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Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Ivermectin (All mammalian food producing species)

On 24 April 2014 the European Commission adopted a Regulation[1] establishing maximum residue limits for ivermectin in all mammalian food producing species, 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.

In veterinary medicine ivermectin is used in cattle, sheep, goats, pigs, horses and reindeer as an antiparasitic, administered subcutaneously, topically or orally as a single dose treatment only.

In human medicine ivermectin is used for the treatment of onchocerciasis.

Maximum residue limits were previously established for ivermectin in fat, liver and kidney for all mammalian food producing species.

On 15 December 2010 the European Commission submitted a request for the review of the opinion on the establishment of maximum residue limits for ivermectin to the European Medicines Agency, focussing particularly on the possibility to establish a MRL for muscle.

Based on the available data, the Committee for Medicinal Products for Veterinary Use recommended, on 12 September 2013, maximum residue limits for ivermectin in fat, liver, kidney and muscle in all mammalian food producing species.

Subsequently, the Commission recommended on 19 February 2014 that maximum residue limits in all mammalian food producing species are established. This recommendation was confirmed on 12 March 2014 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 24 April 2014.

[1] Commission Implementing Regulation (EU) No 418, O.J. L124, of 25.04.2014

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European public MRL assessment report (EPMAR)

Ivermectin (establishment of a maximum residue limit for muscle)

Summary of the scientific discussion for the establishment of MRLs

Substance name:	Ivermectin
Therapeutic class:	Agents acting against endo- and ectoparasites
Procedure number:	EU/ART11/10/184/EC
Applicant:	European Commission
Target species:	All mammalian food producing species
Therapeutic indication:	Antiparasitic (acting against endo and ectoparasites)
Route(s) of administration:	Parenteral route (subcutaneous and intramuscular), topical and oral

1. Introduction

Ivermectin is a chemically modified fermentation product belonging to the macrocyclic lactone class of endectocides and consisting of a mixture of two homologous compounds, 22,23-dihydroavermectin B1a (H2B1a, not less than 80%) and 22,23-dihydroavermectin B1b (H2B1b, not more than 20%). Ivermectin is a potent ecto- and endo-parasitic agent with broad spectrum of activity which covers nematodes and arthropods. The substance increases the membrane permeability to chloride ions, mediating the paralysis of the nematodes and certain classes of ectoparasites.

In veterinary medicine ivermectin is extensively used in cattle, sheep, goats, pigs, horses and reindeer at doses of 0.1 – 0.5 mg/kg bw subcutaneously, topically or orally as a single dose treatment only.

In human medicine ivermectin is used for the treatment of onchocerciasis.

Ivermectin was previously assessed by the CVMP and an ADI of 10 µg/kg bw/day (600 µg/person/day) was established.

Currently, ivermectin is included in table 1 of the Annex to Commission Regulation (EU) No 37/2010 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Ivermectin	22,23-Dihydro-avermectin B1a	All mammalian food producing species	100 µg/kg 100 µg/kg 30 µg/kg	Fat Liver Kidney	For porcine species the fat MRL relates to 'skin and fat in natural proportions' Not for use in animals producing milk for human consumption	Antiparasitic agents/Agents acting against endo- and ectoparasites

On 15 December 2010 the European Commission submitted to the European Medicines Agency a request under Article 11 of Regulation (EU) No 470/2009 to issue a new opinion on the substance ivermectin including the possibility to establish a MRL for the tissue muscle. The request from the Commission follows concerns raised with regard to the control of residues in particular when no tissues other than muscle are available for sampling, which is frequently the case with imported meat. It has been argued that the absence of a MRL for muscle leads to a lack of clarity over the level of residues in muscle acceptable as not representing a concern to consumer safety.

On 9 June 2011 the CVMP adopted an opinion which recommended a muscle MRL and limits for injection sites as shown in the table below:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Ivermectin	22,23-Dihydro-avermectin B1a	All mammalian food producing species	30 µg/kg 100 µg/kg 100 µg/kg 30 µg/kg	Muscle Fat Liver Kidney	For porcine species the fat MRL relates to 'skin and fat in natural proportions' Not for use in animals from which milk is produced for human consumption The MRL for muscle does not apply to the injection site, where residue levels should not exceed 1300 µg/kg	Antiparasitic agents/Agents acting against endo and ectoparasites

On 25 October 2011 the European Commission requested the Committee to reconsider its opinion of 9 June 2011 and to amend the part of the opinion that recommends a residue limit for the injection site in the "Other provisions" of Table I of the Annex to Commission Regulation (EU) 37/2010.

2. Scientific risk assessment

2.1. Safety assessment

In 1992, the CVMP established an ADI for ivermectin of 0.2 µg/kg bw/day, i.e. 12 µg/person/day based on a NOEL of 0.1 mg/kg for maternal toxicity in a mouse teratogenicity study applying a safety factor of 500. This ADI was the same as the one established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). In 1993, JECFA re-evaluated the ADI for ivermectin and concluded, on the basis of new human data, that the safety factor applied to this same NOEL could be reduced to 100, resulting in an ADI of 1 µg/kg bw/day corresponding to 60 µg/person/day. After reviewing this re-evaluation the CVMP established the same revised ADI.

Subsequently, in 2003, an application was submitted for the modification of the MRLs for bovine, porcine and ovine species, *Equidae* and deer and requesting revision of the toxicological ADI to take into account data from human clinical trials in healthy volunteers and parasite-infected patients, and reports of individuals exposed to ivermectin as a result of accidental or deliberate ingestion as the basis for modification of the ADI.

Further to the evaluation of the new data the CVMP concluded that the dog toxicity data were the most relevant for the establishment of the toxicological ADI. The NOEL of 0.5 mg/kg bw/day observed in the 14-week repeated-dose dog study was used as the basis for the calculation of the new ADI using a uncertainty factor of 50 (at a dose of 1 mg/kg bw mydriasis and slight weight loss were observed). The lower uncertainty factor compared to the standard factor of 100 was justified by the fact that the data suggested that ivermectin may reach threshold levels for overt toxicity more readily in dogs than humans based on comparison of pharmacokinetics and the fact that human and non-human primate toxicological data were available. An ADI of 10 µg/kg bw/day (600 µg/person per day) was established for ivermectin.

Furthermore, the Committee considered that the availability of new human safety data that accounts for the same central nervous system neuropharmacological interactions that are present in the dog, provides reassurance that the ADI established from the dog study is appropriate.

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

2.2. Residues assessment

Maximum residue limits for ivermectin for all mammalian food producing species were previously established in fat, liver and kidney. The CVMP concluded at that time that as residue concentrations were persistently low in non injection site muscle, this tissue was unsuitable for monitoring purposes and therefore no MRL for muscle was recommended. Considering the need to ensure the control of residues in particular when no other tissues than muscle are available for sampling, the Commission requested the revision of the CVMP opinion including the possibility to establish a MRL for muscle. No new residue depletion studies were submitted with the request however findings of residues of ivermectin in imported meat that have been reported by competent authorities for residue control were available.

A summary of the data already available and previously evaluated in the different species is provided below.

For the purpose of the current evaluation the previously submitted data were re-considered in particular with regard to residues in muscle.

2.2.1. Pharmacokinetics in target species

In animal tissues ivermectin residues are essentially found as unbound residues. Similar tissue residue distribution patterns exist in cattle, sheep, swine and rats. However, the residue depletion half-lives in liver and fat are approximately 4 to 5 times shorter in sheep and rats than in cattle and swine, reflecting a more rapid metabolism in sheep and rats. In cattle and rats the major liver metabolite was 24-hydroxymethyl-H_2B_{1a} and in swine the major liver metabolites were 3´-O-desmethyl-H_2B_{1a} and 3´-O-desmethyl-H_2B_{1b}. The parent drug accounted for at least 50% of the total residues in tissues from cattle up to 14 days, in sheep up to 5 days, in swine up to 7 days and in rats up to 3 days after treatment. Seven days after subcutaneous treatment 1.5% and 62% of the dose were recovered in urine and faeces, respectively. The parent drug has been found to account for 39-78% of the faecal radioactivity in cattle, sheep and rat.

The plasma concentration profile in deer treated subcutaneously with ivermectin showed that maximum plasma concentration was reached approximately 28 hours after treatment with 0.2 and 0.4 mg/kg bw. The peak plasma concentrations were 15.3 µg/l and 28.3 µg/l, respectively. The plasma half-lives of ivermectin in deer treated with 0.2 mg/kg or 0.4 mg/kg were approximately 4 days.

2.2.2. Residue depletion studies

Cattle

Four residue studies in cattle were presented. In three studies cattle were dosed percutaneously with 0.5 or 1.0 mg ivermectin/kg bw and in one study cattle were dosed subcutaneously with 0.2 mg/kg bw. These studies show that the highest concentrations of residues in tissues of cattle were found in liver followed by fat, kidney and muscle except for the injection site muscle.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has calculated the percentage of the marker residue (22,23-dihydroavermectin B1a) of the total residues in cattle 28 days post treatment. The marker accounted for 67% in muscle, 37% in liver, 54% in kidney and 18% in fat of total residues and the distribution of residues between tissues was 1:2:11:27 for muscle, kidney, fat and liver, respectively.

Pigs

In a radiometric residue depletion study, 12 pigs were given a single tritium labelled ($C_{22, 23}$ positions) ivermectin dose of 0.4 mg/kg bw subcutaneously. Three animals in each group were killed on days 1, 7, 14 and 28 days after treatment. Fat total residue levels were the highest followed by liver. Total residue levels in fat were 384, 152, 28 and 6 µg/kg; in liver were 199, 112, 22, and 3 µg/kg on 1, 7, 14 and 28 days after treatment respectively. Kidney total residue levels were 106, 55 and 10 µg/kg whereas muscle total residue levels were 43, 25 and 4 µg/kg after 1, 7 and 14 days respectively. The average marker to total residue ratios were 0.27, 0.41, 0.3 and 0.39 µg/kg for liver, kidney, fat and muscle respectively.

In another radiometric residue depletion study, 15 pigs (male and female) were given tritium labelled (C22, 23 positions) ivermectin at a dose rate of 0.1 mg/kg bw/day for 7 days in the feed. Total

radioactive residue levels in liver were 237.1, 43, 10.7, 4.1 and 2.7 µg/kg and those in fat were 207.2, 63.6, 18, 8 and 4.5 µg/kg at 4 hours, 3, 7, 14 and 21 days after treatment respectively.

In a residue depletion study where pigs were administered a single subcutaneous dose of 0.4 mg/kg bw, the highest residue levels were found at the injection site samples, followed by fat, liver, kidney and then muscle at all time points. Mean injection site residues were 12500, 5100, 1110, 2300, 2500 and 230 µg/kg at 1, 3, 5, 7, 10 and 14 days after treatment respectively. Peak residue levels were found after 3 days in all of the other tissues. Liver residue levels were 67, 69, 53, 41, 23 and 13 µg/kg and fat residue levels were 74, 110, 91, 73, 47 and 24 µg/kg on days 1, 3, 5, 7, 10 and 14 days after treatment respectively.

Sheep

In a radiometric residue depletion study, 12 sheep were given a single oral (intraruminal) tritium labelled (C22, 23 positions) ivermectin dose of 0.3 mg/kg bw. Three animals were killed on days 1, 3, 5 and 7 days after treatment. The average total concentration in liver were 238, 125, 25, 44 µg/kg at 1, 3, 5 and 7 days after treatment respectively. At the same time points, average total residue concentrations in fat were 307, 153, 63, 73 µg/kg; in kidney were 72, 46, 12, 13 and in muscle were 55, 50, 9 and 10 µg/kg. The ratios of marker (H2B1a) to total residues at 3 days after treatment were 0.51, 0.51, 0.44 and 0.52 µg/kg for liver, fat, kidney and muscle, respectively.

In a residue depletion study, 30 sheep (male and female) were given oral doses of 0.3 mg ivermectin/kg bw in a micellar vehicle. The highest residues (marker residue, H_2B_{1a}) were found in fat followed by liver. Residue levels in liver were 72, 12, 11 and 8 µg/kg; in fat were 145, 32, 11 and 9 µg/kg; in kidney were 30, 5, 2 and 1 µg/kg and in muscle were 20, 4, 2 and 2 µg/kg at 1, 3, 5 and 7 days after treatment respectively.

In a residue depletion study where sheep were administered a three subcutaneous doses of 0.3 mg/kg bw at weekly intervals, the highest residue levels were found at the injection site samples, followed by fat, liver, kidneys and then muscle at all time points. Mean injection site residues were 17000, 2900, 2300, 460 and 220 µg/kg at 3, 7, 10, 14 and 28 days after last treatment respectively. Peak residue levels were found after 7 days in all of the other tissues. Liver residue levels were 160, 190, 97, 55 and 7.2 µg/kg and fat residue levels were 230, 310, 180, 99 and 13 µg/kg at 3, 7, 10, 14 and 28 days after treatment, respectively.

Horses

In a radiometric residue depletion study, 3 horses were given tritium labelled (C22, 23 positions) ivermectin doses of 0.3 mg/kg bw. Two of the animals were administered orally and the remaining one was administered intramuscularly. The animals were then slaughtered after 28 days and the mean total radioactivity levels in those administered orally were 2.64, 3.02, 3.1, 4.26, 4.11 and 3.52 µg/kg and in those administered intramuscularly was 43.2, 17.1, 14.4, 54.2, 47.4 and 36.1 for liver, kidneys, muscle, perirenal fat, omental fat and subcutaneous fat respectively. Total radioactivity levels at the injection site were 64.4 µg/kg. The ratios of marker to total residues were 0.12, 0.22 and 0.36 for liver, kidney and fat, respectively.

In a residue depletion study where horses were administered a single oral dose of 0.3 mg/kg bw, the highest residue levels were found in fat followed by liver. Fat residues were 80 and 10.9 µg/kg and liver residues were 31 and 4 µg/kg on 7 and 14 days after treatment. Residues were detected at 7 days after treatment in kidney (15 µg/kg) and muscle (8.3 µg/kg) but where below the limit of detection at 14 days.

Deer

Following a single percutaneously administered dose of 1 mg/kg (twice the recommended dose) to red deer, the tissue residues decreased progressively with time with highest concentrations found in fat followed by liver, muscle and kidney. The ratios of 22,23-dihydroavermectin B1a between tissues after 28 days, were 6.8:2.5:1.3:1 for fat, liver, kidney and muscle, respectively. At 7 and 28 days after treatment the mean concentrations of 22,23-dihydroavermectin B1a in fat were 292 µg/kg and 13.2 µg/kg, respectively, in liver 180 µg/kg and 9.3 µg/kg, in muscle were 78 µg/kg and 1.4 µg/kg and in kidney were 78 µg/kg and 3.6 µg/kg, respectively.

A single subcutaneous dose of 0.2 mg ivermectin/kg bw was given to reindeer. The ratios of 22,23-dihydroavermectin B1a to total residues in tissues at 17 days after treatment, were in this study 9.5:6.6:2.6:1 for fat, liver, kidney and muscle, respectively. The highest residue concentrations of 22,23-dihydroavermectin B1a 10 and 17 days after treatment, respectively, were 362 µg/kg and 68 µg/kg in back fat, 71 µg/kg and 28 µg/kg in liver, 54 µg/kg and 13 µg/kg in kidney, 40 µg/kg and 11 µg/kg in muscle, and 44 µg/kg and 9 µg/kg in injection site muscle, respectively. The half-lives in the tissues after a single subcutaneous treatment were 7.1 days in the back fat, 2.9 days in the injection site, 4.9 days in muscle, 5.8 days in liver and 5.7 days in kidney.

22,23-dihydroavermectin B_{1a} (H_2B_{1a}) was retained as the marker residue in all tissues and species.

The tissue distribution of residues and the overall ratios of marker to total residues were generally similar with residue levels being the highest in fat and liver tissues. Horses and pigs had slightly different marker/total residue ratios.

The following ratios of marker to total residues (RMT) were established from depletion studies previously assessed by the CVMP and/or JECFA (40th JECFA report, 1993):

Species	**RMT**				
	Liver	**Kidney**	**Muscle**	**Fat**	**IS***
Cattle	0.370	0.540	0.670	0.180	0.8
Sheep	0.510	0.440	0.520	0.510	0.8
Pigs	0.270	0.300	0.390	0.500	0.8
Equidae	0.140	0.280	0.670	0.370	0.8

*IS = Injection site. Value obtained from CVMP assessment of ivermectin referral concerning injectable products for cattle

2.2.3. Monitoring or exposure data

Competent national authorities for residues control have reported findings of residues of ivermectin in imported lean meat at levels ranging from less that 1 µg/kg to higher than 500 µg/kg.

2.2.4. Analytical method for monitoring of residues

A routine analytical method validated in accordance with Volume 8 of the Rules Governing Medicinal Products in the European Union based on HPLC with fluorescence detection was presented in an internationally recognised format for quantifying 22,23-dihydro-avermectin B1a residues in tissues from bovine, porcine and ovine species, *Equidae* and deer. The limit of quantification for all tissues for pigs, *Equidae* and ovine species was 5 µg/kg. For bovine species the limit of quantification was 3 µg/kg for muscle, 5 µg/kg for fat and kidney and 3.6 µg/kg for liver. For deer the limit of quantification was 2 µg/kg for all tissues. The analytical method was also validated at sufficiently high ivermectin levels to account for residue levels that might be expected at injection sites. Although no data were available concerning the use of the analytical method in other mammalian species this method is likely to be applicable to other mammalian species.

The analytical method has been reviewed by the relevant European Reference Laboratory, which noted that the method had been in use for several years and considered that it would be applicable for monitoring compliance with both the existing MRLs and the proposed MRL for muscle.

2.2.5. Findings of EU or international scientific bodies

Ivermectin was evaluated at the 36th, 40th, 54th and 58th JECFA meeting. Following these evaluations and recommendations the Codex Alimentarius established MRLs for ivermectin as follows:

- Liver: 100 µg /kg;
- Fat: 40 µg/kg
- Milk: 10 µg /kg

The marker residue retained by JECFA is ivermectin B1a (synonym for 22,23-dihydro-avermectin B1a).

3. Risk management considerations

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

Microbiological effects are not expected for this type of substance. In addition as MRLs have not been established for milk the assessment of potential effects on mircroorganisms used for industrial food processing is not considered.

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

The CVMP was asked to consider setting a maximum residue limit for ivermectin in muscle in order to allow for the monitoring of meat in particular concerning imports from third countries. As meat imported into the EU often takes the form of lean cuts of muscle, the absence of an MRL for muscle means that it is not possible to control residue levels in imported meat of this type.

Residue depletion data demonstrate that ivermectin residues in kidney and muscle (other than injection site muscle) are low compared to residues in fat and liver in all animal species.

Having considered the issue at length the CVMP noted that:

- it would possible to calculate a muscle MRL based on either (i) residues expected in injection site muscle or (ii) residues expected in non-injection site muscle;
- a muscle MRL based on approach (i) (residue levels expected in injection site muscle) would be of little relevance for residue control authorities. This is because injection sites are scarce while non-injection site muscle is abundant and consequently, except on rare, chance occasions, non-injection site muscle will be sampled by residue control authorities. So in the vast majority of samples residues would be far below the injection site levels used to derive the MRL, even if the withdrawal period were not respected. So compliance with the muscle MRL would provide no information on whether the withdrawal period had been respected or on whether residue levels in other tissues comply with their respective MRLs;
- from a residue control point of view, it would make far more sense to base the muscle MRL on approach (ii) (residue levels that can be expected in non-injection site muscle) as this will be representative of muscle sampled on all but very rare, chance occasions. From a consumer safety

perspective this is also the preferred option, as non-injection site muscle is the muscle regularly consumed;

- If the muscle MRL is based on approach (ii) (residue levels that can be expected in non-injection site muscle), it follows that, at the withdrawal period residues in injection site muscle can be expected to exceed the MRL;
- Annex I of Regulation (EC) No 854/2004, in Section II, Chapter V, indicates that "*meat is to be declared unfit for human consumption if it: …(i) contains residues or contaminants in excess of the levels laid down in community legislation*" (ie above the MRL);
- in practice, as injection sites will not always be easily identifiable, it cannot be assumed that they will always be removed from the food chain;
- possible future need to establish an MRL in milk should be taken into account and an appropriate portion of the ADI should be left available for this purpose.

In light of the above the CVMP concludes that the muscle MRL should be set in such a way as to maximise both its relevance for residue control purposes and its ability to protect consumer health – i.e. it should be derived based on residue levels that can be expected in non-injection site muscle.

However, because it cannot be assumed that injection sites will always be removed from the food chain there is also a need to ensure that residues at the injection site do not represent a risk to the consumer. An additional value was therefore derived, which corresponds to the maximum level of residues that would be expected in the injection site at the anticipated withdrawal period (hereafter referred to as the Injection Site Residue Reference Value – ISRRV). The ISRRV was derived as follows: the theoretical maximum daily exposure was calculated on the basis of recommended MRLs for liver, kidney and fat (skin+fat in the case of pig) and the resulting value was compared to the ADI. The ISRRV was then derived in a manner that would allow for residues in 300g of muscle to correspond to the remaining portion of the ADI (whilst leaving aside a small portion of the ADI for milk). The withdrawal period should be derived in a manner that ensures that residues at the injection site will be below this value and that residues in non-injection site muscle, liver, kidney and fat will be below the MRLs for these tissues. In this way, the withdrawal period would not be longer than is necessary in order to ensure consumer safety. Whereas, in the CVMP opinion of 9 June 2011, a value equivalent to an ISRRV was recommended for inclusion in Regulation (EU) No. 37/2010, the current opinion does not propose its inclusion in the regulation or its use for routine residue surveillance. This has been done to take account of the Commission's comment that it would not be feasible for control authorities to consider two different levels for the same tissue (muscle). Rather, the ISRRV provides a value to be used by competent authorities when setting withdrawal periods for injectable ivermectin containing products. The withdrawal period must ensure that residues in non-injection site muscle, as well as in liver, kidney and fat, are below the MRLs and that residues at the injection site are below the ISRRV. In this way the withdrawal period will ensure that, even if a consumer were to ingest an injection site, consumer exposure to residues would not represent a health risk.

The CVMP notes that Article 1 of Directive 2001/82/EC defines the withdrawal period as the period necessary to ensure that foodstuffs do not contain residues in excess of the MRLs. While efforts may be made to remove injection sites, in those instances where they enter the food chain undetected, residues may be present at levels that exceed the muscle MRL. While these residues will not represent a consumer safety concern, the chance sampling of an injection site by a residue control authority would lead to a non-compliant residue finding and possible punitive action against the farmer. Such action would be unfair given that the non-compliant finding would not represent non-compliance with the withdrawal period.

In relation to residue monitoring, in some cases, residue control authorities will have access only to muscle tissue, in which case only muscle tissue will be available for residue monitoring (this is particularly the case for meat imported into Europe). However, where the entire carcass is available, the CVMP recommends that for the purpose of monitoring residues of ivermectin, liver or fat (skin+fat for pigs) should be sampled in preference to muscle. This is because residues in these tissues deplete more slowly than residues in muscle and so will provide a better basis for verifying compliance with the withdrawal period.

3.3. Elaboration of MRLs

Maximum residue limits are established for ivermectin in all mammalian food producing species as follows:

- Fat: 100 µg/kg
- Liver: 100 µg/kg
- Kidney: 30 µg/kg

Residues concentrations were persistently low in non-injection site muscle in all target species. Taking into account the residue distribution, a value of 30 µg/kg for non-injectable site muscle can be recommended.

An Injection Site Residue Reference Value (ISRRV) of 1250 µg/kg[2] was calculated as follows: the theoretical maximum daily intake was calculated on the basis of recommended MRLs for liver, kidney and fat in horses (worst case scenario for the different species) and the resulting value compared to the ADI. The maximum level of residues acceptable for injection site muscle was then calculated so that residues in 300 g of muscle to correspond to 93% of the ADI (this leaves a small portion of the ADI unused to accommodate a possible future MRL in milk). This value was then converted into the ISSRV using a ratio of marker to total residues value of 0.8 for injection site muscle[3].

Withdrawal periods for injectable ivermectin products should ensure that residue levels present in non-injection site muscle, liver, kidney and fat do not exceed the MRLs for muscle, liver, kidney and fat, respectively, and that residue levels present in injection site muscle do not exceed the ISRRV.

Calculation of theoretical daily intake of residues

Detailed calculation of theoretical daily intake of residues

	Tissue	MRL (µg/kg)	MR:TR	Total Residue (µg/kg)	Food Basket (kg)	Residue consumed (µg)
Cattle	Liver	100	0.37	270	0.10	27
	Kidney	30	0.54	56	0.05	3
	Fat	100	0.18	556	0.05	28
	Muscle	30	0.67	45	0.30	13
	ADI (µg/person): 600				**TOTAL TMDI (µg): 71**	**%ADI: 12**

[2] This value is slightly different from the injection site limit recommended in the opinion of 9 June 2011 (1300 µg/kg) because it was noted that consumer intake based on horse MRLs for fat, liver, kidney and ISRRV would equate to 96% of the ADI which would not leave sufficient room to accommodate a possible future MRL for milk.
[3] Value obtained from the CVMP assessment of the ivermectin referral concerning injectable products for cattle

	Tissue	MRL (µg/kg)	MR:TR	Total Residue (µg/kg)	Food Basket (kg)	Residue consumed (µg)
Sheep	Liver	100	0.51	196	0.10	20
	Kidney	30	0.44	68	0.05	3
	Fat	100	0.51	196	0.05	10
	Muscle	30	0.52	58	0.3	17

ADI (µg/person): 600 **TOTAL TMDI (µg): 50** **%ADI: 8**

	Tissue	MRL (µg/kg)	MR:TR	Total Residue (µg/kg)	Food Basket (kg)	Residue consumed (µg)
Pigs	Liver	100	0.27	370	0.10	37
	Kidney	30	0.30	100	0.05	5
	Skin/Fat	100	0.50	200	0.05	10
	Muscle	30	0.39	77	0.30	23

ADI (µg/person): 600 **TOTAL TMDI (µg): 75** **%ADI: 13**

	Tissue	MRL (µg/kg)	MR:TR	Total Residue (µg/kg)	Food Basket (kg)	Residue consumed (µg)
Equidae	Liver	100	0.14	714	0.10	71
	Kidney	30	0.28	107	0.05	5
	Fat	100	0.37	270	0.05	14
	Muscle	30	0.67	45	0.30	13

ADI (µg/person): 600 **TOTAL TMDI (µg): 104** **%ADI: 17**

Excluding intake from injection site muscle but using normal muscle, the percentage of the ADI consumed based on the above calculations will be 12%, 8%, 13% and 17% for cattle, sheep, pigs and *Equidae* respectively. The minimum portion of the ADI that can be used for residues at the injection site was therefore calculated to be 80%. The following table shows the amount of the ADI that is used when the theoretical maximum daily intake (TMDI) is calculated for a food basket including the ISRRV.

Species	ADI (µg/person)	TMDI (excl.muscle) (µg)	ADI left for IS (µg/person)	Max level for IS (µg/kg)	Proposed limit for IS (µg/kg)	%ADI consumed
Cattle	600	58	542	1445	1250	87.8
Sheep		33	567	1512	1250	83.6
Pigs		52	548	1461	1250	86.8
Equidae		90	510	1360	1250	93.1

RMT (ratio of marker to total) of 0.8, daily consumption of 0.3Kg of muscle were used in the calculation.

The theoretical maximum daily intake (TMDI) using residues from injection site muscle (rather than non-injection site) and the other tissues would be 88%, 84%, 87% and 93% for cattle, sheep, pigs and *equidae*, respectively.

Codex Alimentarius set a MRL for ivermectin in milk of 10 µg/kg. In the worst case scenario, using a ratio of marker residue to total residues of 0.5, milk's contribution to the ADI was 30 µg/person i.e. 5% of the ADI. The proposed ISRRV of 1250 µg/kg leaves room to accommodate a possible future milk MRL for ivermectin.

3.4. Considerations on possible extrapolation of MRLs

Extrapolation of maximum residue limits to the relevant minor species have been considered by the CVMP in the previous evaluations of ivermectin. Considering the data available and the scientific principles for the extrapolation of MRLs described in the Volume 8 of the Rules governing medicinal products in the European Union [4] the maximum residue limits initially established for bovine, porcine, ovine, equidae and deer including reindeer were extrapolated in 2004 to all mammalian food producing species.

In line with Article 5 of Regulation (EU) No 470/09, the Committee considered the possibility of further extrapolating the existing MRLs to other species and foodstuffs with a view to ensuring availability of veterinary medicinal products for conditions affecting food producing animals while ensuring a high level of protection of human health. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal species/ food commodities	Extrapolation possible (Yes/No)	Justification
Poultry (including eggs)	No	Metabolism can be significantly different in poultry compared to mammals. Consequently species specific metabolism and residue data are considered necessary to allow adequate evaluation of the risk to consumer safety posed by residues in poultry-derived food commodities. No analytical method for monitoring of residues in poultry tissues (or eggs) was available for evaluation.
Fin fish	No	Metabolism is generally less complicated in fish than in mammals. Consequently, if the marker residue is the parent compound in cattle and pigs it can be assumed that the parent compound would also be a suitable marker residue in fish meat. However, no analytical method for monitoring of residues in fish meat was available for evaluation. Furthermore, in view of the known toxicity of the substance to the environment extrapolation of MRLs without specific information on the potential use of the substance in fish would be highly controversial.
Milk	No	No data are available that would allow conclusions to be drawn on the appropriate marker residue or marker to total residues ratio to use in milk. Data on residues in this commodity are considered necessary in order to allow adequate evaluation of the risk to consumer safety posed by residues in milk. No analytical method for monitoring of residues in milk was available for evaluation.

[4] Notice to applicants and Guideline: Veterinary medicinal products - Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin

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

Having considered that:

- the a toxicological ADI of 10 µg/kg bw/day (600 µg/person per day) was previously established as the overall ADI for ivermectin;
- 22,23-dihydroavermectin B 1a was retained as the marker residue in all tissues and target animal species;
- the tissue distribution of residues and the overall ratios of marker to total residues were generally similar with residue levels being the highest in fat and liver tissues;
- residue concentrations were persistently low in non-injection site muscle;
- residues at the injection site deplete slowly and should be considered for setting withdrawal periods;
- the ratios of marker to total residues were calculated in the different animal species and tissues;
- the Commission and residue control authorities consider that, in order to ensure the feasibility of residue controls, a single residue limit for muscle must be published in Regulation (EU) No. 37/2010;
- an Injection Site Residue Reference Value (ISRRV) of 1250 µg/kg is established for all mammalian food producing species – this value should be taken into account when deriving withdrawal periods;
- a portion of the ADI should be reserved for a possible future need for establishing a MRL for milk,
- for the purpose monitoring of residues of ivermectin it is recommended that, where the entire carcass is available, liver or fat (skin+fat for pigs) should be sampled in preference to muscle as residues in these tissues deplete more slowly than residues in muscle and so will provide a better basis for verifying compliance with the withdrawal period;
- a validated analytical method for the monitoring of residues of ivermectin in edible cattle, sheep, pigs and horse tissues (liver, kidney, fat and muscle) is available;

the CVMP recommends the modification of the entry for ivermectin in table 1 of the Annex to Commission Regulation (EU) No 37/2010 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Ivermectin	22,23-Dihydro-avermectin B1a	All mammalian food producing species	30 µg/kg 100 µg/kg 100 µg/kg 30 µg/kg	Muscle Fat Liver Kidney	For porcine species the fat MRL relates to 'skin and fat in natural proportions' Not for use in animals from which milk is produced for human consumption	Antiparasitic agents/Agents acting against endo and ectoparasites

4. Background information on the procedure

Submission of the request	15 December 2010
Steps taken for assessment of the substance	
Clock started:	16 December 2010
CVMP opinion adopted:	09 June 2011
European Commission requested revision	25 October 2011
CVMP revised opinion	12 September 2013