EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Butafosfan (all mammalian food producing species)

On 10 January 2014 the European Commission adopted a Regulation[1] establishing maximum residue limits for butafosfan 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.

Butasfofan was previously included in Table 1 of the Annex to Regulation 37/2010 with a "no MRL required" classification for bovine species. Bayer Animal Health GmbH submitted to the European Medicines Agency the application for the extension of maximum residue to pigs, on 21 December 2012.

Butafosfan is intended for pigs as a supportive therapy for metabolic disorders, developmental and nutritional disorders in young animals due to rearing diseases and as a tonic in cases of stress, overexertion and reduced resistance in pigs.

Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 13 June 2013 the extension of maximum residue limits for butafosfan to all mammalian food producing species.

Subsequently the Commission recommended on 20 November 2013 that maximum residue limits in all mammalian food producing species are established. This recommendation was confirmed on 11 December 2013 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 10 January 2014.

[1] Commission Implementing Regulation (EU) No 20/2014, O.J. L8/20 , of 11.01.2014

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	butafosfan
Therapeutic class:	Mineral supplements
Procedure number:	EMEA/V/MRL/003610/EXTN/003
Applicant:	Bayer Animal Health GmbH
Target species:	porcine
Intended therapeutic indication:	Metabolic, developmental and nutritional disorders
Route(s) of administration:	Intramuscular

1. Introduction

Butafosfan is [1-(butylamino)-1-methylethyl]-phosphonic acid. The substance is an organic phosphorus compound used as a phosphorus source in cattle. The major indications are disorders of the metabolism especially in young animals. Butafosfan is also used to support the treatment of infertility, tetany and paresis as an adjunct to calcium and magnesium therapy. Butafosfan is administered to cattle as a single dose by intravenous route and the dose may be repeated daily if required. The maximum recommended dose for cattle is 5.6 mg/kg bw.

Butafosfan was previously assessed by the CVMP and a toxicological ADI of 0.6 mg/kg bw, i.e 36 mg/person was established.

Currently butafosfan is included in 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
Butafosfan	NOT APPLICABLE	Bovine	No MRL required	NOT APPLICABLE	For intravenous use only.	NO ENTRY

Bayer Animal Health GmbH submitted the application for the extension of maximum residue limits to porcine species to the European Medicines Agency, on 21 December 2012. The proposed indication for pigs is as a supportive therapy for metabolic disorders, developmental and nutritional disorders in young animals due to rearing diseases and as a tonic in cases of stress, overexertion and reduced resistance in pigs. The proposed recommended dose is 10 mg butafosfan/kg bw for five consecutive days by intramuscular injection.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of butafosfan and established an ADI of 0.6 mg/kg bw, i.e. 36 mg/person based on the NOEL of 60 mg/kg bw/day from a repeated dose toxicity study in dogs and applying a safety factor of 100[2].

[2] CVMP butafosfan summary report (1) EMEA/MRL/630/99-FINAL July 1999

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

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

Two *in vivo* studies and one *in vitro* study have been conducted to characterise the pharmacokinetics of butafosfan in pigs.

The pharmacokinetic parameters of butafosfan were generally comparable between the intramuscular and subcutaneous injection routes and indicated rapid absorption from the injection site and rapid elimination from serum in pigs following a single administration at a dose level of 10 mg/kg bw. Absorption following intramuscular and subcutaneous injection to pigs was rapid with median t_{max} values of 0.5 hours or lower. The terminal elimination half-life in pigs estimated based on 24-hour data following a single dose was 3.5 to 3.7 hours.

Repeated once daily intramuscular injections of 20 mg butafosfan for five days indicated that the pharmacokinetics of butafosfan were not time-dependent and that the accumulation in plasma was insignificant. The pharmacokinetic parameters following individual doses in this study were comparable with those obtained in the single-dose study with the exception of the terminal elimination half-life that was 5.4 hours at day 1 and 6.8 at day 5 (based on 24-hour plasma data) and 14.2 hours at day 5 (based on 48-hour plasma data). Butafosfan was distributed to all investigated tissues; the liver, the kidney, the muscle (loin) and the skin and fat tissue. The highest concentrations were found at 6 hours following the last dose on Day 5, especially in the liver and the kidney, and at 12 hours in the injection site. Urinary excretion of unchanged butafosfan was shown to be the major elimination route in pigs, with 77.8 % of the administered dose recovered in urine within 12 hours following the first dose.

The metabolic stability of butafosfan was investigated in liver microsomes from pigs, cattle and rats. The results showed that butafosfan was highly metabolically stable in all species tested. Less than 12% of butafosfan was degraded when incubated with liver microsomes from pigs, cattle and rats and no metabolites were revealed by the HPLC-MS/MS method used for analysis. This indicated that the Phase I oxidative system, using NADPH as a cofactor, does not contribute or contributes only slightly to the *in vivo* systemic clearance of butafosfan.

2.2.2. Residue depletion studies

A residue depletion study was performed in pigs.

Butafosfan was administered intramuscularly at a dose of 10 mg/kg bw once daily for five consecutive days. A validated analytical method (UPLCD MS/MS) was used for the determination of residues in tissues. The results showed that butafosfan was present in all tissues up to 48 hours following the last dosing on day 5, with the highest levels observed in the kidney at the first sampling at 6 hours. While the depletion from the kidney and the liver was rapid, a slower depletion rate was observed for the injection sites and their surrounding areas. The highest calculated total daily intake of residues was obtained at 6 hours, when the mean (maximum) total intake represented 9% (12.5%) of the ADI. At 48 hours, the residues had depleted to mean levels that corresponded to 0.1 % of the ADI or lower, except for the injection site, for which the mean daily intake of butafosfan represented 1.9% of ADI. The calculated total intake at 48 hours represented 2.2% of the ADI.

2.2.3. Monitoring or exposure data

No monitoring or exposure data were available.

2.2.4. Analytical method for monitoring of residues

No validated analytical method for monitoring of residues of butafosfan has been proposed. The absence of an analytical method is considered acceptable for a 'no MRL required' recommendation.

2.2.5. Findings of EU or international scientific bodies

No information on evaluations by other international scientific bodies was available.

3. Risk management considerations

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

In view of the nature of the substance no data were considered necessary in the context of this evaluation.

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

No such considerations were identified.

3.3. Elaboration of MRLs

From the tissue residue depletion study and the pharmacokinetic studies it can be concluded that butafosfan is rapidly metabolised and eliminated in pigs. The highest concentration was found in kidney at 6 hours following treatment. The concentrations then decreased rapidly in all tissues, with the slowest rate of depletion seen at the injection site.

The theoretical maximum daily intake was 12.5% of the ADI at 6 hours following the last dose. In addition, it should be noted that a consumer may potentially be exposed to residues in milk as well as to residues in porcine tissues. The CVMP previously calculated that exposure to residues in milk would not amount to a maximum of 1.5% of the ADI (CVMP Summary Report for the butafosfan extension to lactating cows – EMEA/MRL/734/00-FINAL). The overall worst case exposure is therefore estimated to amount to 14% of the ADI.

In light of the above, it is considered that there is no 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 butafosfan in pigs, and a "No MRL required" classification can be recommended.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the recommended maximum residue limits for butafosfan to other food producing species and food commodities.

Taking into account the current scientific knowledge, the recommendations on extrapolation are justified as follows:

Animal species/food commodities	Extrapolation possible	Justification
All mammalian food producing species	Yes	Data generated in pigs and cattle indicate that the pharmacokinetic pattern, with rapid elimination, is similar following intravenous, intramuscular and subcutaneous administration. The pharmacokinetic pattern is expected to be similar across mammalian species. The current entry with regard to bovine species includes a restriction for intravenous administration as residue depletion data were previously only available following intravenous administration. The data provided in relation to pigs includes residue depletion from the injection site following intramuscular and subcutaneous administration and the fact that similar elimination patterns are expected across mammalian species allows for removal of the restriction for use in bovine species. The conclusions of the evaluation of the residue depletion data can therefore be extrapolated to all mammalian food producing species.
Poultry	No	Metabolism and pharmacokinetic data are only available in mammals and therefore the conclusions cannot be extrapolated to poultry.
Fin fish	No	The metabolism in fish can differ from the metabolism in mammals. Since no data are

		available for fish extrapolation is not possible.
Honey	No	Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data in other food products cannot be extrapolated to honey.

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

Having considered that:

- a toxicological ADI of 0.6 mg/kg bw (i.e. 36 mg/person) was previously established as the overall ADI for butafosfan;
- butafosfan is rapidly absorbed and eliminated after intramuscular and subcutaneous administration to pigs;
- at 6 hours after treatment by intramuscular injection, the amount of residues from edible tissues in pigs likely to be ingested by consumers represents less than 12.5% of the toxicological ADI;
- exposure to butafosfan residues resulting from the combined ingestion of pig tissues and cattle milk would remain well below the ADI (a maximum of 14% of the ADI);
- the available data supports the view that the pharmacokinetic profile of butafosfan will be similar in all mammalian food producing species;

the Committee concludes that the establishment of maximum residue limits for butafosfan for porcine species is not necessary for the protection of human health, and that the conclusion should apply to all mammalian food producing species, and therefore recommends by consensus the amendment of table 1 of the Annex to Regulation (EU) No 37/2010 with regard to butafosfan as follows:

Pharmacologically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Butafosfan	NOT APPLICABLE	All mammalian food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	Alimentary tract and metabolism / mineral supplements

4. Background information on the procedure

Submission of the dossier:	21 December 2012
Steps taken for assessment of the substance	
Application validated:	16 January 2013
Clock started:	17 January 2013
CVMP opinion adopted:	13 June 2013