ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box (sachet)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Apralan Soluble Powder for use in drinking water/milk for pigs, calves, chickens and rabbits
Apramycin (sulfate)

2. STATEMENT OF ACTIVE SUBSTANCES

1 g contains 552,000 IU apramycin (as apramycin sulfate)

3. PHARMACEUTICAL FORM

Powder for use in drinking water/milk replacer

4. PACKAGE SIZE

50 sachets

5. TARGET SPECIES

Pigs, calves, chickens and rabbits.

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: Zero days.

Calves:
Meat and offal: 28 days.

Chickens:
Meat and offal: Zero days.
Not for use in birds producing or intended to produce eggs for human consumption. Do

not use within 4 weeks of the start of the laying period.
Rabbits:
Meat and offal: Zero days.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once diluted in water, use within 24 hours.
Once diluted in milk replacer, use within 6 hours.
Once opened, use immediately.

11. SPECIAL STORAGE CONDITIONS

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

Eli Lilly and Company Ltd
Elanco Animal Health
Lilly House
Priestley Road
Basingstoke
RG24 9NL

16. MARKETING AUTHORISATION NUMBER(S)

Vm 00006/4084

17. MANUFACTURER'S BATCH NUMBER

Lot:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Sachet

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Apralan Soluble Powder for use in drinking water/milk for pigs, calves, chickens and rabbits
Apramycin (sulfate)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

1 g contains 552,000 IU apramycin (as apramycin sulfate)

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

1 x 10^6 IU
2 x 10^6 IU

4. ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

5. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Pigs:
Meat and offal: Zero days.

Calves:
Meat and offal: 28 days.

Chickens:
Meat and offal: Zero days.
Not for use in birds producing or intended to produce eggs for human consumption. Do not use within 4 weeks of the start of the laying period.

Rabbits:
Meat and offal: Zero days.

6. BATCH NUMBER

Lot:

7. EXPIRY DATE

EXP {month/year}>

Once diluted in drinking water, use within 24 hours.
Once diluted in milk replacer, use within 6 hours.
Once opened, use immediately.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE - COMBINED LABEL AND PACKAGE LEAFLET

Bottle (booklet) and bag (label)

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

Marketing authorisation holder:
Eli Lilly and Company Ltd
Elanco Animal Health
Lilly House
Priestley Road
Basingstoke
RG24 9NL

Manufacturer responsible for batch release:
Elanco France S.A.S., 26 rue de la Chapelle, 68330 Huningue, France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Apralan Powder for use in drinking water/milk for pigs, calves, chickens and rabbits
Apramycin (sulfate)

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

1 g contains 552,000 IU apramycin (as apramycin sulfate)
Light to medium brown granular powder.

4. PHARMACEUTICAL FORM

Powder for use in drinking water/milk

5. PACKAGE SIZE

50 x 10^6 IU (bottle)
1,000 x 10^6 IU (bag)

6. INDICATIONS

Pigs (weaned piglets):
Treatment of bacterial enteritis caused by *Escherichia coli* susceptible to apramycin.

Pre-ruminant calves:
Treatment of bacterial enteritis caused by *Escherichia coli* and clinical outbreaks due to *Salmonella enterica* subsp. *enterica* serovar Dublin (*Salmonella* Dublin) susceptible to apramycin. Treatment should be based on prior confirmation of the *Salmonella* serovars involved or at least the availability of epidemiological data confirming the presence of this serovar.

Chickens:
Treatment of colibacillosis caused by *Escherichia coli* susceptible to apramycin.

Rabbits:
Treatment and metaphylaxis of bacterial enteritis caused by *Escherichia* coli susceptible to apramycin. The presence of the disease in the herd must be established before the product is used.

7. CONTRAINDICATIONS

Do not use in case of hypersensitivity to apramycin.
Do not use in calves with functional rumen.
Do not use in animals suffering from kidney disorders.

8. ADVERSE REACTIONS

None known.
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.

9. TARGET SPECIES

Pigs (weaned piglets), pre-ruminant calves, chickens (broilers) and rabbits.

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

Administration route:
To be administered via the drinking water. Drinking systems should be clean and free of rust to avoid reduction of activity.
In the case of calves it can be administered in milk or milk replacer.

Amounts to be administered:
Pigs:
Administer 12,500 IU apramycin sulfate per kilogram of bodyweight (corresponding to 22.5 mg of product/kg bw), daily for 7 consecutive days.

Calves:
Administer 40,000 IU apramycin sulfate per kilogram of bodyweight (corresponding to 72 mg of product/kg bw), daily for 5 consecutive days.

Chickens:
Administer 80,000 IU apramycin sulfate per kilogram of bodyweight (corresponding to 144 mg of product/kg bw), daily for 5 consecutive days.

Rabbits:
Administer 20,000 IU apramycin sulfate per kilogram of bodyweight (corresponding to 36 mg of product/kg bw), daily for 5 consecutive days.

11. ADVICE ON CORRECT ADMINISTRATION

The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dose, the concentration of the veterinary medicinal product has to be adjusted accordingly.
The weight of the animals should be determined as accurately as possible to avoid underdose.
Medicated water should be the only source of drinking. Medicated water must be renewed every 24 hours.
Solutions in milk and reconstituted milk replacer should be prepared immediately before use. Animals with acute or severe clinical conditions that cannot drink, should receive adequate parenteral treatment.
The amount of product (mg) to be incorporated per 1 l of water or milk should be established according to the following formula:

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

12. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Pigs:
Meat and offal: Zero days.

Calves:
Meat and offal: 28 days.

Chickens:
Meat and offal: Zero days.
Not for use in birds producing or intended to produce eggs for human consumption. Do not use within 4 weeks of the start of the laying period.

Rabbits:
Meat and offal: Zero days.

13. SPECIAL STORAGE PRECAUTIONS

This veterinary medicinal product does not require any special storage conditions.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

14. SPECIAL WARNING(S)

Special precautions for use in animals:
Use of the veterinary medicinal product should be based 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 the target bacteria.
Where a diagnosis of *Salmonella* Dublin is made on the farm, then control measures including on-going monitoring of disease status, vaccination, biosecurity and movement controls should be considered.
National control programmes should be followed where available.
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 apramycin and may decrease the effectiveness of treatment with aminoglycosides due to the potential for cross-resistance.
Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to apramycin or any other aminoglycoside should avoid contact with the product.
This product may cause irritation or sensitisation after skin or eye contact or inhalation.
Avoid contact with the eyes, skin and mucous membranes and inhalation of dust while preparing the medicated water/milk.
Use personal protective equipment consisting of gloves, mask, goggles and protective clothing while handling the product.
Wash hands after use.
In case of eye contact, rinse the affected area with plenty of water. In case of skin contact, wash thoroughly with soap and water. If irritation persists, seek medical advice.
In the case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
In case of onset of symptoms after exposure such as skin rash, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips and eyes or difficult breathing are more serious symptoms and require urgent medical assistance.

Pregnancy and lactation:
Pigs:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation in sows. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Cattle:
The use is not intended during pregnancy or lactation.

Rabbits:
Oral doses of apramycin administered from 6th to the 18th day of pregnancy (including doses below the therapeutic doses), have shown evidence of foetotoxic effects. Do not use during pregnancy.

Lay
Chicken:
Do not use in laying hens and within 4 weeks before the onset of the laying period.

Interaction with other medicinal products and other forms of interaction:
Aminoglycosides may have a negative influence on the kidney function. The administration of aminoglycosides to animals suffering from renal impairment or in combination with substances that also affect renal function may therefore present a risk of intoxication. Aminoglycosides may cause neuromuscular blockade. It is therefore recommended to take such an effect into account when anaesthetising treated animals.

Overdose (symptoms, emergency procedures, antidotes):
Pigs: Pigs have been given up to nine times the recommended use level in their drinking water for 28 days with no untoward reaction.

Calves: Calves were given apramycin in milk replacer daily for five days, at doses up to 120 mg/kg of bodyweight. There was no toxic effect.

Chicken: There was no mortality when chickens were given a single oral dose of 1,000 mg/kg of bodyweight. Chickens were given up to 5 times the recommended level for 15 days with no untoward reaction.

Possible intoxications can be recognised by the following symptoms: soft faeces, diarrhoea, vomiting (weight loss, anorexia, and similar), renal impairment and effects on the central nervous system (reduced activity, loss of reflexes, convulsions, etc.).
Do not exceed the recommended dose.

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

15. 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.

16. DATE ON WHICH THE LABEL WAS LAST APPROVED

April 2021

17. OTHER INFORMATION

Nature and composition of immediate packaging:
4-ply polyethylene terephthalate (PET)/polyethylene/aluminium foil/surlyn ionomer sachet, sealed by heat and pressure. Each sachet contains 1 x 106 IU apramycin and weight of 1.8 g of product. Sachets are packed in cardboard boxes containing 50 sachets.

4-ply polyethylene terephthalate (PET)/polyethylene/aluminium foil/surlyn ionomer sachet, sealed by heat and pressure. Each sachet contains 2 x 106 IU apramycin and weight of 3.6 g of product. Sachets are packed in cardboard boxes containing 50 sachets.

High density polyethylene bottle with polypropylene screw cap. Each bottle contains 50 x 106 IU apramycin and weight of 91 g of product.

Block bottomed laminated paper bag closed by pressurized heat-sealing jaws. Each bag contains 1,000 x 106 IU apramycin and weight of 1,812 g of product.

Not all pack sizes may be marketed.

18. 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.

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

Keep out of the sight and reach of children.

20. EXPIRY DATE

EXP {month/year}
Once diluted in water, use within 24 hours.
Once diluted in milk replacer, use within 6 hours.
Once opened, use within 28 days.

21. MARKETING AUTHORISATION NUMBER(S)

Vm 00006/4084

22. MANUFACTURER'S BATCH NUMBER

Lot:

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

Apralan Soluble
Powder for use in drinking water/milk for pigs, calves, chickens and rabbits

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

Marketing authorisation holder:
Eli Lilly and Company Ltd
Elanco Animal Health
Lilly House
Priestley Road
Basingstoke
RG24 9NL

Manufacturer responsible for batch release:
Elanco France S.A.S., 26 rue de la Chapelle, 68330 Huningue, France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Apralan Soluble
552,000 IU/g powder for use in drinking water/milk for pigs, calves, chickens and rabbits
Apramycin (sulfate)

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

1 g contains 552,000 IU apramycin (as apramycin sulfate).
Light to medium brown granular powder.

4. INDICATION(S)

Pigs (weaned piglets):
Treatment of bacterial enteritis caused by Escherichia coli susceptible to apramycin.

Pre-ruminant calves:
Treatment of bacterial enteritis caused by Escherichia coli and clinical outbreaks due to Salmonella enterica subsp. enterica serovar Dublin (Salmonella Dublin) susceptible to apramycin. Treatment should be based on prior confirmation of the Salmonella serovars involved or at least the availability of epidemiological data confirming the presence of this serovar.

Chickens:
Treatment colibacillosis caused by Escherichia coli susceptible to apramycin.

Rabbits:
Treatment and metaphylaxis of bacterial enteritis caused by Escherichia coli susceptible

to apramycin.
The presence of the disease in the herd must be established before the product is used.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to apramycin.
Do not use in calves with functional rumen.
Do not use in animals suffering from kidney disorders.

6. ADVERSE REACTIONS

None known.
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 (weaned piglets), pre-ruminant calves, chickens (broilers) and rabbits.

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

Administration route:
To be administered via the drinking water. Drinking systems should be clean and free of rust to avoid reduction of activity.
In the case of calves it can be administered in milk or milk replacer.

Amounts to be administered:
Pigs:
Administer 12,500 IU apramycin sulfate per kilogram of bodyweight (corresponding to 22.5 mg of product/kg bw), daily for 7 consecutive days.

Calves:
Administer 40,000 IU apramycin sulfate per kilogram of bodyweight (corresponding to 72 mg of product/kg bw), daily for 5 consecutive days.

Chickens:
Administer 80,000 IU apramycin sulfate per kilogram of bodyweight (corresponding to 144 mg of product/kg bw), daily for 5 consecutive days.

Rabbits:
Administer 20,000 IU apramycin sulfate per kilogram of bodyweight (corresponding to 36 mg of product/kg bw), daily for 5 consecutive days.

9. ADVICE ON CORRECT ADMINISTRATION

The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dose, the concentration of the veterinary medicinal product has to be adjusted accordingly. The weight of the animals should be determined as accurately as possible to avoid underdose.
Medicated water should be the only source of drinking. Medicated water must be renewed every 24 hours.
Solutions in milk and reconstituted milk replacer should be prepared immediately before use.
Animals with acute or severe clinical conditions that cannot drink, should receive adequate parenteral treatment.
The amount of product (mg) to be incorporated per 1 l of water or milk should be established according to the following formula:

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

10. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Pigs:
Meat and offal: Zero days.
Calves:
Meat and offal: 28 days.

Chickens:
Meat and offal: Zero days.
Not for use in birds producing or intended to produce eggs for human consumption. Do not use within 4 weeks of the start of the laying period.

Rabbits:
Meat and offal: Zero days.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
This veterinary medicinal 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 in drinking water according to directions: 24 hours.
Shelf life after dilution in drinking milk replacer according to directions: 6 hours.

12. SPECIAL WARNING(S)

Special precautions for use in animals:
Use of the veterinary medicinal product should be based 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 the target bacteria.
Where a diagnosis of Salmonella Dublin is made on the farm, then control measures including on-going monitoring of disease status, vaccination, biosecurity and movement controls should be considered.
National control programmes should be followed where available.
Use of the veterinary medicinal product deviating from the instructions given in the Summary of product characteristics (SPC) may increase the prevalence of bacteria resistant to the apramycin and may decrease the effectiveness of treatment with aminoglycosides due to the potential for cross-resistance.
Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to apramycin or any other aminoglycoside should avoid contact with the product.
This product may cause irritation or sensitisation after skin or eye contact or inhalation.
Avoid contact with the eyes, skin and mucous membranes and inhalation of dust while preparing the medicated water/milk.
Use personal protective equipment consisting of gloves, mask, goggles and protective clothing while handling the product.
Wash hands after use.
In case of eye contact, rinse the affected area with plenty of water. In case of skin contact, wash thoroughly with soap and water. If irritation persists, seek medical advice.
In the case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
In case of onset of symptoms after exposure such as skin rash, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips and eyes or difficult breathing are more serious symptoms and require urgent medical assistance.

Pregnancy and lactation:
Pigs:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation in sows. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Cattle:
The use is not intended during pregnancy or lactation.

Rabbits:
Oral doses of apramycin administered from 6th to the 18th day of pregnancy (including doses below the therapeutic doses), have shown evidence of foetotoxic effects. Do not use during pregnancy.

Lay:
Chicken:
Do not use in laying hens and within 4 weeks before the onset of the laying period.

Interaction with other medicinal products and other forms of interaction:
Aminoglycosides may have a negative influence on the kidney function. The administration of aminoglycosides to animals suffering from renal impairment or in combination with substances that also affect renal function may therefore present a risk of intoxication.
Aminoglycosides may cause neuromuscular blockade. It is therefore recommended to take such an effect into account when anaesthetising treated animals.

Overdose (symptoms, emergency procedures, antidotes):
Pigs: Pigs have been given up to nine times the recommended use level in their drinking water for 28 days with no untoward reaction.

Calves: Calves were given apramycin in milk replacer daily for five days, at doses up to 120 mg/kg of bodyweight. There was no toxic effect.

Chicken: There was no mortality when chickens were given a single oral dose of 1,000 mg/kg of bodyweight. Chickens were given up to 5 times the recommended level for 15 days with no untoward reaction.

Possible intoxications can be recognised by the following symptoms: soft faeces, diarrhoea, vomiting (weight loss, anorexia, and similar), renal impairment and effects on the central nervous system (reduced activity, loss of reflexes, convulsions, etc.).
Do not exceed 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

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

April 2021

15. OTHER INFORMATION

Nature and composition of immediate packaging:

4-ply polyethylene terephthalate (PET)/polyethylene/aluminium foil/surlyn ionomer sachet, sealed by heat and pressure. Each sachet contains 1 x 106 IU apramycin and weight of 1.8 g of product. Sachets are packed in cardboard boxes containing 50 sachets.

4-ply polyethylene terephthalate (PET)/polyethylene/aluminium foil/surlyn ionomer sachet, sealed by heat and pressure. Each sachet contains 2 x 106 IU apramycin and weight of 3.6 g of product. Sachets are packed in cardboard boxes containing 50 sachets.

High density polyethylene bottle with polypropylene screw cap. Each bottle contains 50 x 106 IU apramycin and weight of 91 g of product.

Block bottomed laminated paper bag closed by pressurized heat-sealing jaws. Each bag contains 1,000 x 106 IU apramycin and weight of 1,812 g of product.

Not all pack sizes may be marketed.

Approved: 06/05/21