductive toxicity, including developmental toxicity

In a one-generation study of reproductive toxicity in rats exposed to concentrations ranging from 50 to 600 mg/kg/day (30 animals/sex/dose), the NOAEL for parental toxicity could not be established as at 50 mg/kg bw/day (the lowest dose tested) mortality occurred in females and there were macroscopic effects on testes and epididymides (small, purple and/or flaccid testes and small epididymides, histology not performed). No NOAEL could be established for reproductive effects in view of the effects on the testes and epididymides seen at the lowest dose of 50 mg/kg bw/day. Although at the dose of 50 mg/kg bw/day no effect on fertility was reported, it cannot be ruled out that the effects on testes and epididymides at 50 mg/kg bw/day were related to reduced fertility observed at higher doses in this study.

The one-generation reprotoxicity study does not satisfy the requirements of VICH Topic GL 22 (Studies to evaluate the safety of residues of veterinary drugs in human food: reproduction toxicity), which recommends a multigeneration study performed according to OECD guideline 416. In addition the study has marked deficiencies and is of poor quality (no histology was performed, effects were poorly described and each treatment group included only 15 animals). Nevertheless, some serious effects of

clodronate were observed, e.g. mortality and effects on testes and epididymides observed at the lowest dose tested, and cannot be ignored. The information available was considered sufficient for the toxicological evaluation of clodronate. It was not considered necessary to request a two-generation study, as it would require the sacrifice of large number of extra animals while the information gained is expected to be limited.

In a developmental toxicity study in rabbits (20 females per dose) exposed to 70, 300 or 700 mg/kg bw/day, the NOAEL for foetal toxicity was 300 mg/kg bw/day, based on reduced litter size at 700 mg/kg bw/day. In a peri- and postnatal toxicity study the NOAEL for foetal/offspring toxicity was 100 mg/kg bw/day, based on reduction of pup weight and pup body weight gain at 200 mg/kg/day, which was already observed at the day of birth. In conclusion, the overall NOAEL for foetal and offspring toxicity is 100 mg/kg bw/day. In the available studies, clodronate was not teratogenic at the dose levels tested.

Genotoxicity

Clodronate was tested in a standard series of genotoxicity test systems, in accordance with VICH guidance:

- *In vitro* tests for gene mutations in bacteria (2 Ames tests);
- *In vitro* tests for chromosomal effects in mammalian cells (4 chromosome aberration tests);
- *In vivo* tests for chromosomal effects using rodent hematopoietic cells (2 micronucleus tests).

Furthermore, two mouse lymphoma mutation assays and an unscheduled DNA synthesis test (all *in vitro*) were provided. In addition, a literature study reported on the frequency of chromosome/chromatid breaks in bone marrow and blood cells of patients with Paget's disease (treated with clodronate).

With the exception of the literature study in which patients with Paget's disease are described, the studies were more or less performed in compliance with the relevant OECD test guidelines. In addition, most of the studies were performed under GLP conditions.

All studies with the exception of one *in vitro* chromosome aberration test, were negative. In one *in vitro* chromosome aberration test however, clodronate was found to induce a weak but statistically significant increase in chromosome aberrations (including gaps) in Chinese Hamster Ovary cells *in vitro* at the highest concentrations tested, 3500 and 4000 µg/ml, but only in the presence of metabolic activation. However, it was noted that the aberration frequencies exceeded the historical solvent control range only if chromosomal gaps were included. The toxicological significance of such gaps is not clear but most of them are not considered to represent true discontinuity in the chromosome and therefore do not have any genetic consequences.

Nevertheless, two *in vivo* studies were provided, and while both were conducted in mouse bone marrow, the studies investigated the effects via two routes of administration and at varying doses. In these micronucleus tests no indication of genotoxic potential of clodronate was found. Also in patients with Paget's disease, there was no indication of an increase in the frequency of chromosome/chromatid breaks in bone marrow and blood cells following chronic treatment with clodronate.

It is therefore concluded that clodronate is not genotoxic.

Carcinogenicity

Two oral (gavage) carcinogenicity studies (50 animals/sex/dose) were available, one in mice and one in rats. In the study in mice doses were 50, 100 and 200 mg/kg bw/day and in the study in rats doses were 45, 150 and 400 mg/kg/bw day.

Clodronate did not increase mortality in an 80-week study in mice or in a 104-week study in rats. In addition, no evidence was found of carcinogenic potency of clodronate in either of the studies.

Although at 45 mg/kg bw/day some effects were observed in mice (a very small decrease in bodyweight and increased trabecular extension in the sternum of females), these were too minor to be considered as adverse. Therefore 45 mg/kg bw/day was retained as the NOAEL (based on dose-dependent effects on body- and organ weight).

In rats, similar effects on trabecular extension were observed. In addition, at 50 mg/kg bw/day, an increase in alveolar cell changes was observed (20 and 14% of males and females versus 2 and 2% of male and female controls). At the top dose (200 mg/kg bw/day) the incidence of alveolar cell changes was increased even more and also an increased incidence of bronchiolitis and interstitial inflammation of the lung was reported. Therefore, due to an increase in alveolar cell changes, the dose level of 50 mg/kg bw/day can be considered as the LOAEL. A NOAEL cannot be derived in rats, since effects were observed at the lowest dose administered (50 mg/kg bw/day).

Studies of other effects including immunotoxicity and neurotoxicity

No specific studies on the immunotoxicity or neurotoxicity of clodronate were provided. This is acceptable because no indications of such effects were observed in the other toxicology studies or in the studies on pharmacodynamics.

2.1.4. Calculation of the toxicological ADI or alternative limit

An overall NOAEL could not be established. At 50 mg/kg bw/day an increase in alveolar cell changes was observed in a 2-year oral study in the rat, while in a study of reproductive toxicity in rats at this dose mortality of the dams around the time of parturition was observed. Therefore 50 mg/kg bw/day is considered to be the overall LOAEL.

A safety factor of 100 is used for inter- and intraspecies variation. An additional safety factor of 2 is used to account for the deficiencies in the reproduction toxicity study and a further factor of 5 is used for extrapolation of the LOAEL to a NOAEL; a factor of 5 is chosen in view of the severity of the effect (mortality of dams) observed at the LOAEL. The Committee noted the lower bioavailability in humans when the substance was taken with food, as compared to the bioavailability when given without food. However, in the rat studies used as a basis for the ADI, the substance was given by gavage but food was given *ad libitum* and therefore there is no clear indication that these rats received the test substance without any food present in their gastro-intestinal tract. Therefore the Committee did not consider it necessary to adjust the safety factor further. The overall safety factor is therefore 1000.

Based on the LOAEL of 50 mg/kg bw/day and the total safety factor of 1000 a toxicological ADI of 0.05 mg/kg bw is established.

2.1.5. Overview of microbiological properties of residues

Clodronate is not expected to possess antimicrobial activity as there is no literature to indicate the contrary and as the closely related molecule tiludronic acid showed no evidence of reported microbiological activity.

2.1.6. Calculation of microbiological ADI

As the substance is not expected to possess antimicrobial activity the establishment of a microbiological ADI is not relevant.

2.1.7. Observations in humans

Case reports from human use of clodronate revealed side effects at doses in the range of 13.3 and 17.3 mg/kg bw/day.

2.1.8. Findings of EU or international scientific bodies

Clodronate has not been evaluated by any other EU or international scientific bodies.

2.1.9. Overall conclusions on the ADI

As the toxicological ADI of 0.05 mg/kg bw is lower than the pharmacological ADI of 0.13 mg/kg bw and as a microbiological ADI was not considered relevant, the toxicological ADI is retained as the overall ADI.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

Bioavailability was not specifically studied in horses, however, it is not expected to be very different from that observed in other animal species studied (mice, rats, minipigs and humans), where clodronate was poorly absorbed. Specific metabolism studies with clodronate were not performed in horses, however, given the similarity of the pharmacokinetic profiles between species it may be concluded that the substance is not metabolised in horses. No distribution data are provided for horses, but based on data in other species bone is considered the tissue to which the substance is preferentially distributed.

A plasma kinetic study in horses revealed that the AUC and C_{max} were proportional to dose.

The T_{max} was between 35 and 40 minutes for all doses administered. At the maximum recommended dose (900 mg), the plasma half-life was 5.6 hours; clodronate was not detected in plasma after 24 hours.

After single intramuscular administration in horses, females had a higher AUC, C_{max}, half-life and T_{max} compared to males.

2.2.2. Residue depletion studies

A radiolabel residue study in horse was provided, studying the levels of clodronate residues in edible tissues. In this study, clodronate disodium was administered by the recommended administration route (i.e. intramuscular) at the recommended dose of 1.8 mg/kg bw (maximum of 900 mg/horse). The dose was divided over 3 injection sites (with a maximum volume of 5 ml per injection site corresponding to a maximum of 300 mg clodronate disodium per injection site). The study only included one slaughter time point, i.e. 12 hours after administration, therefore no information was available on the residue depletion profile and there were no data to ascertain that the 12 hour time point was consistent with the peak residue concentrations in tissues. The raw data presented with the study revealed that the measurements in tissues showed extreme variation, even when analysing aliquots of the same sample. Occasionally samples with incurred residues showed no radioactive count at all, while on other occasions the radioactivity appeared to be extremely high. This high variation could not be explained. Samples were re-tested until a series of measurements of acceptable variation and assumed correctness was obtained. These values were then selected for calculating the averages and for reporting. The remaining values were discarded. The Committee had serious concerns in relation to the measurements and the way the data were used. In the absence of a clear and acceptable explanation for the variation, there appeared to be no scientific ground for accepting or rejecting values as being correct. The study was not considered to be robust and therefore the data were not regarded as being sufficiently reliable. The Committee concluded that these data could not be used for the calculation of the residue intake for consumers.

A second, non-radiolabelled study was provided in which horses were treated with the recommended dose (up to a maximum 900 mg/horse, corresponding to 1.6 - 1.8 mg/kg bw), via the recommended route of administration (intramuscular injection), but this time administered over two injection sites (i.e. 7.5 ml of the product per injection site), one each side of the neck. Twelve horses were treated and slaughtered in groups of three at the timepoints 12, 24, 48 and 96 hours after treatment. Clodronate was shown to be readily and quickly absorbed from the injection site. The 12-hour timepoint was confirmed as being the one where peak residues were measured. Clodronate was used as the marker residue, which is appropriate, as it has been shown to undergo very little metabolism. There were again marked differences between the results of the analyses of the two different injection sites from each horse, although there was no within-sample variability as seen in the radiolabel study. The study was considered to reliably demonstrate the tissue distribution and depletion over time of clodronate in horses. At 12 hours, the highest levels were seen in kidney samples ($1743 \pm 235 \mu\text{g}/\text{kg}$), followed by injection sites ($902 \pm 58 \mu\text{g}/\text{kg}$), liver ($146 \pm 43 \mu\text{g}/\text{kg}$) and fat (all values below the limit of quantification of $40 \mu\text{g}/\text{kg}$). No muscle samples distant from the site of injection were taken, but the Committee agreed that the results from the samples taken from the area surrounding the core injection sites could be considered as an overestimate of the maximum residues likely to be found in muscle, as indicated from the radiolabel study. All levels in surround muscle tissues were below the limit of quantification of the analytical method used ($600 \mu\text{g}/\text{kg}$). The data from this study were used to calculate the consumer residue intake.

Selection of marker residue and ratio of marker to total residues

Clodronate is hardly metabolised or not metabolised at all, and therefore is considered a suitable marker residue, with a marker to total residues ratio of 1.

2.2.3. Monitoring or exposure data

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

2.2.4. Analytical method for monitoring of residues

An analytical method described in line with international standards was provided and was conducted according to GLP. The methods for muscle and kidney, liver and fat were validated according to international guidelines, with regard to linearity, selectivity, accuracy and precision, carry over, limit of detection, limit of quantification, stability and assay robustness. ¹⁸O₃-clodronic acid was used as the internal standard. The lower limit of quantification was 600 µg/kg in muscle and kidney and 40 µg/kg in liver and fat. Although the validation was well-performed there are some minor concerns (relating to the specificity of the method and the stability studies) that would need to be addressed before the method could be considered fully validated in line with Volume 8 of the Rules governing medicinal products in the EU.

The relevant European reference laboratory was consulted on the analytical method and agreed with the conclusions above. The laboratory also pointed out that because only one fragment ion is measured, in line with Commission Decision 657/2002/EC the method would not be considered acceptable for a confirmatory method.

2.2.5. Findings of EU or international scientific bodies

Clodronate disodium has not been evaluated by any other EU or international scientific bodies.

3. Risk management considerations

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

No data were provided but as microbiological effects are not expected for this substance such data are not required.

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

No data were provided but none are expected for this type of substance.

3.3. Elaboration of MRLs

Based on the results of the non-radiolabelled residue study, an ADI of 0.05 mg/kg (3000 µg/60 kg person) and the standard food basket, the Committee calculated the maximum residue intake that would result from consumption of tissues from treated horses

Based on the highest residue values in the non-radiolabelled residue depletion study at the 12 hour timepoint, the intake of residues, including the injection site, would represent about 14% of the ADI; even if the total dose were to be administered as a single injection, and the injection site were ingested, the intake would be approximately 23%:

Tissue	Daily intake according to EU foodbasket:	Highest level found	Consumption level	%ADI (3000 µg)
Muscle (injection site)	300 g	941 µg/kg	282.3 µg	9.4%
Fat	50 g	<40 µg/kg	2 µg	0.1%
Kidney	50 g	1930 µg/kg	96.5 µg	3.2%
Liver	100 g	193 µg/kg	19.3 µg	0.6%
Total %ADI using 1 x 7.5 ml injection site=				13.3%
Total %ADI using 2 x 7.5 ml injection site=				22.7%

This estimate based on the highest residue levels found includes kidney and liver, and those commodities from horses are normally not consumed.

In light of the above, it is considered that there is very little risk of consumers being exposed to residues at levels above the ADI, and consequently the establishment of numerical MRLs is not considered necessary for the protection of human health. In line with Article 14(5) of Regulation (EC) No. 470/2009, the absence of the need to establish a numerical MRL is considered to have been demonstrated for the use of clodronate disodium in horses, and a "No MRL required" classification can be recommended. However, since there are no data on residues in milk, and clodronate is hydrophilic and has an affinity for calcium (demonstrating that there is a possibility that residues *may* occur in milk), it is considered that a restriction should be applied in order to avoid use of the substance in animals producing milk for human consumption.

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 clodronate in horses to other food producing species and commodities. However, the horse is considered a minor species in the EU with regards to food production and consequently the residue depletion data provided were based on reduced data requirements for a minor species, in line with the CVMP Guideline on safety and residues data requirements for veterinary medicinal products intended for minor uses or minor species (EMA/CVMP/SWP/66781/2005). The CVMP does not consider it appropriate to extrapolate MRLs derived using a reduced data package to other species. The CVMP also considers that, based on the proposed indication and mode of action, it is not likely that this active substance would be used in any food species other than horses.

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

having considered that:

- the toxicological ADI of 0.05 mg/kg bw (i.e. 3 mg per person) was retained as the overall ADI for clodronate;

- clodronate residues were highest 12 hours after administration and the highest levels were found in kidneys (mean residue 1743 µg/kg) followed by injection site (mean 902 µg/kg), liver (mean 146 µg/kg) and fat (below the LOQ);
- based on the highest residue concentrations seen in tissues at 12 hours, the intake of residues from all tissues including the injection site would represent 23% of the ADI;
- the MRL status recommended for clodronate in horses is based on a reduced data package and so should not be extrapolated to other species or commodities;

the Committee concludes that the establishment of maximum residue limits for clodronate disodium in equine species is not necessary for the protection of human health and therefore recommends the inclusion of clodronic acid (in the form of disodium salt) in table 1 of the Annex to Regulation (EU) No 37/2010 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Clodronic acid (in the form of disodium salt)	NOT APPLICABLE	<i>Equidae</i>	No MRL required	NOT APPLICABLE	Not for use in animals from which milk is produced for human consumption	Musco-skeletal system / drugs for treatment of bone diseases

4. Background information on the procedure

Submission of the dossier	26 November 2013
Steps taken for assessment of the substance	
Application validated:	11 December 2013
Clock started:	12 December 2013
Adoption of opinion	8 May 2014