SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

UK/IE - Apralan Soluble Powder for use in drinking water/milk replacer for pigs, calves, chickens and rabbits
FR - Apralan drinkable powder for administration into the drinking water / milk replacer for pigs, calves, chickens and rabbits
ES - Girolan powder for administration in drinking water or in milk replacer for pigs, bovine (calves), chickens and rabbits
NL- APRALAN Soluble 100% powder for use in drinking water / milk replacer for pigs, calves, chickens and rabbits
IT - Apralan Soluble Powder powder for use in drinking water / milk replacer for pigs, calves, chickens and rabbits
DK - Apralan Vet
PT- Apralan Powder for oral solution for use in drinking water or milk replacer for pigs, calves, chickens and rabbits.
DE - Apralan Soluble Powder for use in drinking water/milk replacer for pigs, calves, chickens and rabbits

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g contains:

Active substance:
Apramycin ……552,000 IU* (as apramycin sulfate)

* IU – international units

Excipients:
None.

3. PHARMACEUTICAL FORM

Powder for use in drinking water/milk replacer.
Light to medium brown granular powder.

4. CLINICAL PARTICULARS

4.1 Target species

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

4.2 Indications for use, specifying the target species

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.

4.3 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.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

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 replacer.
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.

4.6 Adverse reactions (frequency and seriousness)

None known.

4.7 Use during pregnancy, lactation or lay

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.

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

4.8 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.

4.9 Amounts to be administered and administration route

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 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.

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.
Medicated reconstituted milk replacer should be prepared immediately before use. Milk replacer should not exceed 40°C when the powder is introduced.
. 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 replacer should be established according to the following formula:

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

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

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.

4.11 Withdrawal period(s)

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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Intestinal antiinfectives, antibiotics.
ATCvet code: QA07AA92.

5.1 Pharmacodynamic properties

Apramycin is a broad-spectrum bactericidal aminoglycoside antibiotic whose action results from the binding to the 30S subunit of the ribosome, preventing protein synthesis and disrupting the membrane permeability of bacteria. Apramycin is effective against Gram-negative bacteria (*Salmonella* and *Escherichia coli*).

Resistance mechanisms: Different aminoglycoside 3-N acetyltransferase enzymes (AAC-3) have been related with resistance to apramycin. These enzymes confer different cross-resistance against other aminoglycosides. Some strains of *Salmonella* Typhimurium DT104 in addition to resistance against betalactams, streptomycin, tetracyclines and sulphonamides carry a conjugative resistance plasmid against apramycin. Apramycin resistance can be influenced by co-selection (resistance to apramycin has been described to be located in the same mobile genetic element that other resistant determinants in *Enterobacteriaceae*) and cross resistance (*e. g.* with gentamicin).

Resistance developed by chromosomal resistance is minimal for most of the aminoglycosides.

5.2 Pharmacokinetic particulars

The oral administration of apramycin is intended for antimicrobial activity within the gut; apramycin is poorly absorbed, but absorption may be increased in young animals and in animals with disrupted intestinal barrier.

Absorption:
Absorption may be high in new-born animals but rapidly decreases in the first weeks of life.

Calves. Serum levels peak at approximately 6 hours with a value of 2.4 µg/ml following oral administration of 40 mg apramycin/kg of bodyweight.

Distribution, biotransformation and excretion:
Apramycin is mainly excreted through faeces, under active form, and only a small quantity is excreted in the urine.

Pigs. Very little metabolism of apramycin takes place in the animal.
Dosing 10 kg pigs with ^{14}C apramycin resulted in approximately 83% being recovered from the faeces, and 4% from the urine, as ^{14}C apramycin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Major incompatibilities

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

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after dilution in drinking water according to directions: 24 hours.
Shelf life after dilution in milk replacer according to directions: 6 hours.
For single-dose presentations (sachets):
Shelf life after first opening the immediate packaging: use immediately.
For multidose presentations (bottle and bag):
Shelf life after first opening the immediate packaging: 28 days.

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

4-ply polyethylene terephthalate (PET)/polyethylene/aluminium foil/surlyn ionomer sachet, sealed by heat and pressure. Each sachet contains 1 x 10^6 IU apramycin sulfate 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 10^6 IU apramycin sulfate 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 10^6 IU apramycin sulfate and weight of 91 g of product. The cap is lined with a glued in induction heat seal liner constructed from Surlyn, aluminium, paper and polyester

Block bottomed laminated low density polyethylene, aluminium and kraft paper bag closed by pressurized heat-sealing jaws . Each bag contains 1,000 x 10^6 IU apramycin sulfate and weight of 1,812 g of product.

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

Vm 00006/4084

9. DATE OF FIRST AUTHORISATION

20 October 1992

10. DATE OF REVISION OF THE TEXT

October 2019

Approved: 09 October 2019