Annex I

List of the names, pharmaceutical form, strengths of the veterinary medicinal products, animal species, route of administration and marketing authorisation holders in the Member States

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Bulgaria	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Сантиола 50 mg/ml инжекционен разтвор за говеда и овце	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Bulgaria	Industrial Veterinaria, S.A Esmeralda 19 Esplugues de Llobregat Barcelona 08950 Spain	Роленол	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Croatia	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola, 50 mg/mL, otopina za injekciju, za goveda i ovce	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Czech Republic	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola 50 mg/ml injekční roztok pro skot a ovce	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Denmark	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola Vet	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Estonia	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
France	LILLY France 24 Boulevard Vital Bouhot 92200 Neuilly Sur Seine France	FLUKIVER	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Hungary	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola 50 mg/ml oldatos injekció szarvasmarhák és juhok részére A.U.V.	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Ireland	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola 50 mg/ml solution for injection for cattle and sheep	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Latvia	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Lithuania	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola 50 mg/ml injekcinis tirpalas galvijams ir avims	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Romania	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola 50 mg/ml raztopina za injiciranje za govedo in ovce	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Slovenia	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola 50 mg/ml raztopina za injiciranje za govedo in ovce	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Laboratorios e Industrias Iven, S.A. Luis I, 56. Poligono Industrial Vallecas 28031 Madrid Spain	Endoectiven	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Spain	CENAVISA, S.L. Cami Pedra Estela s/n Reus (Tarragona) 43205 Spain	TELCEN	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Spain	S.P. VETERINARIA, S.A. Ctra. Reus-Vinyols, KM.4,1 Riudoms (Tarragona) 43330 Spain	ENDOEX 50 mg/ml SOLUCION INYECTABLE	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Spain	Industrial Veterinaria, S.A Esmeralda 19 Esplugues de Llobregat Barcelona 08950 Spain	ROLENOL	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
Sweden	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola vet.	Closantel	50 mg/ml	solution for injection	cattle, sheep	sheep: subcutaneous
United Kingdom	KRKA d.d. Šmarješka cesta 6 Novo mesto 8501 Slovenia	Santiola 50 mg/ml Solution for Injection for Cattle and Sheep	Closantel	50 mg/ml	solution for injection	sheep	sheep: subcutaneous

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

Overall summary of the scientific evaluation of veterinary medicinal products containing 50 mg closantel per ml (as a single active substance) presented as solutions for injection for subcutaneous use in sheep (see Annex I)

1. Introduction

Closantel is a salicylanilide anthelmintic, a synthetic antiparasitic agent with efficacy against liver fluke, haematophagous nematodes and larval stages of some arthropods in sheep and cattle. The recommended doses are 2.5 mg or 5 mg closantel per kg body weight (bw) for cattle and sheep, depending on the parasitic species and/or parasitic life stage at the time of treatment.

An application was submitted under Article 13(1) of Directive 2001/82/EC, i.e., a generic application for a marketing authorisation under the decentralised procedure for the veterinary medicinal product Santiola, containing 50 mg closantel per ml, with Ireland as Reference Member State (IE/V/0377/001/DC). The reference product is Flukiver 50 mg/ml Solution for Injection, which has been authorised in various Member States since 1989.

Another (nationally-authorised) version of Flukiver Solution for Injection has been authorised in France since 1981; the marketing authorisation for this product was varied in 2016 and the withdrawal periods for sheep (meat and offal) were increased from 77 days to 107 days as a result of data provided during the variation procedure.

The proposed sheep meat withdrawal period for the generic product, Santiola, was 77 days, in line with the Irish reference product (although the target species 'sheep' was removed from the reference product during the application procedure for Santiola), but not in accordance with the data provided by France during the procedure.

It has been noted that there are different approved withdrawal periods for sheep (meat and offal) for veterinary medicinal products containing 50 mg closantel per ml (as a single active substance) presented as solution for injection for subcutaneous use in sheep across the EU, i.e., between 28 days and 107 days. The UK therefore considered that it is necessary to refer the matter to the CVMP in the interests of protecting consumer safety in the Union and requested the Committee to review all available residue depletion data and recommend withdrawal periods for sheep (meat and offal).

2. Discussion of data available

Qualitative and quantitative composition

Information was received regarding the composition of the affected products (n = 5). Two of the product formulations are very similar, being solutions with similar excipients, and using a similar proportion of water and propylene glycol as the vehicle. One of these products ('Flukiver 5%') was used in the pivotal residues study, Study 1. However, there are some significant differences between this and the other product formulations that are in the scope of this referral procedure. The product used in Study 2 'Endoex Solucion Injectable', has a level of propylene glycol that is not comparable to the product used in Study 1. Another product has propylene glycol as the main vehicle, and includes no water for injections. The last product is formulated with a large percentage of glycerol formal. Formulation differences may make a difference to how the active substance is absorbed from the injection site, and also, therefore, the overall residues depletion pattern. There were no residues depletion data provided for the last two products mentioned.

Data were provided on the physicochemical properties of the different solvents used in these product formulations, particularly regarding their relative viscosities, and how this would affect absorption from the injection site. The viscosity of propylene glycol is greater than that of glycerol formal which is greater than the viscosity of water. It has been shown that, in general, the higher the viscosity of the product, the slower the rate of absorption from the injection site. It was considered that the presence of glycerol formal in one product would have less of an effect than propylene glycol on the overall viscosity of the product, when compared to that of water. Considering the relative proportions of these excipients, there was no reason to expect the viscosity of the product containing glycerol formal would be greater than that of some of the other products included in this referral.

It was also shown that, in general, the higher the volume of injection, the slower the rate of absorption from the injection site.

Pharmacokinetics

Data were provided, based on the pharmacokinetics of closantel, that demonstrated that the formulation differences, and thereby the potential differences in the rates of absorption from the injection site, would not affect the overall elimination from the edible tissues, other than from the injection site itself.

When administered parenterally, closantel is absorbed relatively quickly into the systemic circulation (T_{max} = 8 – 24 h) and is highly bound to albumin in the plasma. It is slowly released from plasma and very slowly metabolised, and is therefore retained in the circulation for a long time; the plasma elimination half-life in sheep is 22.7 days. Most (90%) of a dose of closantel is excreted unchanged in the bile/faeces after intramuscular administration, but only 10% within 48 hours, after which the rate slows further so that 1 – 2% of the dose is eliminated each day.

Thus, it is considered that the rate of absorption from the injection site, which is measured in hours/days, will have a negligible influence on the rate of elimination from the edible tissues, which is measured in weeks.

Residue depletion in sheep meat and offal

Residues depletion data were submitted by two of the affected marketing authorisation holders.

Study 1

A GLP-compliant residue depletion study in sheep was submitted, conducted with the veterinary medicinal product ‘Flukiver 5%’, a product containing 50 mg closantel per ml. The product was administered via subcutaneous injection to sheep at the single recommended dose of 5 mg closantel per kg body weight. The study was conducted in 2016 with 20 treated animals (five mixed-sex groups of four animals) and a control group consisting of two untreated animals.

All edible tissues, including injection sites, were sampled on days 19, 40, 61, 89, and 103 after treatment and analysed using an SPE-LC-MS/MS method of analysis, validated in line with current requirements.

The concentrations of closantel residues were below the respective maximum residue limits (MRLs) at 19 days after administration in kidney, 40 days in muscle and fat, and 89 days in liver. Residues at the injection site were below the MRL for muscle at 61 days post administration.

The residue depletion data for the marker tissue, liver, do not allow for a statistical determination of a withdrawal period (the assumption of normal distribution of the errors was not met). As a result, a

withdrawal period of 107 days was determined, using the 'alternative' method, in line with CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95)[1].

Study 2

A GLP-compliant residue depletion study in sheep was submitted, conducted with the veterinary medicinal product 'Endoex Solucion Injectable', a product containing 50 mg closantel per ml. The product was administered via subcutaneous injection to sheep, at the single recommended dose of 5 mg closantel per kg body weight. The study was conducted in 2009, with 30 treated animals (5 mixed-sex groups of six animals) and a control group consisting of one untreated animal.

Based on the results of a preliminary non-GLP study, only the injection site tissues were collected for analysis. However, considering the results of this pilot study, and the limited information that they provide, this conclusion might not be adequate, as the residue concentrations in the sampled tissues did not fall below the respective MRLs; therefore, it was not possible to know which would be the withdrawal period determining tissue from these data.

In the GLP study, the injection sites were sampled on days 2, 7, 14, 24 and 29 days after treatment and analysed using an HPLC-FD method of analysis, validated in line with current requirements.

The concentration of closantel residues in the core injection site samples were below the MRL at 29 days after administration. A 41-day withdrawal period was determined, following statistical evaluation of the residues depletion data using the WT1.4 software.

Discussion

The differences between the two residues studies have been considered.

The two products used in the studies include almost the same excipients, but in different quantities. The main non-aqueous vehicle, propylene glycol, is present in both products in different quantities. The different quantities included may lead to the products having different viscosities, resulting in different rates of absorption of closantel from the injection site; however, this parameter is not considered to affect the elimination rate from the edible tissues, other than at the injection site itself. The specified pH of the products used in studies 1 and 2 were in the same range; the effect of pH to explain any differences can thus be ruled out.

Consideration has been given to the absolute amounts injected at the subcutaneous injection site. Both studies administered a dose of 5 mg/kg body weight; however, due to differences in the weights of the animals used in the two studies, the volume of product administered was different (6.7 - 8.4 ml administered in Study 1; 3.6 - 5.8 ml administered in Study 2). This is considered to be an important parameter affecting the residues at the injection site.

In addition, different breeds of sheep were used in each of the studies provided. The first study used Merino crosses, which are bred for meat production, whereas the second study used Ripollesa, which are bred for both meat and milk production. The female sheep were not lactating during the conduct of the study. It cannot be concluded from the data available whether these breed differences had any influence on the depletion patterns seen.

Finally, consideration has been given to the analytical methods that were used. The analysis of the sheep tissues differed between the two studies, with study 1 using LC-MS/MS as their analytical method, and study two using HPLC-FD. Both marketing authorisation holders provided reports detailing the validation of the analytical method used, and the performance characteristics were mostly described in accordance with current standards. In terms of sensitivity, the limit of quantification in Study 1 was determined as 150 µg/kg in muscle, whereas the limit of quantification in Study 2 was

[1] CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95) - link

less sensitive, at 500 µg/kg. The limit of detection for muscle was also lower in Study 1 (<2 µg/kg) than in Study 2 (492 µg/kg).

As data were collected for injection sites, only, in Study 2, it could have been possible to combine or compare data from studies 1 and 2 for depletion from this tissue, only. However, it is not considered that the conduct of the two studies was sufficiently similar to allow this comparison, and therefore to conclude on the impact that formulation may have had on injection site depletion.

The available data demonstrate that the liver is the withdrawal period determining tissue and that the rate of elimination from edible tissues would not be influenced by the rate of absorption from the injection site and thereby impacted by product formulation. Therefore, the Committee considered that the proposed WP of 107 days derived from Study 1 can be extrapolated to all concerned products.

The CVMP considered whether it would be necessary to restrict the volume of injection, to mitigate any uncertainties around the effect of formulation differences at the injection sites. This mitigation measure was thoroughly evaluated and discussed by the CVMP, and determined to be unnecessary. The reasoning being that:

- The tissue-specific withdrawal period determined from Study 1 for liver was 28 days longer than that for injection sites, which leaves a suitably long time for any additional injection site residues to deplete before the 107-day withdrawal period is complete.
- Although there is some uncertainty as to how the differences in formulation would affect the rate of depletion from the injection sites, the injection volumes used in Study 1 were considered to be reasonable worst case due to the weights of the animals used and the mg/kg, rather than mg/animal, dosing regimen, when compared to the recommended weights of animals in VICH GL 48[2].

3. Benefit-risk assessment

Introduction

The CVMP was requested to review all available residue depletion data for the veterinary medicinal products containing 50 mg closantel per ml (as a single active substance), presented as a solution for injection for subcutaneous use in sheep and recommend withdrawal periods for meat and offal derived from treated sheep.

Benefit assessment

While the efficacy of the concerned products in sheep has not been specifically assessed as part of this referral, the products under assessment are considered to be effective in the treatment and prevention of infestations with named parasites.

Risk assessment

Quality, target animal safety, user safety, environmental risk and parasitic resistance for the concerned veterinary medicinal products have not been assessed in this referral procedure.

A risk has been identified regarding the length of the authorised withdrawal periods for sheep (meat and offal), which, for some products, may be insufficient to allow residues of closantel to fall below the authorised MRLs in all edible tissues by the end of the withdrawal period, thereby posing a risk to consumers of meat and offal from sheep treated with these products.

[2] VICH topic GL48: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: Marker-residue-depletion studies to establish product withdrawal periods (EMA/CVMP/VICH/463199/2009) https://www.ema.europa.eu/documents/scientific-guideline/vich-gl48-studies-evaluate-metabolism-residue-kinetics-veterinary-drugs-food-producing-animals_en.pdf

Risk management or mitigation measures

To ensure the safety of consumers of food and food products derived from animals treated with products containing closantel, the European Commission has set MRLs for closantel in the edible tissues of sheep. In order for closantel-derived residues to deplete below the MRLs, a sufficient time between treatment and slaughter must be allowed. Two residues depletion studies were provided by the MAHs involved in the procedure, which were not comparable in terms of the reliability of the data, study design and reporting, and subsequently their outcomes. However, based on the data assessed during this procedure, it is possible to make a recommendation to have a 107-day withdrawal period for sheep (meat and offal) for the concerned products containing 50 mg closantel per ml (as a single active substance) presented as a solution for injection for subcutaneous use in sheep.

The Committee considered that, due to the slow and limited metabolism of closantel, the high protein binding and retention in plasma, and the long elimination time from tissues, the differences seen in the product formulations, which may lead to different rates of absorption from the injection site, should not influence the final rate of elimination from the edible tissues, other than at the injection site itself.

An additional risk mitigation measure of restricting the maximum injection volumes was considered by the CVMP, but ultimately it was decided that this was not required to ensure consumer safety. The reasoning being that:

- The tissue-specific withdrawal period determined from Study 1 for liver was 28 days longer than for injection sites, leaving a long time for any additional injection site residues to deplete before the 107-day withdrawal period is complete.
- Although there is some uncertainty as to how the differences in formulation would affect the rate of depletion from the injection sites, the injection volumes used in Study 1 were considered to be reasonable worst case, due to the weights of the animals used, and the mg/kg dosing regimen, when compared to the recommended weights of animals in VICH GL 48.

Evaluation and conclusions on the benefit-risk balance

Having considered the grounds for referral and the data available, the CVMP concluded that the withdrawal periods for meat and offal derived from treated sheep should be amended to 107 days to provide assurance for consumer safety.

The overall benefit-risk balance for the concerned veterinary medicinal products remains positive subject to the recommended changes in the product information (see Annex III).

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- from the data provided, it is concluded that the full residues depletion study provided for ‘Flukiver 5%’ (Study 1) could be considered as the pivotal study, as it was well-reported, and conformed well to current requirements. Study 2 investigated injection sites only, and the data from this study cannot be compared with, or combined with, the data from Study 1 due to differences in the conduct of the studies. In addition, the data provided by Study 2 was not considered to be suitable to set withdrawal periods, even for the product used in that study, since residues depletion was investigated at the injection site only.
- the data from Study 1 show that the liver is the withdrawal period determining tissue, and that the ‘alternative method’, as recommended in CVMP note for guidance on the approach towards

harmonisation of withdrawal periods (EMEA/CVMP/036/95), should be used to determine the withdrawal period as the statistical assumptions are not all met when trying to use the preferred statistical analysis. The first timepoint where all residues are below the authorised MRL is at 89 days, and, with the addition of a safety span of 20% to take into account the variability of depletion between the animals used, a withdrawal period of 107 days is calculated.

- as data have been provided that demonstrate that the impact of the formulation on the rate of absorption from the injection site is of minor significance compared to the very slow rate of elimination from the other edible tissues, the withdrawal period of 107 days derived in Study 1 can be extrapolated to all concerned products.
- with regard to the need for a maximum injection volume to be recommended in case of any difference in depletion on injection site residues, the CVMP does not consider it necessary to restrict the use of these products in this way.
- on the basis of the available data, the CVMP considered the withdrawal periods for meat and offal derived from treated sheep should be amended to provide assurance for consumer safety;
- the CVMP considered that the overall benefit-risk balance for the products under this procedure remains positive subject to amendments in the product information;

the CVMP has recommended variations of the marketing authorisations for veterinary medicinal products containing 50 mg closantel per ml (as a single active substance) presented as solutions for injection for subcutaneous use in sheep (see Annex I) in order to amend the summaries of product characteristics, labelling and package leaflets in line with recommended changes in the product information as set out in Annex III.

Annex III

Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

Summary of product characteristics

4.11 Withdrawal period(s)

Sheep:

Meat and offal: 107 days.

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

Labelling

8. WITHDRAWAL PERIOD

Sheep:

Meat and offal: 107 days.

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

Package leaflet

10. WITHDRAWAL PERIOD

Sheep:

Meat and offal: 107 days.

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.