

Annex I

List of the names, pharmaceutical forms, strength of the veterinary medicinal products, animal species, route of administration, withdrawal period and applicant/marketing authorisation holders in the member states

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration	Recommended dose	Withdrawal period
Belgium	Cross Vetpharm Group Limited Broomhill Road Tallaght, Dublin 24 Ireland	Selenate Long Acting 50 mg/ml, suspension injectable pour bovins	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Czech Republic	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	SELENATE Long Acting 50 mg/ml injekční suspenze pro skot	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Germany ¹	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selenate LA 5%	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Denmark	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selongatum Long Acting, Suspension til injektion	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Estonia	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selenate Long Acting, 50 mg/ml, süstesuspensioon veistele	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days

¹ Marketing authorisation not granted

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration	Recommended dose	Withdrawal period
Spain	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Dalmasel L.A. 50 mg/ml, suspensión inyectable para bovino	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
France	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	SELENATE LA SUSPENSION INJECTABLE 50 MG/ML POUR BOVINS	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Ireland	Tairgi Tread-Lia Baile na Sceilge Teo Ballinskelligs Killarney Co. Kerry Ireland	B.V.P. Barium Selenate Injection	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 mg Se/kg body weight corresponding to the following: Cattle (adult): 6-10 ml Cattle (young): 3-8 ml Calves: 1-2 ml	Meat and offal: 31 days Milk: Zero days
Ireland	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selenate Long Acting 50 mg/ml Suspension for Injection for Cattle	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Lithuania	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	SELENATE LONG ACTING 50 mg/ml injekcinė suspensija galvijams	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration	Recommended dose	Withdrawal period
Latvia	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selenate Long Acting 50 mg/ml suspensija injekcijām liellopiem	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Poland	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selenate Long Acting 50 mg/ml zawiesina do wstrzykiwań dla bydła	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Romania	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selenate Long Acting 50 mg/ml Suspensie injectabilă pentru bovine	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Slovakia	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	SELENATE Long Acting 50 mg/ml injekčná suspenzia pre hovädzi dobytok	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
Sweden	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selongatum vet. 50 mg/ml injektionsvätska, suspension för nötkreatur	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg body weight	Meat and offal: 31 days Milk: Zero days
United Kingdom	Cross Vetpharm Group Limited Broomhill Road Tallaght Dublin 24 Ireland	Selenate Long Acting 50 mg/ml Suspension for Injection for Cattle	Barium selenate	Suspension for injection	50 mg/ml	Cattle	Subcutaneous injection	1 ml per 50 kg bodyweight	Meat and offal: 31 days Milk: Zero days

Annex II

Scientific conclusions and grounds for refusal of the granting of the marketing authorisation and for suspension of the existing marketing authorisations

Overall summary of the scientific evaluation of long acting formulations for injection containing barium selenate for all food producing species (*see annex I*)

1. Introduction

Barium selenate has been used in slow-release injectable veterinary medicinal products for therapeutic and prophylactic use against selenium deficiencies in cattle and sheep. It is administered as a subcutaneous injection at a dose of 1 mg selenium/kg body weight (bw).

Selenium is an essential micronutrient for animals as well as humans, but is highly toxic if taken in excess and has only a very small safety margin between vital and toxic dose levels.

On 14 September 2011, the Federal Office of Consumer Protection and Food Safety of Germany submitted a notification for a referral procedure under Article 35 of Directive 2001/82/EC for all long acting formulations for injection containing barium selenate for all food producing species. Germany referred the matter to the CVMP due to serious human health concerns related to exposure to injection site residues from use of long-acting barium selenate containing injectable veterinary medicinal products.

The referral procedure started on 15 September 2011. The procedure involved 3 veterinary medicinal products with 18 marketing authorisations granted nationally or subject to on-going applications under a decentralised procedure. The decentralised procedure was finalised during the referral procedure and the resulting national marketing authorisations have been granted except in Germany. It should be noted that during the referral procedure the marketing authorisations for a veterinary medicinal product authorised for use in sheep were voluntarily withdrawn by the marketing authorisation holder. This product was excluded from the referral procedure accordingly, but the data made available to the CVMP concerning the product were taken into account in this assessment. Thus, to the CVMP's knowledge, at present there are no authorised long acting injectable products containing barium selenate for use in target species sheep.

The complete list of all veterinary medicinal products involved in this referral procedure is provided in annex I above.

2. Discussion

The veterinary medicinal products concerned in the referral are given as single subcutaneous injections and contain 177.48 mg barium selenate/ml suspension for injection, equivalent to 50 mg selenium. Cattle are treated at a dose of 1 mg selenium/kg bw, resulting in doses of 2 ml for calves (i.e. 355 mg barium selenate corresponding to 100 mg selenium) and up to 10 ml for adult cattle (i.e. 1,775 mg barium selenate corresponding to 500 mg selenium).

Background (MRL status)

In 1999 the CVMP assessed barium selenate in the context of an application for the establishment of maximum residue limits under Regulation (EEC) No 2377/90. In 2000, following the CVMP recommendation barium selenate was included in Annex II of Regulation (EEC) No 2377/90 for bovine and ovine species, and is, subsequent to the implementation of Regulation (EC) 470/2009 replacing Regulation 2377/90, included in Table 1 of the Annex of Regulation (EU) No 37/2010 for bovine and ovine species, with no maximum residue limit (MRL) required. This assessment was based on an estimated tolerable upper daily intake in humans corresponding to 0.6 mg selenium/person/day (10 µg/kg bw) and the assumption that oral bioavailability of selenium from barium selenate would be very

low (although no quantitative estimate was performed). The available residue data indicated that there is practically no depletion of barium selenate from the injection site. It was noted in the MRL summary report that measures should be in place to avoid consumption of injection sites.

The upper tolerable level for selenium intake was established in the EU by the Scientific Committee on Food (in 2000) at a lower level of 0.3 mg selenium/person/day (5 µg/kg bw) and was in 2006 confirmed by the Scientific Panel on Dietetic Products, Nutrition and Allergies of the European Food Safety Authority (EFSA). In addition, the data base for the assessment of the oral bioavailability of selenium from barium selenate and its likely uptake and toxicity pathways following oral ingestion has become more complete and additional data on acute selenium toxicity, especially in humans, have become available.

Residue data

Following injection of barium selenate, residues of selenium in tissues other than the injection site are low, not detectable or at least far below any level of toxicological concern. For the injection site however, all residue depletion studies consistently show that following treatment at recommended doses of barium selenate there is virtually no depletion of residues, which remain at the injection site for a prolonged period of time. Residues recovered from the injection site in cattle were in the range from 77% to 99% of the injected doses at 30 to 119 days following injection.

In another residue depletion study a product with a colourant specifically aimed at marking the injection site was used. Despite this, residue levels at the injection site were highly variable, suggesting that sampling failed to identify the true injection site accurately and consistently. The study also showed that even one year after treatment high amounts of selenium were found at the injection site (up to 53.229 mg/kg).

Despite the slow rate of residue depletion, a withdrawal period of 31 days for cattle meat and offal has been set for the concerned veterinary medicinal products (see annex I). The scientific rationale for this withdrawal period is not known as no product specific residue depletion data for the above-mentioned veterinary medicinal were provided in this referral procedure.

Toxicity

There is no ADI set for barium selenate but two different upper tolerable levels for selenium intake for chronic toxicity are available. In the CVMP MRL summary report a figure of 0.6 mg selenium/person/day was at the time considered appropriate. The EFSA subsequently set a tolerable upper level at 0.3 mg selenium/person/day based on a no observed effect level (NOEL) of 850 µg/day for clinical selenosis in a human study.

With regard to acute toxicity reference is made to studies measuring LD₅₀ values. In principle LD₅₀ is not accepted as an endpoint from which calculations are made to estimate toxicity relevant for consumer risk assessments, acknowledging that the LD₅₀ is a very severe endpoint (where half of the test animals die). For consumer safety any adverse effects, even mild ones, are relevant and therefore the reference dose to be considered is the level at which no adverse effects (NO(A)EL) can be expected. However, in this case no data on acute toxicity using more sensitive acute endpoints were available. LD₅₀ in rats and mice for selenate and selenite are typically in a range of approximately 1 mg/kg bw to 10 mg/kg bw. Also human data give evidence of severe acute effects of selenium at oral dose levels of 5 mg to 22.3 mg selenium/kg (as sodium selenite or sodium selenate), with partly fatal outcomes.

Oral bioavailability of selenium from barium selenate

Data has been provided to estimate the oral bioavailability of selenium following ingestion of residues of barium selenate. Based on the data available at the time of the MRL evaluation it was assumed that

the available fraction would be very low. CVMP has now been presented with data from an *in vitro* study simulating conditions in the human gastrointestinal tract. This study indicates that at least 5% to 10% of ingested selenium from barium selenate is bioavailable when present in a normal food matrix. This figure is much higher than what was assumed when the MRL decision was taken.

The findings of the *in vitro* study are supported by theoretical considerations based on physico-chemical properties of barium selenate, indicating that relevant amounts of selenium could be bioavailable from orally ingested barium selenate i.e. the intake of residues from an injection site would, by simple theoretical estimation based on the solubility product constant, lead to a bioavailable exposure of approximately 15 mg selenium (i.e. 3% of the selenium dose at the injection site) in each litre of water in the intestinal tract. This lower-bound estimate did not take into account that under acid pH conditions (gastric acid) and in the presence of sulphate ions (average intake in food of 500 mg/person/day, (WHO, 2004))² the solubility may considerably increase.

The indication of significant oral bioavailability was also supported by an *in vivo* study in sheep (Archer and Judson, 1994)³. This study showed that orally ingested barium selenate (doses of 100 mg or 250 mg per animal similar to those present at injection sites) was absorbed/bioavailable in the gastrointestinal tract. However, the design of this study did not allow for an estimation of the bioavailable selenium fraction and thus these data are supportive only.

Risk characterisation

Comparisons of estimated bioavailable doses of selenium following ingestion of an injection site show that the amounts of selenium heavily exceed the toxicological thresholds. Using the upper tolerable level established by EFSA of 0.3 mg selenium/person/day it is concluded that the bioavailable fraction of 5% (25 mg) of one injection site would exceed the reference value more than 80 times. Considering that the lowest LD₅₀ is less than 10 times the possible consumer's exposure it is obvious that also a fraction of an injection site might cause toxicity if ingested.

Risk management measures

Adequate risk mitigation measures to avoid injection site residues entering the food chain are not currently in place.

The withdrawal period of 31 days does not guarantee depletion of residues from the injection site to safe levels as barium selenate residues remain at injection sites for long periods and if ingested, would provide orally bioavailable selenium. At present no appropriate withdrawal periods can be set for these veterinary medicinal products.

Unmarked injection sites are not clearly identifiable in all animals, especially if long periods of time elapse between injection and slaughter. While the injection sites may not be visible residues levels are still unsafe for human consumption. In addition residue depletion data generated with a product containing a colourant specifically aimed at marking the injection site (ferric oxide), injection sites were not clearly identifiable in all animals and could not be completely removed.

Therefore, removal of injection sites at slaughterhouses is not considered to be a sufficient risk management measure to reliably prevent consumption of injection site tissue.

² WHO (2004): Background document for development of WHO Guidelines for Drinking-water Quality WHO/SDE/WSH/03.04/114

³ Archer, JA and Judson, GJ (1994): Availability of Barium Selenate administered orally to sheep. Proc. Aust. Soc. Anim. Prod. 20, 441.

3. Benefit-risk assessment

Barium selenate fulfils a valuable role in the treatment and prevention of nutritional muscular dystrophy (white muscle disease), poor reproductive performance and ill thrift due to selenium deficiency.

Among available products, long acting injectables represent a convenient alternative but there are other possibilities including:

- injections containing sodium or potassium selenite, authorised for horses, cattle, sheep and pigs;
- long acting intraruminal devices containing sodium selenate, authorised for cattle only⁴;
- dietary supplementation.

Due to their formulations, these alternative products for the treatment and prevention of disease relating to selenium deficiency are less convenient for some cases requiring treatment. Therefore, from an animal husbandry perspective it is therefore unfortunate if the long acting injectables containing barium selenate are not available.

However, the available information indicates that the use of veterinary medicinal products containing barium selenate administered subcutaneously pose a significant threat to human health due to persistent selenium residues at the injection site. The risk mitigation measures used at present are not suitable to prevent consumer risk for the reasons described above.

In the EU presence of harmful residues in food in concentrations above the level considered as safe is not permissible. Risk mitigation measures currently in place are not suitable to ensure consumer safety of food derived from animals treated with long acting injectable products containing barium selenate.

When weighing the benefit for animal health in prevention and treatment of selenium deficiencies against the risk to public health via residues in food, the benefit-risk balance for long-acting injectable veterinary medicinal products containing barium selenate is considered to be negative.

Therefore the CVMP has recommended to suspend the existing marketing authorisations of all long-acting injectable veterinary medicinal products containing barium selenate until data ensuring consumer safety following use of the products are provided.

4. Re-examination procedure

Following the CVMP opinion of 10 April 2013 on this referral procedure, Cross Vetpharm Group Limited and Tairgi Tread-Lia Baile na Sceilge Teo (Ballinskelligs Veterinary Products – BVP) requested a re-examination of that CVMP opinion. The detailed grounds for the re-examination were submitted on 10 June 2013.

The grounds for re-examination of the CVMP opinion of 10 April 2013 focused on the following arguments:

- the validity of the conclusion, based on the *in vitro* bioavailability study, that bioavailable residues of barium selenate would make up 5-10% of the total residues (the higher figure for lower concentrations);
- the fact that ingestion of barium selenate injection sites will be a rare event and consequently the use of the acceptable daily intake (ADI) as the relevant health based guidance value in the

⁴ Products also contain cobalt and copper

evaluation of consumer safety concerns is questionable and that a more appropriate value would be the calculated LD₅₀;

- the fact that injections are administered subcutaneously limits the risk and furthermore accidental intramuscular injection is very unlikely;
- conclusions on bioavailability in sheep drawn from the Archer and Judson (1994)³ study cannot be readily extrapolated to humans;
- risks could be further mitigated by dividing the dose into two injections given into opposite sides of the neck; in practice risks will also be mitigated as Official Veterinarians working at slaughterhouse will see blemishes resulting from barium selenate injections and ensure that the relevant areas of tissue are discarded;
- pharmacovigilance systems would be expected to detect serious adverse events resulting from consumption of meat containing barium selenate residues; the fact that no such events have been detected supports the conclusion that barium selenate injection sites do not pose a threat to consumer safety.

CVMP conclusion after re-examination

The CVMP assessed the detailed grounds for the re-examination and the CVMP's conclusions in relation to each of the bullets above are summarised below:

- although a number of concerns in relation to the *in vitro* bioavailability study were raised, the CVMP accepted the overall conclusion of the study and used a figure of 5% in its calculations of bioavailable residues. However, the CVMP highlighted that conclusions based on this value should be considered with care as there can be no certainty in relation to the accuracy of the derived bioavailability figure for predicting bioavailability *in vivo*;
- the CVMP acknowledged that consumption of barium selenate injection sites is likely to be a rare event. However, in line with the CVMP guideline on injection site residues (EMEA/CVMP/542/03)⁵, for substances for which there is no MRL for muscle, the reference value used in the assessment of injection site residues is normally the ADI. Furthermore, while it is the case that the ADI is based on repeated exposure, the alternative threshold proposed by the marketing authorisation holders (i.e. the LD₅₀) is not appropriate as this represents the value at which 50% mortality is expected. Any health based reference value must be capable of reflecting non-serious adverse effects;
- the CVMP noted that the guideline on injection site residues applies similarly independent on whether the injection is given subcutaneously or intramuscularly;
- the CVMP concluded that the study by Archer and Judson (1994)³ could not be used for the purpose of determining bioavailability. It could only be considered that the data obtained in this study do not contradict the *in vitro* data. Thus the figure of 5% bioavailability is still considered appropriate for use in residue calculations;
- in relation to the possibility of dividing the dose into two injections and administering one into each side of the neck, the CVMP considered that the issues related to safe levels of bioavailable selenium residues are not resolved by dividing into two injections. In order to ensure that the level of selenium at a single injection site does not exceed the estimated safe level of 0.3 mg/person/day, then the maximum acceptable volume for adult cattle would be 0.12 ml and more than 80 injections would be needed for a full dose. In relation to the comments that barium selenate injection sites will be trimmed off and discarded at the slaughter house, the CVMP

⁵ CVMP guideline on injection site residues (EMEA/CVMP/542/03) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004429.pdf

considered that this would indeed happen in those cases where the injection sites are still detectable, i.e. at early timepoints. However, injection sites cannot be expected to be identifiable months or possibly years following administration. Consequently trimming of the injection site is not considered to represent a fully effective risk mitigation measure;

- the CVMP acknowledged that pharmacovigilance systems can be expected to detect extremely serious cases of poisoning resulting from use of veterinary medicinal products containing barium selenate. However, the evaluation of consumer safety concerns needs to consider all possible adverse effects (not only the most severe), and these are unlikely to be detected by pharmacovigilance systems. In general, as in this case, absence of pharmacovigilance data cannot be used as justification of the absence of any adverse effects in consumers.

After reviewing all the documentation submitted by the marketing authorisation holders, the CVMP concluded that there were not sufficient scientific grounds to change the overall conclusions of 10 April 2013, which concluded that the benefit-risk balance for the products concerned is negative and that such veterinary medicinal products could pose a significant threat to human health due to persistent selenium residues at the injection site.

Based on the lowered upper tolerable limit (0.3 mg/person/day) for selenium intake, the new information on bioavailability of residues and additional toxicity data in humans, a review of the MRL opinion for barium selenate is recommended in order to protect human health, in accordance with Article 11 of Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009.

Grounds for refusal of the granting of the marketing authorisation and for suspension of the existing marketing authorisations

Whereas

- the CVMP considered that all residue depletion studies consistently show that, following treatment at recommended doses, barium selenate remains at injection sites for long time periods after treatment and virtually no depletion of residues from the injection site occurs, resulting in high levels of barium selenate at injection site;
- the CVMP considered that based on the new information from an *in vitro* study simulating conditions in the human gastrointestinal tract, at least 5% of ingested selenium from barium selenate is bioavailable when present in a normal food matrix;
- the CVMP considered that risk management measures to avoid injection site residues are currently not in place and could not be identified in this procedure due to a lack of information and sufficient data to evaluate such measures;
- the CVMP considered that the benefit-risk balance for the long-acting formulations for injection containing barium selenate for all food producing species is negative as the products could pose a significant threat to human health,

the CVMP has recommended the refusal of the granting of the marketing authorisation and for suspension of the existing marketing authorisations for long-acting formulations for injection containing barium selenate for all food producing species (see annex I).

The condition for lifting the suspension of the marketing authorisations is described in annex III.

Annex III

Condition for lifting the suspension of the marketing authorisations

National Competent Authorities, coordinated by a reference Member State, shall ensure that the following condition is fulfilled by the marketing authorisation holders:

The marketing authorisation holders should provide data and propose measures that will ensure consumer safety following use of the products and in particular:

1. Suitable risk mitigation measures have to be proposed and supported by appropriate scientific data which demonstrate that selenium residues in edible tissues from treated animals, including the injection site, exceeding the upper tolerable intake value of 0.3 mg/person/day do not enter the food chain.

It should be noted that if staining of injection sites via use of a colourant is proposed, suitable data have to be provided confirming that the pigment persists visibly at the injection site for a justified period of time. This implies that the colourant has the same distribution behaviour and residence time as barium selenate. As previous studies indicated, barium selenate remains at the injection site for a long time. The appropriateness of the covered time period needs to be justified and advice provided on identification and removal of the contaminated injection site area.