ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE
150 g polypropylene container with inner bag of LDPE.
1.5 kg polypropylene container with inner bag of LDPE.
5 kg polypropylene container with inner bag of LDPE.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Linco-Sol 400 mg/g powder for use in drinking water for pigs and chickens
Lincomycin (as lincomycin hydrochloride)

2. STATEMENT OF ACTIVE SUBSTANCES

Active substance:
Lincomycin (as hydrochloride) 400 mg/g

3. PHARMACEUTICAL FORM

Powder for use in drinking water

4. PACKAGE SIZE

150 g
1.5 kg
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 period:
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}
Shelf-life after first opening of container: 3 months.
Shelf-life after reconstitution in drinking water: 24 hours.
Once broached, use by:

11. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original container in order to protect from moisture.

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

Dispose of waste material in accordance with local requirements.

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

Lavet Pharmaceuticals Ltd.
2143 Kistarcsa
Batthyany u. 6.
Hungary

16. MARKETING AUTHORISATION NUMBER

Vm 32823/4005

17. MANUFACTURER'S BATCH NUMBER

Batch: {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Linco-Sol 400 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
Lavet Pharmaceuticals Ltd., 2143 Kistarcsa, Batthyany u. 6., Hungary

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Linco-Sol 400 mg/g powder for use in drinking water for pigs and chickens
Lincomycin

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

Each gram contains:
Active substance:
Lincomycin (as lincomycin hydrochloride) 400 mg

White or almost 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 use in cases of known resistance to lincosamides.
Do not administer, and do not allow access to water containing lincomycin to horses, ruminants, guinea pigs, hamsters, chinchillas and rabbits as this could result in severe gastro-intestinal disturbance.
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 two 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.

Do not store above 25°C.
Store in the original container in order to protect from moisture.
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: 3 months.
Shelf-life after 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 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 EN 149 or a non-disposable respirator conforming to European Standard EN 140 with a filter EN 143), gloves and safety glasses should be warn 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.
Do not smoke, eat or drink when handling the product.
Wash hands and any exposed skin with soap and water immediately after use.

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.

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

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

Medicines should not be disposed of via wastewater or household waste.
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

March 2020

15. OTHER INFORMATION

Nature and composition of immediate packaging
150 g polypropylene container with inner bag of LDPE.
1.5 kg polypropylene container with inner bag of LDPE.
5 kg polypropylene container with inner bag of LDPE.
Not all pack sizes may be marketed.

In Italy:
Pharmacotherapeutic group: lincosamide antibiotic, ATCvet code: QJ01FF02

In the United Kingdom:
When the container is opened for the first time, using the in-use shelf-life which is specified on this package leaflet, the date on which any product remaining in the container should be discarded should be worked out. This discard date should be written in the space provided on the label.

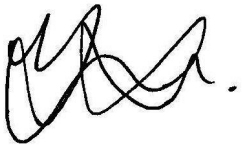
Pharmacodynamic properties
Lincomycin is a lincosamide antibiotic derived from *Streptomyces lincolensis* which inhibits protein synthesis. Lincomycin binds to the 50S sub-unit of the bacterial ribosome close to the peptidyl transfer centre and interferes with the peptide chain elongation process by 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.

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.



Approved: 26 March 2020