Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal products, 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
Belgium	Zoetis Belgium SA Rue Laid Burniat 1 1348 Louvain-la-Neuve Belgium	Lincocin 40%	Lincomycin (as lincomycin hydrochloride)	400 mg/g	Powder for oral solution	Pigs, poultry (broilers)	Oral use (via drinking water)
Denmark	Zoetis Finland Oy Tietokuja 4 00330 Helsinki Finland	Lincocin Vet	Lincomycin hydrochloride	400 mg/g	Powder for oral solution	Pigs	Oral
France	Zoetis France 10 rue Raymond David 92240 Malakoff France	LINCOCINE POUDRE SOLUBLE	Lincomycin hydrochloride	400 mg/g	Powder for oral solution	Pigs, chickens	Oral
Germany	Zoetis Deutschland GmbH Schellingstr. 1 D-10785 Berlin Germany	Albiotic Pulver 400 mg/g zum Eingeben über das Trinkwasser für Schweine	Lincomycin hydrochloride	470,6 mg lincomycin HCl/g (corresponding to 400 mg lincomycin/g)	powder for use in drinking water	Pigs	Oral
Hungary	Zoetis Hungary Kft. Budapest, Alkotás u. 53., 1123 Hungary	Lincocin 400 mg/g por belsőleges oldathoz A.U.V.	Lincomycin hydrochloride	400 mg/g	Powder for oral solution	Pigs, chickens	In drinking water use
Ireland	Zoetis Belgium S.A 2nd Floor, Building 10 Cherrywood Business Park Loughlinstown Co. Dublin Ireland	Lincocin Soluble Powder	Lincomycin hydrochloride	400 mg/g	Powder for oral solution	Pigs	Oral via the drinking water
Poland	Zoetis Polska Sp. z o.o. Postępu 17B 02-676 Warsaw Poland	Lincocin 40% 400 mg/g proszek do sporządzania roztworu doustnego dla świń i kur	Lincomycin (as lincomycin hydrochloride)	400 mg/g	Powder for oral solution	Pigs, chickens	In drinking water use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE United Kingdom	Lincocin Soluble Powder 400 mg/g Powder for Oral Solution	Lincomycin	400 mg/g	Powder for oral solution	Pigs	In drinking water use

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 Lincocin and its associated names (see Annex I)

1. Introduction

Lincocin is a powder for oral solution containing 400 mg lincomycin per gram product. The active substance lincomycin is a lincosamide antibiotic and is produced by *Streptomyces lincolnensis*. It is bacteriostatic and primarily active against Gram-positive bacteria (both aerobic and anaerobic), Gram-negative anaerobic bacteria and mycoplasma.

On 5 July 2016 the European Commission sent a referral notification under Article 34 of Directive 2001/82/EC to the European Medicines Agency for Lincocin and its associated names. The European Commission referred the issue due to divergent national decisions having been taken by the Member States (EU/EEA) resulting in discrepancies in the product information for Lincocin and its associated names (thereafter called Lincocin).

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

- Target species
- Indications
- Posology
- Withdrawal periods.

2. Discussion of data available

Pigs

Pigs were already authorised as a target species for all products concerned by this referral procedure. Concerning the indication for treatment and metaphylaxis of swine dysentery caused by *Brachyspira hyodysenteriae* and/or other bacteria susceptible to lincomycin, the marketing authorisation holder presented Minimum Inhibitory Concentration (MIC) data from several studies (including recent proprietary studies performed in 2016), clinical trials and studies from the scientific literature. With regard to the *in vitro* susceptibility data, although there is no standardised methodology for determination of the MIC for antibiotics against *B. hyodysenteriae*, it was evident that the majority of isolates fall outside the apparent wild-type population. The clinical data provided indicated that Lincocin was effective for the treatment of swine dysentery caused by *B. hyodysenteriae*; however, the studies in question were conducted in the period 1977-1993 and the MICs of isolates were not determined in the majority of clinical studies submitted. Therefore, the high *in vitro* resistance level in *B. hyodysenteriae* constitutes a major uncertainty as to the clinical effectiveness of Lincocin. In addition, in a recent referral procedure under Article 35 of Directive 2001/82/EC for all veterinary medicinal products containing a combination of lincomycin and spectinomycin to be administered orally to pigs or chickens (EMEA/V/A/110)[1], the CVMP concluded that indications relating to swine dysentery caused by *B. hyodysenteriae* were not sufficiently supported and should be deleted from the product information. As the conclusions from the aforementioned referral procedure (EMEA/V/A/110) can be extrapolated to the current

[1] CVMP opinion for a referral procedure (EMEA/V/A/110) under Article 35 of Directive 2001/82/EC for veterinary medicinal products containing a combination of lincomycin and spectinomycin to be administered orally to pigs and/or poultry – link

procedure, the CVMP concluded that this indication should also be deleted from the product information for Lincocin.

In support of the indication for treatment and metaphylaxis of enzootic pneumonia caused by *Mycoplasma hyopneumoniae* the marketing authorisation holder provided *in vitro* susceptibility data, including a recent proprietary study, and clinical data, including field studies.

It should be noted that no standardised procedures for MIC testing of antimicrobial agents against mycoplasmas and no clinical breakpoints exist, which has made the comparison of results of different studies difficult. Nevertheless, based on the MIC data provided including the study conducted by the marketing authorisation holder in 2016, it could be concluded that the susceptibility pattern of *M. hyopneumoniae* to lincomycin has not changed significantly over the last 20–25 years.

With regard to the clinical data, several of the studies submitted by the marketing authorisation holder were conducted with an in-feed formulation of lincomycin. The bioequivalence between the soluble powder and the premix formulation was investigated in two studies, but could not be formally demonstrated. However, as the pharmacokinetic parameters were greater upon administration of the soluble powder, and it is generally recognised that soluble powders are likely to result in a better bioavailability of the active substance in comparison to in-feed formulations, the CVMP accepted that clinical results relating to the premix formulation could be extrapolated to the soluble powder. Some of the studies in which lincomycin was administered in feed were considered to demonstrate a therapeutic and/or metaphylactic effect of lincomycin against enzootic pneumonia. The doses used in these studies were in line with the proposed dose of 10 mg/kg body weight. The marketing authorisation holder also provided additional data from one study which investigated the efficacy of lincomycin as the soluble powder, administered in drinking water to pigs on a farm with known problems with enzootic pneumonia. Overall, considering the scope of procedure the CVMP was of the opinion that the indication 'Treatment and metaphylaxis of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*' was adequately justified.

Additionally, the CVMP considered that the following warning needed to be added to section 4.4 'Special warnings for each target species' of the summary of product characteristics (SPC):

"The susceptibility of *Mycoplasma hyopneumoniae* to antimicrobial agents is difficult to test *in vitro* owing to technical constraints. In addition, there is a lack of clinical breakpoints for both *M. hyopneumoniae* and *C. perfringens*. Where possible, therapy should be based on local (regional, farm level) epidemiological information concerning the response of enzootic pneumonia/necrotic enteritis to treatment with lincomycin."

The dosing regimen for the indication was not changed and remained at 10 mg lincomycin/kg body weight daily for 21 consecutive days. Section 4.9 'Amounts to be administered and route of administration' of the SPC was nevertheless modified, mainly for the purpose of increased clarity.

With regard to the withdrawal period, a satisfactory residue depletion study in pigs was provided by the marketing authorisation holder. The number of animals (18 castrated males and 18 females) included in the study and their weights (36.5 to 71 kg) were adequate. The dosage used (approximately 10 mg lincomycin/kg body weight/day administered in drinking water) was considered to be representative of the maximum amount of lincomycin recommended for the product. The slaughter times (0 hours after 3 days of medication and 0, 6, 12 and 24 hours after 21 days of medication) were well distributed to support the proposed zero-day withdrawal period. The description and validation of the GC/MS analytical method was considered acceptable.

Based on the results from the study and the calculations made by the CVMP, it was concluded that a zero-day withdrawal period for pig meat and offal may not be safe for the consumers as the first time point at which all samples were below their respective maximum residue limits (MRLs) was 12

hours. A withdrawal period of 1 day was therefore recommended for pig meat and offal as this gives a sufficient margin of safety.

Chickens

Chickens were authorised as a target species in Belgium, France, Hungary and Poland.

To support the proposed harmonised indication for treatment and metaphylaxis of necrotic enteritis caused by *Clostridium perfringens*, the marketing authorisation holder presented *in vitro* susceptibility data, including a recent proprietary study from 2016, clinical studies and data from the scientific literature.

The *in vitro* data from published literature and from the marketing authorisation holder's own study indicated that the MIC distribution for lincomycin was wide and not unimodal. For example, the results of the study conducted by the marketing authorisation holder in 2016 with 92 European isolates showed a MIC range of 0.5 µg/ml to >256 µg/ml and a tri-modal MIC distribution for lincomycin against *C. perfringens* (peaks at 1 µg/ml, 8 µg/ml and >256 µg/ml), with the majority of isolates falling outside the apparent wild-type population. This is similar to that seen in most of the earlier studies. It was concluded that the susceptibility pattern of *C. perfringens* to lincomycin has not changed significantly over the last 25 years. However, there was no definitive evidence that strains of *C. perfringens* with high MICs for lincomycin may be clinically resistant. Indeed, there was evidence, albeit from a subclinical infection model, that MIC values above those for the apparent wild-type population do not necessarily correlate to a lack of clinical effectiveness of lincomycin (Lanckriet *et al*., 2010)[2]. It might be the case that local intestinal concentrations of lincomycin exceed the MIC of non-wild-type isolates.

A dose titration study investigated the therapeutic effect of various levels of lincomycin administered via drinking water on necrotic enteritis in broilers under simulated natural conditions. It was calculated that a concentration of 16.9 mg/l was the minimal dose that would give the maximum effect; this corresponds with a calculated dose of 3.9 mg/kg body weight. The dosage of 3.9 mg/kg body weight was investigated in another two trials with similar designs, under simulated natural conditions. Both of these studies included 1116 birds which were divided into treatment and negative control groups. In both studies significant differences were noted in mortality rates between birds treated with lincomycin (0% and 0.7%, respectively) and negative controls (14% and 7.5%, respectively). Although the studies were conducted in the USA in the 1980s and MICs of the isolates responsible for necrotic enteritis in two of the studies are not known, the marketing authorisation holder has determined the MICs of *C. perfringens* isolates obtained from chickens in the USA in the 1990s. Upon comparison to more recent EU isolates (2011–2016), the MIC distributions are similar, being tri-modal with peaks differing by one doubling dilution at the most. As such, these data are considered to support extrapolation of the findings from the abovementioned studies conducted in the USA in the 1980s to the current EU situation.

In conclusion, considering that the susceptibility pattern of *C. perfringens* to lincomycin has not changed significantly over the last 25 years and the lack of a definite correlation between MICs and clinical efficacy and in the context of the procedure, the CVMP considered that the indication is adequately justified and hence chickens can be retained as a target species.

For chickens, the currently authorised dose and the harmonised proposal was to administer 3-6 mg lincomycin per kg of body weight daily for 7 consecutive days. It seemed to be in line with the posology assessed in the studies provided; however, the two-fold dose range with no clear guidance for the end-user as to when to administer the product at either the higher or lower limit of the range was considered to be ambiguous. A single (optimal) dose level was considered

[2] Lanckriet *et al.* (2010). The effect of commonly used anticoccidials and antibiotics in a subclinical necrotic enteritis model. Avian Pathology, 39, 63.

preferable; based on the data available and taking into account the variability of water intake and hence the dose ingested by the treated animals, a dose rate of 5 mg lincomycin per kg of body weight for 7 days was proposed. This exceeded the minimum effective dose rate (3.9 mg/kg) established in the dose evaluation study and was within the range tested in the dose confirmation and target animal safety studies. The CVMP acknowledged the difficulties in determining a single dose and agreed that although somewhat arbitrarily selected, the proposal for a dose rate of 5 mg lincomycin per kg of body weight for 7 days is acceptable. The minimum effective dose would appear to be approximately 4 mg/kg per kg of body weight and selection of this dose would result in a maximal therapeutic index. However, given the variability in active substance intake that can result from dosing via drinking water and the good safety profile for lincomycin, a dose greater than the minimum effective dose was considered to be justifiable.

Additionally the wording of section 4.9 ‘Amounts to be administered and route of administration’ of the SPC was extensively modified, with the main aim of increasing clarity.

Regarding the determination of the withdrawal period, no residue depletion studies have been conducted with Lincocin in chickens using a modern (HPLC) assay method. Older studies, using microbiological methods, are available and indicate that a zero-day withdrawal period could be appropriate; however, these studies are not considered to have been conducted to current standards.

An up-to-date residue depletion study was provided with a soluble powder containing a combination of lincomycin and spectinomycin, and the dose of lincomycin that was administered was approximately 3 to 5 times higher than the recommended dose for Lincocin. Tissue residues levels were measured in composite samples from 4 birds at 0, 2 and 7 days after the end of treatment. At 2 days after the end of treatment, residues in liver, kidney and muscle were all below the MRLs. One composite muscle sample out of three had residues slightly above the MRL (57 µg/kg versus 50 µg/kg). Based on the observed depletion pattern, a 5-day withdrawal period was shown to be appropriate for the combination product.

The CVMP noted that a residue depletion study using Lincocin itself (or a bioequivalent product) would have been preferable. However, in light of the fact that the lincomycin dose given in the study provided was several times higher than the recommended dose for Lincocin, and the duration of treatment was similar, it was considered that the available study provides a rather conservative result, even though the possibility of pharmacokinetic interactions between lincomycin and spectinomycin were not addressed. For this reason the above study could be accepted for the determination of the chicken meat and offal withdrawal period for Lincocin.

Therefore, it was considered that the proposed withdrawal period of 5 days can be regarded as safe for the recommended dosing regimen of 5 mg of lincomycin per kg of body weight per day for 7 days. In addition, older studies conducted with Lincocin in chickens, and in which a microbiological method was used to measure residues, provide further reassurance that a withdrawal period of 5 days is safe for consumers.

Regarding laying hens, there are no data to support a withdrawal period in eggs; hence, the use of the product should not be authorised in laying birds producing eggs for human consumption.

3. 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 Lincocin and its 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.

Lincocin is a powder for oral solution containing 400 mg lincomycin per gram product. The active substance lincomycin is a lincosamide antibiotic and is produced by *Streptomyces lincolnensis*. It is bacteriostatic and primarily active against Gram-positive bacteria (both aerobic and anaerobic), Gram-negative anaerobic bacteria and mycoplasma.

Benefit assessment

The following indications for Lincocin and its associated names can be supported based on the data provided:

Pigs:

Treatment and metaphylaxis of enzootic pneumonia caused by *Mycoplasma hyopneumoniae.*

Chickens:

Treatment and metaphylaxis of necrotic enteritis caused by *Clostridium perfringens.*

Pigs

In support of the indication for treatment and metaphylaxis of enzootic pneumonia caused by *Mycoplasma hyopneumoniae* the marketing authorisation holder provided *in vitro* susceptibility data including a recent proprietary study and clinical data including field studies.

Despite the lack of standardised procedures for MIC testing of antimicrobial agents against mycoplasmas and clinical breakpoints, based on the MIC data provided it could be concluded that the susceptibility pattern of *M. hyopneumoniae* to lincomycin has not changed significantly over the last 20–25 years.

The provided clinical data demonstrated that Lincocin was effective in the treatment and metaphylaxis of enzootic pneumonia caused by *M. hyopneumoniae* when administered at 10 mg lincomycin per kg of body weight for 21 consecutive days.

The benefit-risk balance in relation to the use of Lincocin against swine dysentery caused by *B. hyodysenteriae* is considered to be negative due to development of acquired resistance and high uncertainty about its impact in terms of *in vivo* efficacy. The indication against swine dysentery caused by *B. hyodysenteriae* could no longer be maintained and was removed.

Chickens

To support the proposed harmonised indication for treatment and metaphylaxis of necrotic enteritis caused by *Clostridium perfringens*, the marketing authorisation holder presented *in vitro* susceptibility data including a recent proprietary study from 2016, clinical studies and data from the scientific literature.

The *in vitro* data from published literature and from the marketing authorisation holder's own study indicated that the MICs for lincomycin had wide ranges and were not unimodal. It was concluded that the susceptibility pattern of *C. perfringens* to lincomycin has not changed significantly over the last 25 years. However, there was no definitive evidence that strains of *C. perfringens* with high MICs for lincomycin may be clinically resistant.

The provided clinical data demonstrated that Lincocin was effective in the treatment and metaphylaxis of necrotic enteritis caused by *C. perfringens* at a dose rate of 5 mg lincomycin per kg of body weight for 7 consecutive days.

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 target animal safety and user safety did not present new issues. The harmonised warnings and precautions proposed in the product information were considered adequate to ensure safety to users of the product.

Given the results from the provided residue depletion study and the calculations made by the CVMP, a withdrawal period of 1 day was recommended.

Based on the documentation provided, the proposed withdrawal period of 5 days for chicken meat and offal was considered to be safe for the consumers. As there were no data to support a withdrawal period in laying hens, the use of the product should not be authorised in laying birds producing eggs for human consumption.

The possible risk for the environment has not been considered as part of this referral. However, as the dosing regimens and indications have not been extended, there is no increase in the exposure of the environment to the active substance.

The risks associated with use of Lincocin and its associated names are those generally attributed to antimicrobials which are used in food-producing animals, i.e. development of antimicrobial resistance in target bacteria, dissemination of resistant bacteria/resistance factors etc.

Although these risks have 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 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. Macrolides, lincosamides and streptogramins antimicrobials are listed by WHO (2017)[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 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’.
- The revised harmonised SPC of Lincocin contains the necessary information to ensure the safe and effective use of the product.

Evaluation and conclusions on the benefit-risk balance

Lincocin has been shown to be efficacious for the treatment and metaphylaxis of enzootic pneumonia caused by *M. hyopneumoniae* in pigs.

Lincocin has also been proven to be efficacious in the treatment and metaphylaxis of necrotic enteritis caused by *C. perfringens* in chickens.

[3] World Health Organization (2017). Critically important antimicrobials for human medicine – 5th rev. Geneva. Licence: CC BY-NC-SA 3.0 IGO – link

Risks for users were considered low and adequate information is included in the product information to ensure the safety for the user.

Satisfactory withdrawal periods have been set to provide assurance of consumer safety.

Having considered the grounds for referral and the data provided by the marketing authorisation holder, the CVMP concluded that the benefit-risk balance of the product remains positive for use in pigs and chickens subject to the recommended changes in the product information.

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

Whereas

- 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 holder and considered all the overall submitted data;

the CVMP has recommended the amendment of the marketing authorisations for Lincocin 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

Lincocin 400 mg/g powder for use in drinking water

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Lincomycin (as lincomycin hydrochloride) 400 mg/g

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for use in drinking water.
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs and chickens

4.2 Indications for use, specifying the target species

Pigs
Treatment and metaphylaxis of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*.
The presence of the disease in the group must be established before the product is used.

Chickens
Treatment and metaphylaxis of necrotic enteritis caused by *Clostridium perfringens*.
The presence of the disease in the group must be established before the product is used.

4.3 Contraindications

Do not use in cases of known hypersensitivity to the active substance or to any of the excipients.
Do not administer, and do not allow access to water containing lincomycin, to rabbits, hamsters, guinea pigs, chinchillas, horses or ruminants as this could result in severe gastro-intestinal disturbance.
Do not use in cases of known resistance to lincosamides.
Do not use in cases of hepatic dysfunction.

4.4 Special warnings for each target species

Medicated drinking water uptake can be affected by the severity of the disease. In case of insufficient uptake of water, pigs should be treated parenterally.

The susceptibility of *Mycoplasma hyopneumoniae* to antimicrobial agents is difficult to test *in vitro* owing to technical constraints. In addition, there is a lack of clinical breakpoints for both *M. hyopneumoniae* and *C. perfringens*. Where possible, therapy should be based on local (regional,

farm level) epidemiological information concerning the response of enzootic pneumonia/necrotic enteritis to treatment with lincomycin.

4.5 Special precautions for use

Special precautions for use in animals
Use of the veterinary medicinal product preferably should be based on identification of the target pathogen and susceptibility testing of the bacteria isolated from the animal. However, also see text under section 4.4. Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Use of the veterinary medicinal product deviating from the instructions given in the summary of product characteristics may increase the prevalence of bacteria resistant to the lincomycin and may decrease the effectiveness of treatment with other lincosamides, macrolides and streptogramin B due to the potential for cross-resistance.
Repeated or prolonged use should be avoided by improving the farm management and hygiene practices.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
This product contains lincomycin and lactose monohydrate, either of which can cause allergic reactions in some people. People with known hypersensitivity to lincomycin or any other lincosamide, or to lactose monohydrate, 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 EN140 with a filter EN143), gloves and safety glasses should be worn when handling and mixing the product. If respiratory symptoms develop following exposure, seek medical advice and show this warning to the physician.
In case of accidental exposure to the skin, eyes or mucous membranes, wash the affected area thoroughly with plenty of water. 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.
Wash hands and any exposed skin with soap and water immediately after use.
Do not eat, drink or smoke while handling the product.

4.6 Adverse reactions (frequency and seriousness)

On rare occasions, pigs given lincomycin-medicated water may develop diarrhoea/soft stools and/or mild swelling of the anus within the first 2 days after onset of treatment. On rare occasions some pigs may show reddening of the skin and mild irritable behaviour. These conditions are usually self-correcting within 5-8 days without discontinuing the lincomycin treatment. Allergic/hypersensitive reactions occur on rare occasions.

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

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats have not produced any evidence of teratogenic effects, although foetotoxicity has been reported. The safety of the veterinary medicinal product has not been

established during pregnancy, lactation or lay in the target species. Use only according to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Antagonism may exist between lincomycin and macrolides such as erythromycin and other bactericidal antibiotics; concurrent use is therefore not recommended due to competitive binding at the 50S ribosomal subunit of the bacterial cell.
The bioavailability of lincomycin may decrease in the presence of gastric antacids or activated charcoal, pectin or kaolin.
Lincomycin can potentiate neuromuscular effects of anaesthetics and muscle relaxants.

4.9 Amounts to be administered and administration route

For use in drinking water.

Dosing guidance and recommended doses:
To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing.
The intake of medicated water depends on the physiological and clinical condition of the animals. In order to obtain the correct dosage, the concentration of the lincomycin has to be adjusted accordingly.
The uptake of water should be monitored frequently.
The medicated water should be the only source of drinking water for the animals for the entire duration of the treatment period.
After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

Dosage:

Pigs:
Enzootic pneumonia: 10 mg lincomycin per kg of body weight (corresponding to 25 mg product per kg bodyweight) for 21 consecutive days.

Chickens:
Necrotic enteritis*:* 5 mg lincomycin per kg of body weight (corresponding to 12.5 mg product per kg bodyweight) for 7 consecutive days.

The concentration to be used depends on the actual body weight and the water consumption of the animals and can be calculated according to the following formula:

$$\frac{\text{Dosage (mg product per kg body weight per day)} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Average daily water intake (litre/animal)}} = \text{\_\_\_ mg product per litre drinking water}$$

The use of suitably calibrated weighing equipment is recommended if part packs are used. The daily amount is to be added to the drinking water in such a way that all medication will be consumed within 24 hours. Medicated drinking water should be freshly prepared every 24 hours. No other source of drinking water should be available.

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

A dosage greater than 10 mg lincomycin per kg of body weight may cause diarrhoea and loose stools in pigs.

In case of accidental overdose, the treatment must be stopped and restarted at the recommended dose level.
There is no specific antidote, treatment is symptomatic.

4.11 Withdrawal period(s)

Pigs:
Meat and offal: 1 day.

Chickens:
Meat and offal: 5 days.
Not authorised for use in laying birds producing eggs for human consumption

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use; Lincosamides.
ATC Vet Code: QJ01FF02

5.1 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 causing premature peptidyl-tRNA dissociation from the ribosome.
Lincomycin is active against some gram-positive bacteria (*Clostridium perfringens*) and mycoplasmas (*Mycoplasma hyopneumoniae*).
While the lincosamides are generally considered to be bacteriostatic agents, the activity depends 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 macrolides, lincosamides and streptogramins group. However, the most prevalent mechanism in 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.

5.2 Pharmacokinetic particulars

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.
Crossing the intestinal barrier, lincomycin is widely distributed to all tissues, especially the lungs and joint cavities; the volume of distribution is about 1 litre. The elimination half-life of lincomycin is greater than 3 hours. Approximately 50% of lincomycin is metabolised in the liver. Lincomycin undergoes enterohepatic circulation. Lincomycin is eliminated unchanged or in the form of various metabolites in bile and urine. High concentrations of the active form are observed in the intestine.

Chickens were administered lincomycin hydrochloride in the drinking water at a level of approximately 34 mg/litre (5.1-6.6 mg/kg body weight) for seven days. Metabolites comprised more than 75% of total residues in the liver. Unmetabolised lincomycin declined at a slightly faster half-life (t½ = 5.8 hours) than total residue. Lincomycin and one unknown metabolite comprised >50% of the muscle residue at zero hours. The excreta contained mostly unmetabolised lincomycin (60-85%) during treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Lactose monohydrate

6.2 Major incompatibilities

Do not mix with any other veterinary medicinal product

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 5 years.
Shelf life after first opening the immediate packaging: use immediately.
Shelf life after dilution or reconstitution according to directions: 24 hours.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

White high density polyethylene (HDPE) bottle containing 150 g or 1.5 kg powder for use in drinking water with a tamper evident low density polyethylene (LDPE) lid.

Pack sizes:
Bottle of 150 g
Bottle of 1.5 kg

Not all pack sizes may be marketed.

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 products 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

Dispensing conditions: Veterinary medicinal product subject to veterinary prescription.
Administration conditions: Administration under the control or direct responsibility of a veterinary surgeon.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Bottles containing 150 g or 1.5 kg

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Lincocin 400 mg/g powder for use in drinking water
Lincomycin (as lincomycin hydrochloride)

2. STATEMENT OF ACTIVE SUBSTANCES

Each g contains 400 mg lincomycin (as lincomycin hydrochloride).

3. PHARMACEUTICAL FORM

Powder for use in drinking water.

4. PACKAGE SIZE

150 g
1.5 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(S)

Withdrawal periods:
Pigs: Meat and offal: 1 day.
Chickens: Meat and offal: 5 days.
Not authorised for use in laying birds producing eggs for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}: MMM/YY
Once opened: use immediately.
Once diluted or reconstituted according to directions: use within 24 hours.

11. SPECIAL STORAGE CONDITIONS

None.

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 {number}:

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Lincocin 400 mg/g powder for use in drinking water

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

Lincocin 400 mg/g powder for use in drinking water.
Lincomycin

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

Each g contains:
Lincomycin (as lincomycin hydrochloride) 400 mg

White to off-white powder.

4. INDICATION(S)

Pigs
For the treatment and metaphylaxis of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*.
The presence of the disease in the group must be established before the product is used.

Chickens
For the treatment and metaphylaxis of necrotic enteritis caused by *Clostridium perfringens*.
The presence of the disease in the group must be established before the product is used.

5. CONTRAINDICATIONS

Do not use in cases of known hypersensitivity to the active substance or to any of the excipients.
Do not administer, and do not allow access to water containing lincomycin, to rabbits, hamsters, guinea pigs, chinchillas, horses or ruminants as this could result in severe gastro- intestinal disturbance.
Do not use in cases of known resistance to lincosamides.
Do not use in cases of hepatic dysfunction.

6. ADVERSE REACTIONS

On rare occasions, pigs given lincomycin-medicated water may develop diarrhoea/soft stools and/or mild swelling of the anus within the first 2 days after onset of treatment. On rare occasions some pigs may show reddening of the skin and mild irritable behaviour. These conditions are usually self-

correcting within 5-8 days without discontinuing the lincomycin treatment. Allergic/hypersensitive reactions occur on rare occasions.

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

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, 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.

Dosing guidance and recommended doses:
To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing.
The intake of medicated water depends on the physiological and clinical condition of the animals. In order to obtain the correct dosage, the concentration of the lincomycin has to be adjusted accordingly.
The uptake of water should be monitored frequently.
The medicated water should be the only source of drinking water for the animals for the entire duration of the treatment period.
After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

Dosage:

Pigs:
Enzootic pneumonia: 10 mg lincomycin per kg of body weight (corresponding to 25 mg product per kg bodyweight) for 21 consecutive days.

Chickens:
Necrotic enteritis*:* 5 mg lincomycin per kg of body weight (corresponding to 12.5 mg product per kg bodyweight) for 7 consecutive days.

The concentration to be used depends on the actual body weight and the water consumption of the animals and can be calculated according to the following formula:

$$\frac{\text{Dosage (mg product per kg body weight per day)} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Average daily water intake (litre/animal)}} = \text{\_\_\_ mg product per litre drinking water}$$

9. ADVICE ON CORRECT ADMINISTRATION

The use of suitably calibrated weighing equipment is recommended if part packs are used. The daily amount is to be added to the drinking water in such a way that all medication will be consumed within 24 hours. Medicated drinking water should be freshly prepared every 24 hours. No other source of drinking water should be available.

10. WITHDRAWAL PERIOD(S)

Pigs:
Meat and offal: 1 day.

Chickens:
Meat and offal: 5 days.
Not authorised for use in laying birds producing eggs for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

This veterinary product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Shelf life after first opening the container: use immediately.
Shelf life after dilution or reconstitution according to directions: 24 hours.

12. SPECIAL WARNING(S)

Special warnings for each target species:
Medicated drinking water uptake can be affected by the severity of the disease. In case of insufficient uptake of water, pigs should be treated parenterally.
The susceptibility of *Mycoplasma hyopneumoniae* to antimicrobial agents is difficult to test *in vitro* owing to technical constraints. In addition, there is a the lack of clinical breakpoints for both *M. hyopneumoniae* and *C. perfringens*. Where possible, therapy should be based on local (regional, farm level) epidemiological information concerning the response of enzootic pneumonia/necrotic enteritis to treatment with lincomycin.

Special precautions for use in animals:
Use of the veterinary medicinal product preferably should be based on identification of the target pathogen and susceptibility testing of the bacteria isolated from the animal. However, also see text under Special warnings for each target species.
Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.
Use of the veterinary medicinal product deviating from the instructions given in the summary of product characteristics may increase the prevalence of bacteria resistant to the lincomycin and may decrease the effectiveness of treatment with other lincosamides, macrolides and streptogramin B due to the potential for cross-resistance.
Repeated or prolonged use should be avoided, by improving the farm management and hygiene practices.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
This product contains lincomycin and lactose monohydrate, either of which can cause allergic reactions in some people. People with known hypersensitivity to lincomycin or any other lincosamide, or to lactose monohydrate, 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 EN140 with a filter EN143), gloves and safety glasses should be worn when handling and mixing the product. If respiratory symptoms develop following exposure, seek medical advice and show this warning to the physician.
In case of accidental exposure to the skin, eyes or mucous membranes, wash the affected area thoroughly with plenty of water. 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.
Wash hands and any exposed skin with soap and water immediately after use.
Do not eat, drink or smoke while handling the product.

Pregnancy and lactation:
Laboratory studies in rats have not produced any evidence of teratogenic effects, although foetotoxicity has been reported. The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay in the target species. Use only according to the benefit-risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
Antagonism may exist between lincomycin and macrolides such as erythromycin and other bactericidal antibiotics; concurrent use is therefore not recommended due to competitive binding at the 50S ribosomal subunit of the bacterial cell.
The bioavailability of lincomycin may decrease in the presence of gastric antacids or activated charcoal, pectin or kaolin.
Lincomycin can potentiate neuromuscular effects of anaesthetics and muscle relaxants.

Overdose (symptoms, emergency procedures, antidotes):
A dosage greater than 10 mg lincomycin per kg of body weight may cause diarrhoea and loose stools in pigs.
In case of accidental overdose, the treatment must be stopped and continued at the recommended dose level.
There is no specific antidote, treatment is symptomatic.

Incompatibilities:
Do not mix with any other veterinary medicinal product.

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

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

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 causing premature peptidyl-tRNA dissociation from the ribosome.
Lincomycin is active against some gram-positive bacteria (*Clostridium perfringens*) and mycoplasmas (*Mycoplasma hyopneumoniae*).
While the lincosamides are generally considered to be bacteriostatic agents, the activity depends 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 macrolides, linconsamides and streptogramins group. However, the most prevalent mechanism in 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.

Pharmacokinetic particulars
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.
Crossing the intestinal barrier, lincomycin is widely distributed to all tissues, especially the lungs and joint cavities; the volume of distribution is about 1 litre. The elimination half-life of lincomycin is greater than 3 hours. Approximately 50% of lincomycin is metabolised in the liver. Lincomycin undergoes enterohepatic circulation. Lincomycin is eliminated unchanged or in the form of various metabolites in bile and urine. High concentrations of the active form are observed in the intestine.

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Pack sizes:
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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.