Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal product, animal species, route of administration, marketing authorisation holders in the Member States

Member State EU / EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Zoetis Österreich GmbH Floridsdorfer Hauptstraße 1 1210 Vienna Austria	Linco-Spectin forte-lösliches Pulver für Tiere	Lincomycin (as lincomycin-hydrochlorid-monohydrat) and spectinomycin (as spectinomycin sulfate)	22.2 g lincomycin and 44.5 g spectinomycin per 100 g	Powder for oral solution	Pigs Chickens	Oral
Belgium	Zoetis Belgium SA Rue Laid Burniat, 1 1348 Louvain-la-Neuve Belgium	Linco-Spectin 100	Lincomycin (as lincomycin hydrochloride) and Spectinomycin (as spectinomycin sulphate)	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs Chickens	Oral
Bulgaria	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	Линко-Спектин 100 разтворим прах/Linco-Spectin 100 Soluble Powder	Lincomycin (as lincomycin hydrochloride), Spectinomycin (as spectinomycin sulphate)	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs Poultry - hens, chickens and turkeys	Oral
Cyprus	Zoetis Hellas SA L. Mesogion 253- 255 15451, N. Psichico Athens Greece	Linco-Spectin 100 SP, Powder for oral solution for chickens	Lincomycin Spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Chickens	Oral
Czech Republic	Zoetis Česká republika, s.r.o. Stroupežnického 17 Praha 5 150 00 Czech Republic	LINCO SPECTIN 100 plv. sol.	Lincomycin and spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs Poultry	Oral
Denmark	Zoetis Finland Oy Tietokuja 4 FI 00330 Helsinki Finland	Linco-Spectin Vet.	Lincomycin and spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for solution in drinking water	Pigs Chickens	Oral

Estonia	Pfizer Manufacturing Belgium N.V. Rijksweg 12 B-2870 Puurs Belgium	Linco-Spectin 100 Soluble Powder	Lincomycin/ Spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs Poultry (broilers)	Oral
France	Zoetis 23/25 Avenue Du Docteur Lannelongue 75014 Paris France	LINCO-SPECTIN 100	Lincomycin spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs	Oral
Germany	Zoetis Deutschland GmbH Schellingstraße 1, D-10785 Berlin Germany	Lincospectin Pulver zum Eingeben über das Trinkwasser für Schweine, Hühner (Broiler, Junghennen) und Puten	Lincomycin and spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder	Pigs Chicken (broiler, pullet) Turkey	Oral
Greece	Zoetis Hellas SA L. Mesogion 253- 255 15451, N. Psichico Athens Greece	LINCO SPECTIN 100	Lincomycin and spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Pouder for oral solution	Chickens (broilers)	Oral
Hungary	Zoetis Hungary Kft. Alkotás u. 53. H-1123 Budapest Hungary	Linco-Spectin 100 por belsőleges oldathoz A.U.V.	Lincomycin hydrochloride and spectinomycin sulphate	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs Chickens Turkeys	Oral

Ireland	Pfizer Healthcare Ireland Trading as Pfizer Animal Health, Ringaskiddy, Co. Cork Ireland	Linco-Spectin 100 Soluble Powder	Lincomycin (as Lincomycin Hydrochloride) and Spectinomycin (as spectinomycin sulphate)	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution. Pale yellow to light tan soluble powder	Pigs and poultry (non-layers)	Pigs: Linco-Spectin 100 Soluble Powder is formulated for administration via drinking water. A fresh solution should be prepared each day. Poultry: For dosing via the drinking water.
Italy	ZOETIS ITALIA S.r.l. Via Andrea Doria, 41 M 00192 Roma Italy	LINCOSPECTIN Polvere orale per uso in acqua da bere per polli da carne e suini	LINCOMYCIN (as Hydrochloride) SPECTINOMYCIN (as Sulfate)	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Oral powder for use in drinking water	Pigs Chickens	Oral
Latvia	Pfizer Animal Health MA EEIG Ramsgate Road Sandwich, Kent CT13 9NJ United Kingdom	Linco-Spectin 100	Lincomycin hydrochloride, spectinomycin sulfate	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Soluble powder for oral solution	Pigs Poultry	Oral
Lithuania	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	Linco-Spectin 100	Lincomycin hydrochloride Spectinomycin sulphate	33.3 g 66.7 g	Soluble Powder	Pigs Poultry (non-layers)	Oral
Luxembourg	Zoetis Belgium SA Rue Laid Burniat, 1 1348 Louvain-la-Neuve Belgium	LINCO-SPECTIN 100	Lincomycin and spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs Poultry	Oral

The Netherlands	Zoetis BV Rivium Westlaan 74, 2909 LD Capelle a/d Ijssel The Netherlands	Linco-Spectin 100	Lincomycin and spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Oral powder	Pigs Poultry, not eggs for human consumption	oral
Poland	Zoetis Polska Sp. z o.o. ul. Postępu 17B 02-676 Warszawa Poland	Linco-Spectin 100 (222g + 444g)/ 1000g, proszek do sporządzania roztworu doustnego dla świń, kur, indyków, kaczek i gołębi	Lincomycin and spectinomycin	222 g lincomycin and 444 g spectinomycin per 1000 g	Powder for oral solution	Pigs Chickens Turkeys Duck Pigeon	Oral
Portugal	Zoetis Portugal, Lda Lagoas Park, Edifício 10 2740-271 Porto Salvo Portugal	LINCO-SPECTIN 100	Lincomycin and Spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Oral Powder	Pigs Poultry (broilers, pullets and turkeys)	Oral
Romania	Pfizer Animal Health MA EEIG Ramsgate Road Sandwich, Kent CT13 9NJ United Kingdom	LINCO-SPECTIN 100	Lincomycin and spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Soluble powder	Pigs Chickens Turkeys	Oral
Slovakia	Zoetis Česká republika, s.r.o. Stroupežnického 17 Praha 5 150 00 Czech Republic	Linco-Spectin 100	Lincomycinum (ut Lincomycini hydrochloridum, Spectinomycinum (ut Spectinomycini sulfas tetrahydricus)	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs Poultry	Oral
Slovenia	Zoetis Belgium SA, Rue Laid Burniat 1, 1348 Louvain-la-Neuve Belgium	LincoSpectin 100 prašek za peroralno raztopino za prašiče in perutnino	Lincomycin, Spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for oral solution	Pigs Poultry	Oral
Spain	Zoetis Spain, S.L. Avda. de Europa 20B Parque empresarial La Moraleja 28108 Alcobendas, Madrid Spain	LINCO-SPECTIN 100	Lincomycin and spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Oral powder	Pigs Poultry	Oral

United Kingdom	Zoetis UK Limited 5th Floor, 6 St. Andrew Street EC4A 3AE London United Kingdom	Linco-Spectin 100 Soluble Powder, Powder for Oral Solution	Lincomycin Spectinomycin	33.3 g lincomycin and 66.7 g spectinomycin per 150 g	Powder for Oral Solution	Pigs Poultry	Pigs: for administration via drinking water. Poultry: for administration as the sole daily source of drinking water until consumed, followed by non-medicated water for the rest of the day, if necessary

Annex II

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

1. Overall summary of the scientific evaluation of Linco-Spectin 100 and its associated names (see Annex I)

Introduction

Linco-Spectin 100 is a powder for oral solution containing 33.3 g lincomycin (as lincomycin hydrochloride) and 66.7 g spectinomycin (as spectinomycin sulphate) per 150 g pack. Lincomycin is a lincosamide antibiotic, closely related to macrolide and streptogramin B antimicrobials. It inhibits protein synthesis through binding to the 50S bacterial ribosome subunit. It is mainly active against Gram-positive bacteria and obligate anaerobes, and against mycoplasmas. Lincomycin distributes well into tissues and is known to produce high intracellular concentrations. Spectinomycin is classified as an aminocyclitol antibiotic, close to aminoglycosides; it inhibits protein synthesis by binding to the 30S ribosomal subunit. The activity spectrum of spectinomycin includes mycoplasmas, aerobic gram-negative bacteria, and gram-positive cocci. Spectinomycin is poorly absorbed by the gastro-intestinal tract and does not easily cross membranes.

On 28 September 2012, Belgium sent a referral notification under Article 34(1) of Directive 2001/82/EC, as amended, to the CVMP/European Medicines Agency for Linco-Spectin 100 and its associated names. Belgium referred the issue due to divergent national decisions having been taken by the EU Member States resulting in discrepancies in the product information for Linco-Spectin 100 and its associated names.

The main areas of disharmony in the existing product information relate to:

* Target species;
* Indications;
* Posology;
* Withdrawal periods.

Discussion of data available

Pigs

The indication for swine dysentery caused by *Brachyspira hyodysenteriae* and associated pathogens was substantiated trough a review of literature and old proprietary *in vitro* susceptibility data, a newly conducted *B. hyodysenteriae* MIC survey, and old clinical studies.

Literature and the proprietary old *in vitro* susceptibility data show that the overall lincomycin minimum inhibitory concentration (MIC) range for *B. hyodysenteriae* is very wide and the population MIC_{50} and MIC_{90} values are high. In the new MIC survey using 25 isolates from Belgium, a lincomycin-spectinomycin MIC range of 1:2 to 32:64 µg/ml was obtained, with a MIC_{50} of 16:32 and a MIC_{90} of 32:64 µg/ml. This reflects the ready acquisition of resistance determinants by the bacterium. Pringle *et al.* (2012)[1] have proposed an epidemiological cut-off of >1 µg/ml for lincomycin, with which 90 to 100% of the isolates are classified as "resistant *in vitro*". For those reasons, despite that the available data show no negative evolution over time, it could not be excluded that the results obtained in the old clinical studies conducted at the time of product development do not reflect clinical efficacy in modern outbreaks of swine dysentery. However, no precise clinical breakpoint has been established and from the data provided it seems that *in vitro* susceptibility was not correlated to clinical efficacy. No recent

[1] Pringle, M. *et al* - Antimicrobial susceptibility of porcine *Brachyspira hyodysenteriae* and *Brachyspira pilosicoli* isolated in Sweden between 1990 and 2010. Acta Vet Scand. 2012 Sep 21;54:54.

clinical data were provided to substantiate this claim. The discrepancy might be related to the fact that various enteric bacteria may contribute to the pathogenesis of the disease, and efficacy could be obtained in strains with relatively high MIC values due to high local antimicrobial concentration in the gut. Spectinomycin has no significant clinical effect on *B. hyodysenteriae*. It is speculated by the marketing authorisation holder that spectinomycin might have an effect on associated pathogens related to swine dysentery; however, such an effect has not been formally demonstrated *in vivo* on specific pathogens.

The *in vitro* susceptibility data for *Escherichia coli* and *Salmonella* were not extensive but among them there were data from a newly conducted good laboratory practice (GLP)-compliant pan-European MIC survey involving 100 *E. coli* and 100 *Salmonella* isolates from clinical cases. In this study the MIC range was from 4:8 µg/ml up to ≥256:512, with high MIC_{90} values of >256 µg/ml for spectinomycin, and a seemingly bimodal distribution. This is indicative of a significant rate of high-level resistance although no firm clinical breakpoint has been set. This could be partly related to natural resistance in those bacterial species.

Clinical efficacy at the proposed dosing regimen of 10 mg/kg body weight (bw) for 7 days in swine dysentery was supported by two duplicate trials in laboratory conditions, and by two field clinical studies. These were not GLP or good clinical practice (GCP)-compliant and the target clinical and bacteriological condition was not well defined in the study reports. Also in one of the field studies the target condition was a mixed enteric and respiratory infection involving *Salmonella* and *Mycoplasma*, which is only poorly relevant to the claimed indication. The combination lincomycin-spectinomycin was also shown to be superior to each individual active substance. Although in those studies doses were expressed as concentrations in drinking water so that actual doses in terms of mg/kg bw could only be estimated, the estimations were deemed sufficiently close to the recommended regimen. Moreover the harmonised dosing regimen is the one recommended in a vast majority of the Member States.

Taking into account all data, the CVMP considered that this indication can be maintained.

In support of the indication for proliferative enteropathy caused by *Lawsonia intracellularis*, a literature review on *in vitro* susceptibility data was provided, as well as two older clinical efficacy studies.

The results of the literature MIC data, which concern only a few isolates, overall indicate high MIC values for both lincomycin and spectinomycin. There is no established clinical breakpoint.

In a GLP challenge study, pigs were treated with the recommended 10 mg/kg bw dose, but for 21 days instead of 7 days. The combination showed beneficial effects as regards lesion reduction and zootechnical endpoints, and bacterial shedding was completely stopped. The combination was superior to lincomycin alone. In a GCP-compliant, multicentre field study, pigs were treated as recommended and medication with Linco-Spectin 100 for 7 and 14 days was efficacious for the treatment of ileitis in pigs; there was no benefit of treating pigs suffering from ileitis longer than 7 days.

Although the scarce data available indicates that *in vitro* activity of the active substances against *L. intracellularis* is poor, considering the well-established use of the product in the EU and that the pharmacovigilance reports do not show any reports for lack of efficacy, it can be argued that the clinical situation is not directly correlated with the clinical efficacy of the product. This could be due to combined intra- and extracellular action of lincomycin and spectinomycin, respectively. Moreover *L. intracellularis*, like *Brachyspira* spp. and other atypical gut organisms, is probably dependent on conditions established in the gut by other bacteria.

Taking into account all data, the CVMP considered that this indication can be accepted.

The proposed withdrawal time of 0 days was well supported by a residue study where pigs were treated using the proposed harmonised dosing regimen 10 mg/kg bw/day for 7 days, and is considered acceptable by the CVMP.

Taking into account the scope of this Article 34 referral procedure, the proposed indication for *L. intracellularis* in pigs was deemed acceptable. Regarding *B. hyodysenteriae,* including the points already mentioned, several issues were identified:

* All modern authors appear to agree that there is widespread resistance of *B. hyodysenteriae* to lincomycin, although there is no clinical breakpoint available and it is not known to which extent strains with increased MICs are clinically resistant;

* There are no new clinical trials, field trials or publications demonstrating the effectiveness of the lincomycin-spectinomycin combination against modern outbreaks of swine dysentery, and based on current approved dosing regimens.

However, the CVMP considered the indication for *B. hyodysenteriae* should be maintained, taking into account the scope of this Article 34 referral procedure.

Nevertheless, a clear warning as to the possibility of treatment failure due to clinically resistant strains in *B. hyodysenteriae* and associated Enterobacteriaceae (*E. coli*) should be included in section 4.4. Special warnings for each target species of the summary of product characteristics (SPC). Also, information as to widespread decreased susceptibility in *B. hyodysenteriae* and as to the bimodal distribution in *E. coli* should be added to section 5.1. Pharmacodynamic properties. Likewise, information about the lack of data on the development of resistance in *L. intracellularis* should be included in the above mentioned sections of the SPC.

Chickens

The indication for chronic respiratory disease (CRD) associated with *Mycoplasma gallisepticum* and *E. coli* was supported by two recent MIC surveys and by older literature MIC data. Furthermore, in addition to old experimental and field clinical efficacy studies, a recent proprietary challenge study was presented, where a total of 210 chickens were used to test efficacy of the product against induced *E. coli* and/or *M. gallisepticum* infection.

In the proposed harmonised SPC all references to prophylactic treatment were deleted, which was confirmed by the CVMP.

Among *in vitro* susceptibility data for *M. gallisepticum*, a new MIC survey of lincomycin-spectinomycin (1:2 ratio) was carried out on 60 isolates, and showed a MIC range of [0.25:0.5 – 8:16 µg/ml], and MIC_{50}/MIC_{90} values of 0.5:1 and 2:4 µg/ml, respectively. Overall, considering also older literature data, the relatively narrow MIC ranges and low MIC_{50} and MIC_{90} values, together with a monomodal distribution are indicative of a low resistance level which seems not to be evolving. The combination might have a synergistic effect in *Mycoplasma*, but the clinical significance of this was not investigated.

For *E. coli*, a newly conducted pan-European MIC survey, involving 67 chicken isolates and 33 turkey isolates, showed a wide MIC range (from 2:4 to ≥256:512 µg/ml), a high spectinomycin MIC_{90} (256 µg/ml) and a bimodal distribution. Overall and considering also the older literature data, a rate of clinical resistance of at least 10% was suggested. This might be due partly to natural resistance. However, again no firm breakpoint has been established. There is no evidence that this situation is evolving.

It is known from the pharmacokinetic properties of spectinomycin that only negligible amounts are absorbed from the gut and that in any case, blood levels do not reach MIC concentrations within the respiratory tract of chickens after oral administration; in addition, spectinomycin is polar and does not

readily cross membranes and distribute into the intracellular compartment. On the basis of *in vitro* tests, it has been hypothesised that a metabolite or degradation product of spectinomycin was produced in the gut and was able to reach the infection site and interfere with *E. coli* adherence to the respiratory mucosa, but this has not been validated (Goren *et al.*, 1988)[2]. Thus, it is unclear as to the value of a combination product for this indication versus a monotherapy product (e.g. lincomycin).

Several old challenge laboratory studies showed efficacy of the combination against experimental inoculations with *Mycoplasma spp.* and/or *E. coli* in chickens. The efficacy appeared better than with lincomycin alone, and slightly better than with spectinomycin alone. However, the used dosing regimens were very unclear and possibly range from the proposed dose of 50 mg/kg bw/day to the highest approved dose of 150 mg/kg bw. In a newly provided GCP-compliant challenge study the product used at 50 mg/kg/day for 7 days was shown to be effective in reducing clinical signs and lesions associated with *E. coli* and/or *M. gallisepticum* experimental infection in chickens, although the bacterial re-isolation rate was high – and its reduction was non statistically significant for *E. coli* – and the MIC values of the infective strains were at the very lower end of the range determined in the MIC surveys. This study was the only formal demonstration of the benefit of the 50 mg/kg bw dose, and the obtained challenge was only mild to moderate, with no observed mortality.

Older field studies typically used a dose regimen of 150 mg/kg bw in a first phase followed by 50 mg/kg bw in a second phase; they were considered poorly relevant as they focus on systematic prophylaxis and zootechnical/economical endpoints. The harmonised dose of 50 mg/kg bw is overall the lowest approved one among the national authorisations and the most frequent recommendation for treatment only.

As spectinomycin is poorly absorbed by the gastro-intestinal tract and does not readily cross membranes, its efficacy might relate at least partly to non-specific effects on the gut flora or to the effects of a metabolite.

Additionally, the long-term use of the product and the absence of reported lack of efficacy in the pharmacovigilance data have been noted.

The withdrawal time is supported by a study where chickens were treated at 500 mg/kg bw during their first week of life and at 60 mg/kg during their third week of life; depletion follow-up was conducted only after the second phase. The proposed withdrawal time of 5 days is considered sufficient by the CVMP when chickens are treated using the proposed harmonised dosing regimen 50 mg/kg bw/day for 7 days.

After an overall assessment in the context of the harmonisation of an already approved product, and for the reasons listed below, the CVMP considered that 50 mg/kg bw for 7 days can be accepted as the harmonised dose in chickens:

* A dose of 50 mg/kg bw is the most frequent recommendation for “treatment” among the concerned SPCs. In several other SPCs, the dose is expressed as a drinking water concentration which amounts to about 50 mg/kg bw in a significant part of the animals;
* In the newly provided clinical efficacy study the product clearly induced improvement of clinical signs of CRD and reduced the extent of bacterial invasion. It was the only available trial where the 50 mg/kg bw dose was firmly shown to be beneficial in a treatment context, although the challenge was rather mild (e.g. no mortality was recorded);

[2] Goren E, de Jong WA, Doornenbal P. Therapeutic efficacy of medicating drinking water with spectinomycin and lincomycin-spectinomycin in experimental *Escherichia coli* infection in poultry. Vet Q. 1988 Jul;10(3):191-7

* Resistance to the concerned compounds in the target bacteria shows no unfavourable evolution over time and no greater concern than for other compounds used similarly;

* A detrimental shift to the use of other molecules considered as more important to public health (e.g. fluoroquinolones) might occur in case the product is withdrawn in chickens.

Therefore it was considered by the CVMP that the indication in chickens should be maintained, however it should be adapted as follows: “For the treatment and prevention of CRD caused by *Mycoplasma gallisepticum* and *E. coli*, associated with a low mortality rate. The presence of the disease in the flock must be established before the product is used.”

Benefit-Risk assessment

Introduction

This benefit-risk evaluation is performed in the context of Article 34 of Directive 2001/82/EC, which in the present procedure has the purpose of obtaining harmonisation within the EU of the conditions of authorisation for the product Linco-Spectin 100 (and associated names). The referral leads to full harmonisation of the product information. This evaluation focuses on issues in regards to the harmonisation that may change the benefit-risk balance.

Linco-Spectin 100 (and associated names) is a powder for use in drinking water containing the active substances lincomycin (222 mg/g) and spectinomycin (444.7 mg/g). It has been authorised in 24 EU Member States. The first marketing authorisation was granted in 1972.

Benefit assessment

Direct benefits

Pigs

The product is used in the proposed indications (swine dysentery and proliferative enteropathy) for several decades in many EU Member States, on the basis of the complementary activity spectra of lincomycin and spectinomycin on the primary pathogens *B. hyodysenteriae* and *L. intracellularis* and the potentially associated enteric pathogens such as *E. coli*.

Clinical efficacy in swine dysentery at a dosing regimen close to the recommended harmonised regimen of 10 mg/kg bw for 7 days is supported by older laboratory and field clinical studies, despite the fact that these are not GLP or GCP-compliant and that the clinical and bacteriological criteria for inclusion are not always precisely defined in the study reports. Lincomycin and spectinomycin were shown to be more effective than each individual substance.

Clinical efficacy against proliferative enteropathy is substantiated through one GLP laboratory study and one GCP multicenter field study, except that in the laboratory study the animals were treated for 21 days. The combination was shown to be superior to lincomycin alone. In the challenge study the bacterial infection seemed to be eradicated.

Literature data indicate that decreased susceptibility in *B. hyodysenteriae* could be overcome to some extent by the high concentrations attained locally. Despite the poor *in vitro* activity of the active substances against *L. intracellularis*, the combination might be effective due to combined intra- and extracellular action of lincomycin and spectinomycin, respectively. In addition efficacy might be influenced by the conditions established in the gut by various associated enteric bacteria.

Pharmacovigilance reports have not reported a lack of efficacy of Linco-Spectin 100 in the recommended harmonised indications in pigs.

Chicken

In chicken the product is already indicated in many EU Member States for the treatment of CRD, associated to *Mycoplasma* and/or *E. coli.* The most frequent dosing recommendation for treatment is 50 mg/kg bw/day*;* few SPCs recommend 150 mg/kg bw and some other ones give only a concentration in water, which corresponds approximately to 50 mg/kg bw.

Although the mechanism of action at the systemic level of spectinomycin administered orally is not elucidated, its clinical benefit and the benefit of the combination seems to be demonstrated in several older laboratory challenge studies; however, the dosing regimens applied in these studies can only be estimated and likely range from the harmonised dose of 50 mg/kg bw/day to at least the highest approved dose of 150 mg/kg bw/day. The older field studies were conducted in a context of systematic prophylaxis and used two-phase dosing regimens; the conditions of those studies do not provide support for the proposed 50 mg/kg bw dose.

In a newly provided GCP challenge study the product used at 50 mg/kg bw/day for 7 days was shown to be effective in reducing clinical signs, lesions and bacteriological re-isolation associated to *E. coli* and/or *M. gallisepticum* experimental infection in chickens, although the bacterial re-isolation rate was high, with a non-statistically significant reduction for *E. coli,* and the MIC of the infective strains was low when compared to most field strains. This study is the only formal demonstration of the benefit of the 50 mg/kg bw dose, and the obtained challenge was only mild to moderate, with no observed mortality.

Pharmacovigilance reports have not reported a lack of efficacy of Linco-Spectin 100 in the proposed harmonised indication in chicken.

Indirect benefits

Particularly in chicken respiratory diseases, the availability of Linco-Spectin 100 could limit the use of other antimicrobials considered as more critical for animal and human health, e.g. fluoroquinolones.

Risk assessment

Since the dosing regimens recommended by the CVMP have not been increased, and the indications have not been extended with regard to those approved in most SPCs, the assessment of the tolerance in the target species does not present new issues. Old tolerance studies are available for pigs, chickens and turkeys. Tolerance is still adequately reflected by the harmonised texts for SPC sections 4.5 (i) Special precautions for use in animals, 4.6 Adverse reactions (frequency and seriousness) and 4.10 Overdose.

Also, as the dosing regimens and indications have not been extended, there is no change in the assessment of user safety.

Consumer safety remains ensured by the recommended harmonised withdrawal periods of 0 days in pig and 5 days in chickens.

The recommended harmonised dosing regimens do not lead to increased exposure of the environment to the active substances.

Possible resistance generated by lincomycin use in animals may impact animal health, including through cross-resistance with macrolides. Resistance against macrolides and lincosamides has emerged among animal pathogens and is common in some species. In *Brachyspira hyodysenteriae* nearly all isolates are resistant at least regarding the wild-type *in vitro* susceptibility. Therefore, even though no evolution over time appears from the provided literature data, it cannot be excluded that the results obtained in the old clinical studies conducted at the time of product development do not reflect clinical efficacy in modern outbreaks of swine dysentery.

Although this risk has not been unequivocally assessed, the possibility of impact on human health through cross-resistance to clindamycin and other substances of the macrolides, lincosamides and streptogramins (MLS) group is a reality. Human and animal bacteria share the same resistance determinants. Resistance can be a direct concern when affecting zoonotic pathogens such as *Campylobacter* and *Enterococcus*, or can be transferred horizontally to human pathogens via mobile genetic elements. MLS antimicrobials are listed by WHO (AGISAR, 2009)[3] as critically important for the treatment of certain zoonotic infections in humans (such as *Campylobacter* infections).

Risk management or mitigation measures

The potential risk of resistance development which might impact product efficacy, and overall animal and human health, is limited through:

* The restriction of the indications to those that are adequately substantiated by efficacy data;
* The deletion of all recommendations for prophylactic use;
* The inclusion of information about resistance status and warnings about prudent use as regards resistance, in SPC sections 4.4 Special warnings for each target species, 4.5 (i) Special precautions for use in animals and 5.1 Pharmacodynamic properties.

Evaluation of the benefit-risk balance

Further to the assessment of the available data, the CVMP considered that the benefit-risk balance for the target species pigs remains positive. The possible impact on clinical efficacy of the high *in vitro* resistance rate evidenced in *B. hyodysenteriae* was not assessed in recent clinical studies; however, in the context of this Article 34 referral procedure, aiming at harmonising the conditions of authorisation of an already approved product, it was considered that the indication should not be removed on that basis.

In chickens, in order to reflect the fact that in the only study formally demonstrating efficacy of the 50 mg/kg dose against CRD clinical signs and lesions, the challenge was mild to moderate with no mortality recorded, it is proposed to amend the indication as follows:

"For the treatment and prevention of chronic respiratory disease (CRD) caused by *Mycoplasma gallisepticum* and *Escherichia coli*, and associated with a low mortality rate.

The presence of the disease in the flock must be established before the product is used."

The overall benefit-risk balance of the product for use in pigs and chickens was deemed positive subject to the recommended changes in the product information (see Annex III).

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

Whereas

* the CVMP considered the scope of the referral was the harmonisation of the summary of product characteristics, labelling and package leaflet;
* the CVMP reviewed the summary of product characteristics, labelling and package leaflet proposed by the marketing authorisation holders and considered all the overall submitted data;

[3] Report of the first meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), 15-19 June 2009. http://www.who.int/foodsafety/foodborne_disease/AGISAR_2009_report_final.pdf?ua=1

the CVMP has recommended the amendment of the marketing authorisations for Linco-Spectin 100 and its associated names as referred in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

Summary of product characteristics, labelling and package leaflet

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 222 mg/g + 444.7 mg/g powder for use in drinking water for pigs and chickens

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:

Lincomycin (as lincomycin hydrochloride)	222 mg/g
Spectinomycin (as spectinomycin sulphate)	444.7 mg/g.

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for use in drinking water.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs and chickens.

4.2 Indications for use, specifying the target species

Pigs
For the treatment and prevention of dysentery caused by *Brachyspira hyodysenteria* and for the treatment and prevention of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis*, and associated enteric pathogens (*Escherichia coli*).
The presence of the disease in the group must be established before the product is used.

Chickens
For the treatment and prevention of chronic respiratory disease (CRD) caused by *Mycoplasma gallisepticum* and *Escherichia coli*, and associated with a low mortality rate.
The presence of the disease in the flock must be established before the product is used.

4.3 Contraindications

Do not use in case of hypersensitivity to the active substances or any of the excipients.
Do not use in case of hepatic dysfunction.
Do not allow rabbits, rodents (e.g. chinchillas, hamsters, guinea pigs), horses or ruminants to access to water or feeds containing lincomycin. Ingestion by these species may result in severe gastrointestinal effects.
Do not use in laying hens.

4.4 Special warnings for each target species

In *E. coli*, a significant part of the strains show high MIC values (minimum inhibitory concentrations) against the lincomycin-spectinomycin combination and may be clinically resistant, although no breakpoint is defined.
Due to technical constraints the susceptibility of *L. intracellularis is* difficult to test *in vitro*, and data about the lincomycin-spectinomycin resistance status in that species are lacking.

4.5 Special precautions for use

Special precautions for use in animals

Lincomycin resistance is widespread in *B. hyodysenteriae* and may lead to clinical treatment failure.

It is sound clinical practice to base treatment on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of target bacteria.
Use of the veterinary medicinal product deviating from the instructions in the SPC may increase the risk of development and selection of resistant bacteria and decrease the effectiveness of treatment with macrolides due to the potential for cross-resistance.

The oral use of preparations containing lincomycin is only indicated in swine and chickens.
Do not leave access to the medicated water for other animals. Lincomycin may lead to severe gastrointestinal disturbances in other animal species.

The repeated or prolonged use should be avoided, by improving the farm management and disinfection practices.

Diagnosis should be reconsidered if improvement is not seen after 5 days.

Sick animals have a reduced appetite and an altered drinking pattern, and severely affected animals may therefore require parenteral treatment.

This powder is for use in drinking water only and should be dissolved before use.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to lincomycin, spectinomycin or soybean millfeed should avoid contact with the veterinary medicinal product. Care should be taken not to raise and inhale any dust. Contact with skin and eyes should be avoided.
Personal protective equipment consisting of approved dust masks (either a disposable half mask respirator conforming to European Standard EN149 or a non-disposable respirator conforming to European Standard EN 140 with a filter EN 143), gloves and safety glasses should be worn when handling and mixing the product.
Wash hands and any exposed skin with soap and water immediately after use.
If symptoms such as skin rash or persistent eye irritation appear after exposure, seek medical advice immediately and show the package leaflet or label to the physician.

4.6 Adverse reactions (frequency and seriousness)

Cases of diarrhoea or soft faeces and/or perianal region inflammation have been encountered in healthy pigs at the start of treatment. The symptoms disappeared within 5 to 8 days without interruption of the treatment.
Rare cases of irritability/excitation, skin rash/pruritus were also observed.
Allergic/hypersensitive reactions are rare but can occur and require stopping treatment with the veterinary medicinal product. A symptomatic treatment must be implemented.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)

- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Pigs
The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Laboratory studies in dogs and rats have not produced any evidence of reproductive, foetotoxic or teratogenic effects for lincomycin or spectinomycin.
Lincomycin is excreted in milk.
Use only accordingly to benefit-risk assessment by the responsible veterinarian.

Chickens
Do not use in birds in lay.

4.8 Interaction with other medicinal products and other forms of interaction

In general mixture with other medicines should be avoided.
The combination of lincosamides and macrolides is antagonistic, due to competitive binding to their target sites. Combination with anaesthetics may lead to possible neuromuscular blocking.
Do not administer with kaolin or pectine as they impair lincomycin absorption. If co-administration is mandatory, respect a delay of two hours between intakes.

4.9 Amounts to be administered and administration route

For use in drinking water.

The recommended dosage rates are:

Pigs: 3.33 mg lincomycin and 6.67 mg spectinomycin/kg bw/day, for 7 days. This amounts to 15 mg powder/kg bw/day for 7 days.
Chickens: 16.65 mg lincomycin and 33.35 mg spectinomycin/kg bw/day, for 7 days. This amounts to 75 mg powder/kg bw/day for 7 days.

Treatment should be initiated as soon as first clinical signs occur.

For the preparation of drinking water, the incorporation rate of the veterinary medicinal product in water will depend on the body weight of the animals and their actual daily intake of water.

To ensure a correct dosage and avoid underdosing, mean body weights in the group of animals and daily water consumption should be determined as accurately as possible.

The medicated drinking water should be the sole source of drinking water for the treatment duration. Any medicated water which is not consumed within 24 hours should be discarded.

In case of disease accompanied with significant decrease in water intake, parenteral treatment may have to be initiated.

Use the following indications as a basis for the precise calculation of incorporation rate of the veterinary medicinal product in drinking water.

Pigs:

To determine the volume of dilution (in litres of drinking water) required for 150 g of the veterinary medicinal product, use the following formula:

$$\text{Volume (L) for 150 g of the veterinary medicinal product} = \frac{10{,}000 \times [\text{daily water consumption per animal (L)}]}{\text{average body weight of one pig (kg)}}$$

In pigs 150 g of the veterinary medicinal product corresponds to the dose for 10,000 kg of body weight per day.

As an indication, standard water intake varies around 0.15 L/kg bw/day. The table below shows the volume of water to be used for dilution of 150 g of the veterinary medicinal product.

Water consumption	150 g of powder = 100 g antibiotic activity should be diluted in…
0.1 L/kg bw/day	1,000 L of drinking water
0.15 L/kg bw/day	1,500 L of drinking water
0.2 L/kg bw/day	2,000 L of drinking water
0.25 L/kg bw/day	2,500 L of drinking water

Chickens:

To determine the volume of dilution (in litres of drinking water) for 150 g of the veterinary medicinal product, use the following formula:

$$\text{Volume (L) for 150 g of the veterinary medicinal product} = \frac{2{,}000 \times [\text{daily water consumption per bird (L)}]}{\text{average body weight of one bird (kg)}}$$

150 g of the veterinary medicinal product corresponds to the dose for 2,000 kg of body weight per day.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

In the event of overdose in pigs, a change in the consistency of the faeces (soft faeces and/or diarrhoea) may be observed.
In chickens treated at several times the recommended dose, enlargement of the caecum and abnormal caecum content was observed.
In case of accidental overdose, the treatment should be interrupted and restarted at the recommended dose.

4.11 Withdrawal period(s)

Pigs:
Meat and offal: Zero days.
Chickens:
Meat and offal: 5 days.

Not authorised for use in birds producing eggs for human consumption, including replacement chicks which are intended to produce eggs for human consumption.

Animals must not be slaughtered for human consumption during treatment.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, lincomycin combinations.
ATCvet code: QJ01FF52.

5.1 Pharmacodynamic properties

"Product name (to be completed nationally)" is a combination of two antibiotics, lincomycin and spectinomycin, having a complementary spectrum of activity.

Lincomycin
Lincomycin is a lincosamide antibiotic derived from *Streptomyces lincolnensis* which inhibits protein synthesis. Lincomycin binds to the 50S sub-unit of the bacterial ribosome close to the peptidyl transfer centre and interferes with the peptide chain elongation process by inhibiting the formation of the 50S sub-unit and by stimulating ribosomal peptidyl-tRNA dissociation.
Lincomycin is active against gram-positive bacteria, some anaerobic gram-negative bacteria (such as *Brachyspira hyodysenteriae*) and mycoplasmas. It has little or no action against gram-negative bacteria such as *Escherichia coli*.
While the lincosamides are generally considered to be bacteriostatic agents, the activity is depending on the sensitivity of the organism and concentration of the antibiotic. Lincomycin may be either bactericidal or bacteriostatic.
Resistance to lincomycin is frequently conferred by plasmid-borne factors (*erm* genes) coding for methylases modifying the ribosomal binding site and frequently leading to cross-resistance to other antimicrobials of the MLSb group. However, the most prevalent mechanism in *B. hyodysenteriae* and mycoplasmas is the alteration of the binding site through mutational events (chromosomal resistance). Lincomycin resistance mediated by efflux pumps, or by inactivating enzymes, has also been described. There is often complete cross-resistance between lincomycin and clindamycin.

Resistance to lincomycin can readily develop in *B. hyodysenteriae* and most of the isolates studied show decreased susceptibility *in vitro*.

Spectinomycin
Spectinomycin is an aminocyclitol antibiotic derived from *Streptomyces spectabilis*, it has bacteriostatic activity and is active against *Mycoplasma* spp. and against some gram-negative bacteria such as *E. coli*.
The mechanism by which spectinomycin administered orally acts on pathogens at the systemic level despite a poor absorption is not fully elucidated, and might rely partly on indirect effects on the gut flora, or on effects of metabolite(s).
Chromosomal one-step mutation to high-level spectinomycin resistance develops in many enteric bacteria (such as *E. coli*). Plasmid-mediated resistance is less common. Strains with chromosomal resistance do not show cross-resistance with aminoglycosides.

In *E. coli* and *Salmonella* spp. the MIC distribution appears to be bimodal, with a significant number of strains showing high values; this could partly correspond to natural (intrinsic) resistance.

In vitro studies as well as clinical efficacy data show that the lincomycin-spectinomycin combination is active against *Lawsonia intracellularis.*
Due to technical constraints the susceptibility of *Lawsonia intracellularis* is difficult to test *in vitro*, and data about the resistance status in that species are lacking.

5.2 Pharmacokinetic particulars

Lincomycin
In pigs, lincomycin is rapidly absorbed following oral administration. A single oral administration of lincomycin hydrochloride, at dose levels of approximately 22, 55 and 100 mg/kg body weight in pigs, resulted in dose related lincomycin serum levels, detected for 24–36 hours after administration. Peak serum levels were observed at 4 hours after dosing. Similar results were observed following single oral doses of 4.4 and 11.0 mg/kg body weight in pigs. Levels were detectable for 12 to 16 hours, with peak concentrations occurring at 4 hours. A single oral dose of 10 mg/kg body weight was administered to pigs to determine the bioavailability. The oral absorption of lincomycin was found to be 53% ± 19%.

Repeated dosing of pigs with daily oral doses of 22 mg lincomycin/kg body weight for 3 days indicated no accumulation of lincomycin in the species, with no detectable serum levels of antibiotic after 24 hours post administration.

Lincomycin pharmacokinetic studies in pigs show that lincomycin is bioavailable when given intravenously, intramuscularly or orally. The average of the half-lives of elimination of all routes of administration is 2.82 hours in pigs.

In chickens treated with *"product name (to be completed nationally)"* in drinking water at the target dose of 50 mg/kg body weight of total activity (at a ratio of 1:2 lincomycin:spectinomycin) for seven consecutive days, C_{max} after first offering of medicated water was calculated to be 0.0631 µg/ml. C_{max} occurred at 4 hours after introduction of the medicated water.

Spectinomycin
Studies performed in various animal species have demonstrated that spectinomycin undergoes limited absorption from the intestine (less than 4–7%) after oral administration. Spectinomycin exhibits little tendency to protein binding and is poorly liposoluble.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate
Lactose

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: *"to be completed nationally"*.
Shelf life after dilution according to directions: 24 hours.
Any medicated water which is not consumed within 24 hours should be discarded.

6.4. Special precautions for storage

Do not store above 25 °C.
Store in a dry place.

6.5 Nature and composition of immediate packaging

White HDPE bottle containing 150 g or 1.5 kg powder for oral solution with a white tamper evident LDPE lid.
Double LDPE bag containing 4.5 kg powder inside a tamper evident polypropylene tub with a polypropylene lid.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10 DATE OF REVISION OF THE TEXT

To be completed nationally.

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be completed nationally.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Bottles containing 150 g or 1.5 kg and tub containing 4.5 kg

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 222 mg/g + 444.7 mg/g powder for use in drinking water
lincomycin (as lincomycin hydrochloride)/spectinomycin (as spectinomycin sulphate).

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Lincomycin (as lincomycin hydrochloride)	222 mg/g
Spectinomycin (as spectinomycin sulphate)	444.7 mg/g.

3. PHARMACEUTICAL FORM

Powder for use in drinking water

4. PACKAGE SIZE

150 g
1.5 kg
4.5 kg

5. TARGET SPECIES

Pigs and chickens

6. INDICATION(S)

Read the package leaflet before use.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Withdrawal period:
Pigs: Meat and offal: Zero days.
Chickens: Meat and offal: 5 days.
Not authorised for use in birds producing or intended to produce eggs for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP
Shelf life after dilution according to directions: 24 hours.
Any medicated water which is not consumed within 24 hours should be discarded.

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store in a dry place.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

16. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

17. MANUFACTURER'S BATCH NUMBER

Lot:

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:

<Invented name> 222 mg/g + 444.7 mg/g powder for use in drinking water for pigs and chickens

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder and manufacturer responsible for batch release:
To be completed nationally

Manufacturer responsible for batch release:
To be completed nationally

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 222 mg/g + 444.7 mg/g powder for use in drinking water for pigs and chickens

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Active substances:

Lincomycin (as lincomycin hydrochloride)	222 mg/g
Spectinomycin (as spectinomycin sulphate)	444.7 mg/g.

Excipients:
Sodium benzoate, lactose.

4. INDICATION(S)

Pigs
For the treatment and prevention of dysentery caused by *Brachyspira hyodysenteria* and for the treatment and prevention of ileitis (porcine proliferative enteropathy) caused by *Lawsonia intracellularis*, and associated enteric pathogens (*Escherichia coli*).
The presence of the disease in the group must be established before the product is used.

Chickens
For the treatment and prevention of chronic respiratory disease (CRD) caused by *Mycoplasma gallisepticum* and *Escherichia coli*, and associated with a low mortality rate.
The presence of the disease in the flock must be established before the product is used.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to the active substances or any of the excipients.
Do not use in case of hepatic dysfunction.
Do not allow rabbits, rodents (e.g. chinchillas, hamsters, guinea pigs), horses or ruminants access to water or feeds containing lincomycin. Ingestion by these species may result in severe gastrointestinal effects.
Do not use in laying hens.

6. ADVERSE REACTIONS

Cases of diarrhoea or soft faeces and/or perianal region inflammation have been encountered in healthy pigs at the start of treatment. The symptoms disappeared within 5 to 8 days without interruption of the treatment. Rare cases of irritability/excitation, skin rash/pruritus were also observed.
Allergic/hypersensitive reactions are rare but can occur and require stopping treatment with the veterinary medicinal product. A symptomatic treatment must be implemented.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Pigs and chickens

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

For use in drinking water.

The recommended dosage rates are:

Pigs: 3.33 mg lincomycin and 6.67 mg spectinomycin/kg bw/day, for 7 days. This amounts to 15 mg powder/kg bw/day for 7 days.
Chickens: 16.65 mg lincomycin and 33.35 mg spectinomycin/kg bw/day, for 7 days. This amounts to 75 mg powder/kg bw/day for 7 days.

Treatment should be initiated as soon as first symptoms occur.

For the preparation of drinking water, the incorporation rate of the veterinary medicinal product in water will depend on the body weight of the animals and their actual daily intake of water.

To ensure a correct dosage and avoid underdosing, mean body weights in the group of animals and daily water consumption should be determined as accurately as possible.

The medicated drinking water should be the sole source of drinking water for the treatment duration. Medicated water should be removed every day and replaced by a new solution.

In case of disease accompanied with significant decrease in water intake, parenteral treatment may have to be initiated.

Use the following indications as a basis for the precise calculation of incorporation rate of the veterinary medicinal product in drinking water.

Pigs:

To determine the volume of dilution (in litres of drinking water) required for 150 g of the veterinary medicinal product, use the following formula:

$$\text{Volume (L) for 150 g of the veterinary medicinal product} = \frac{10{,}000 \times [\text{daily water consumption per animal (L)}]}{\text{average body weight of one pig (kg)}}$$

In pigs 150 g of the veterinary medicinal product corresponds to the dose for 10,000 kg of body weight per day.

As an indication, standard water intake varies around 0.15 L/kg bw/day. The table below shows the volume of water to be used for dilution of 150 g of the veterinary medicinal product.

Water consumption	150 g of powder = 100 g antibiotic activity should be diluted in…
0.1 L/kg bw/day	1,000 L of drinking water
0.15 L/kg bw/day	1,500 L of drinking water
0.2 L/kg bw/day	2,000 L of drinking water
0.25 L/kg bw/day	2,500 L of drinking water

Chickens:

To determine the volume of dilution (in litres of drinking water) for 150 g of the veterinary medicinal product, use the following formula:

$$\text{Volume (L) for 150 g of the veterinary medicinal product} = \frac{2{,}000 \times [\text{daily water consumption per bird (L)}]}{\text{average body weight of one bird (kg)}}$$

150 g of the veterinary medicinal product corresponds to the dose for 2,000 kg of body weight per day.

9. ADVICE ON CORRECT ADMINISTRATION

This powder is for use in drinking water only and should be dissolved before use.
The medicated drinking water should be the sole source of drinking water for the treatment duration.
Medicated water should be removed every day and replaced by a new solution.

The repeated or prolonged use should be avoided, by improving the farm management and disinfection practices.
The veterinary medicinal product should be used based on antimicrobial susceptibility testing. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.
Use of the product deviating from the instructions given in the summary of product characteristics may increase the prevalence of bacteria resistant to lincomycin and spectinomycin and may decrease the effectiveness of treatment with other antimicrobials of the same or related classes, due to the potential for cross resistance.
Diagnosis should be reconsidered if improvement is not seen after 5 days.

10. WITHDRAWAL PERIOD

Pigs:
Meat and offal: Zero days.
Chickens:
Meat and offal: 5 days.
Not authorised for use in birds producing eggs for human consumption, including replacement chicks which are intended to produce eggs for human consumption.

Animals must not be slaughtered for human consumption during treatment.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Do not store above 25 °C.
Store in a dry place.
Any medicated water which is not consumed within 24 hours should be discarded.

Do not use this veterinary medicinal product after the expiry date which is stated on the bottle or bag.
The expiry date refers to the last day of that month.
Shelf life after dilution according to directions: 24 hours.

12. SPECIAL WARNING(S)

Special warnings for each target species:
Lincomycin resistance is widespread in *B. hyodysenteriae* and may lead to clinical treatment failure.

It is sound clinical practice to base treatment on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of target bacteria.
Use of the veterinary medicinal product deviating from the instructions in the SPC may increase the risk of development and selection of resistant bacteria and decrease the effectiveness of treatment with macrolides due to the potential for cross-resistance.
In *E. coli,* a significant part of the strains show high MIC values (minimum inhibitory concentrations) against the lincospectin-spectinomycin combination and may be clinically resistant, although no breakpoint is defined.
Due to technical constraints the susceptibility of *L. intracellularis is* difficult to test *in vitro*, and data about the lincomycin-spectinomycin resistance status in that species are lacking.

Special precautions for use in animals:
The oral use of preparations containing lincomycin is only indicated in swine and chickens.
Do not leave access to the medicated water for other animals. Lincomycin may lead to severe gastrointestinal disturbances in other animal species.
The repeated or prolonged use should be avoided, by improving the farm management and disinfection practices.

Diagnosis should be reconsidered if improvement is not seen after 5 days.
Sick animals have a reduced appetite and an altered drinking pattern, and severely affected animals may therefore require parenteral treatment.
This powder is for use in drinking water and must be dissolved in water and cannot be used as such.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to lincomycin, spectinomycin or soybean millfeed should avoid contact with the veterinary medicinal product. Care should be taken not to raise and inhale any dust. Contact with skin and eyes should be avoided.
Personal protective equipment consisting of approved dust masks (either a disposable half mask respirator conforming to European Standard EN149 or a non-disposable respirator conforming to European Standard EN 140 with a filter EN 143), gloves and safety glasses should be worn when handling and mixing the product.
Wash hands and any exposed skin with soap and water immediately after use.
If symptoms such as skin rash or persistent eye irritation appear after exposure, seek medical advice immediately and show the package leaflet or label to the physician.

Pregnancy and lactation:
Pigs
The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Laboratory studies in dogs and rats have not produced any evidence of reproductive, foetotoxic or teratogenic effects for lincomycin or spectinomycin.
Lincomycin is excreted in milk.
Use only accordingly to benefit-risk assessment by the responsible veterinarian.

Lay:
Chickens
Do not use in birds in lay.

Interaction with other medicinal products and other forms of interaction:
In general mixture with other medicines should be avoided.
The combination of lincosamides and macrolides is antagonistic, due to competitive binding to their target sites. Combination with anaesthetics may lead to possible neuromuscular blocking.
Do not administer with kaolin or pectin as they impair lincomycin absorption. If co-administration is mandatory, respect a delay of two hours between intakes.

Overdose (symptoms, emergency procedures, antidotes):
In the event of overdose in pigs, a change in the consistency of the faeces (soft faeces and/or diarrhoea) may be observed.
In chickens treated at several times the recommended dose, enlargement of the caecum and abnormal caecum content was observed.
Treatment is symptomatic. In case of accidental overdose, the treatment should be interrupted and restarted at the recommended dose.

Incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

To be completed nationally.

15. OTHER INFORMATION

Pharmacodynamic properties
Lincomycin is a lincosamide antibiotic derived from *Streptomyces lincolnensis* which inhibits protein synthesis. Lincomycin binds to the 50S sub-unit of the bacterial ribosome close to the peptidyl transfer centre and interferes with the peptide chain elongation process by inhibiting the formation of the 50S sub-unit and by stimulating ribosomal peptidyl-tRNA dissociation.
Lincomycin is active against gram-positive bacteria, some anaerobic gram-negative bacteria (such as *Brachyspira hyodysenteriae*) and mycoplasmas. It has little or no action against gram-negative bacteria such as *Escherichia coli.*

While the lincosamides are generally considered to be bacteriostatic agents, the activity is depending on the sensitivity of the organism and concentration of the antibiotic. Lincomycin may be either bactericidal or bacteriostatic.
Resistance to lincomycin is frequently conferred by plasmid-borne factors (erm genes) coding for methylases modifying the ribosomal binding site and frequently leading to cross-resistance to other antimicrobials of the MLSb group. However, the most prevalent mechanism in *B. hyodysenteriae* and mycoplasmas is the alteration of the binding site through mutational events (chromosomal resistance). Lincomycin resistance mediated by efflux pumps, or by inactivating enzymes, has also been described. There is often complete cross-resistance between lincomycin and clindamycin.
Resistance to lincomycin can develop in *B. hyodysenteriae* and most of the isolates studied show decreased susceptibility *in vitro*.

Spectinomycin
Spectinomycin is an aminocyclitol antibiotic derived from *Streptomyces spectabilis*, it has bacteriostatic activity and is active against *Mycoplasma* spp. and against some gram-negative bacteria such as *E. coli.*
The mechanism by which spectinomycin administered orally acts on pathogens at the systemic level despite a poor absorption is not fully elucidated, and might rely partly on indirect effects on the gut flora, or on effects of metabolite(s).
Chromosomal one-step mutation to high-level spectinomycin resistance develops in many enteric bacteria (such as *E. coli*). Plasmid-mediated resistance is less common. Strains with chromosomal resistance do not show cross-resistance with aminoglycosides.
In *E. coli* and *Salmonella* spp. the MIC distribution appears to be bimodal, with a significant number of strains showing high values; this could partly correspond to natural (intrinsic) resistance.
In vitro studies as well as clinical efficacy data show that the lincomycin-spectinomycin combination is active against *Lawsonia intracellularis*.
Due to technical constraints the susceptibility of *L. intracellularis* is difficult to test *in vitro*, and data about the resistance status in that species are lacking.

Pharmacokinetic particulars
Lincomycin
In pigs, lincomycin is rapidly absorbed following oral administration. A single oral administration of lincomycin hydrochloride, at dose levels of approximately 22, 55 and 100 mg/kg body weight in pigs, resulted in dose related lincomycin serum levels, detected for 24–36 hours after administration. Peak serum levels were observed at 4 hours after dosing. Similar results were observed following single oral doses of 4.4 and 11.0 mg/kg body weight in pigs. Levels were detectable for 12 to 16 hours, with peak concentrations occurring at 4 hours. A single oral dose of 10 mg/kg body weight was administered to pigs to determine the bioavailability. The oral absorption of lincomycin was found to be 53% ± 19%. Repeated dosing of pigs with daily oral doses of 22 mg lincomycin/kg body weight for 3 days indicated no accumulation of lincomycin in the species, with no detectable serum levels of antibiotic after 24 hours post administration.
Lincomycin pharmacokinetic studies in pigs show that lincomycin is bioavailable when given intravenously, intramuscularly or orally. The average of the half-lives of elimination of all routes of administration is 2.82 hours in pigs.
In chickens treated with *"product name (to be completed nationally)"* in drinking water at the target dose of 50 mg/kg body weight of total activity (at a ratio of 1:2 lincomycin:spectinomycin) for seven consecutive days, C_{max} after first offering of medicated water was calculated to be 0.0631 µg/ml. C_{max} occurred at 4 hours after introduction of the medicated water.

Spectinomycin
Studies performed in various animal species have demonstrated that spectinomycin undergoes limited absorption from the intestine (less than 4–7%) after oral administration. The spectinomycin exhibits little tendency to protein binding and is poorly liposoluble.

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.