# Annex I

# List of the names, pharmaceutical form, strength of the veterinary medicinal products, animal species, routes 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 |
|---|---|---|---|---|---|---|---|
| Denmark | Elanco Animal Health A/S<br>Eli Lilly Danmark A/S<br>Lyskær 3E, 2 tv.<br>DK-2730 Herlev<br>Denmark | Apralan Vet. | Apramycin sulfate | Apramycin sulfate 333 mg/ml equivalent to apramycin 230 mg/ml | Powder for use in drinking water | Calves, pigs | Oral |
| France | Lilly France<br>24 Boulevard Vital Bouhot<br>92200 Neuilly Sur Seine<br>France | APRALAN BUVABLE | Apramycin sulfate | 1 g powder contains 1 g apramycin (as sulfate) | Powder for drinking solution | Calves, pigs, rabbits | Oral |
| Germany | Lilly Deutschland GmbH<br>Abt. Elanco Animal Health<br>Werner-Reimers-Straße 2-4<br>D-61352 Bad Homburg<br>Germany | Apralan soluble, 500 mg/g Pulver zum Eingeben über das Trinkwasser für Schweine (Läufer, Ferkel), Apramycin (als Apramycinsulfat) | Apramycin sulfate | 1 g powder contains 500 mg apramycin as apramycin sulfate in 2.2 ml equivalent to 1 g powder | Powder for use in drinking water | Pigs (piglets and growers) | Oral |
| Ireland | Eli Lilly and Company Limited<br>Elanco Animal Health<br>Priestly Road<br>Basingstoke<br>Hampshire<br>RG24 9NL<br>United Kingdom | Apralan Soluble Powder for oral solution | Apramycin sulfate | 100% w/w | Powder for oral solution | Calves, pigs, chickens | Oral |

| Member State EU/EEA | Marketing authorisation holder | Name | INN | Strength | Pharmaceutical form | Animal species | Route of administration |
|---|---|---|---|---|---|---|---|
| Italy | Eli Lilly Italia SpA<br>Via A. Gramsci, 731/733<br>50019 Sesto Fiorentino<br>(Firenze)<br>Italy | Apralan Solubile polvere per soluzione orale per Suini, Polli da carne e Conigli | Apramycin sulfate | 100 g powder contain 100 g apramycin sulfate | Powder for oral solution | Pigs, Broilers, Rabbits | Oral |
| Portugal | Lilly Portugal Produtos Farmacêuticos, Lda<br>Torre Ocidente<br>Rua Galileu Galilei, N.º 2, Piso 7<br>Fracção A/D<br>1500-392 Lisboa<br>Portugal | Apralan Pó para solução oral para administração na água de bebida para vitelos, suínos e frangos | Apramycin sulfate | Apramycin sulfate equivalent to 50 g apramycin activity per bottle.<br><br>Apramycin sulfate equivalent to 1000 g apramycin activity per bag. | Powder for oral solution | Calves, pigs, chickens | Oral |
| Spain | Elanco Valquímica, S.A.<br>Avda. de la Industria, nº 30<br>Polígono Industrial de Alcobendas<br>28108 Alcobendas<br>(Madrid)<br>Spain | Girolan | Apramycin sulfate | Apramycin sulfate equivalent to 50 g apramycin activity per bottle.<br><br>Apramycin sulfate equivalent to 1000 g apramycin activity per bag. | Powder for oral solution | Cattle, pigs, chickens, rabbits | Oral |
| The Netherlands | Elanco Europe Ltd<br>Lilly House<br>Priestley Road<br>Basingstoke<br>RG24 9NL<br>United Kingdom | Apralan oplosbaar | Apramycin sulfate | 100% | Powder for oral administration | Pre-ruminant calves, pigs, broilers | Oral |

| Member State EU / EEA | Marketing authorisation holder | Name | INN | Strength | Pharmaceutical form | Animal species | Route of administration |
|---|---|---|---|---|---|---|---|
| United Kingdom | Eli Lilly and Company Limited<br>Elanco Animal Health<br>Priestley Road<br>Basingstoke<br>Hampshire<br>RG24 9NL<br>United Kingdom | Apralan Soluble Powder for oral solution | Apramycin sulfate | Apramycin sulfate equivalent to 50 g apramycin activity per bottle.<br><br>Apramycin sulfate equivalent to 1 g apramycin activity per sachet.<br><br>Apramycin sulfate equivalent to 1000 g apramycin activity per bag. | Powder for oral solution | Calves, Pigs, Chickens | Oral |

# 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 Girolan and its associated name Apralan (see Annex I)

## 1. Introduction

Girolan and its associated name Apralan is a powder for use in drinking water/milk containing apramycin sulfate as active substance. Apramycin is a broad-spectrum aminocyclitol antibiotic produced by a strain of *Streptomyces tenebrarius*. Apramycin is bactericidal at minimum inhibitory concentrations (MICs) and is effective against both Gram-negative and Gram-positive bacteria and some strains of mycoplasma.

On 24 June 2016 Spain submitted a referral notification in accordance with Article 34 of Directive 2001/82/EC to the European Medicines Agency (the Agency) for Girolan and its associated name Apralan. The referral notification was based on concerns related to divergent national decisions having been taken by EU Member States resulting in discrepancies in the product information with respect to e.g. target species, indications for use, posology (dosage and duration) and withdrawal periods. The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to give its opinion on this matter and to harmonise the product information for Girolan and its associated name Apralan (thereafter called Girolan).

## 2. Discussion of data available

The CVMP noted that throughout the product information of Girolan the active substance was expressed as 'g of apramycin activity'. This was not considered acceptable, as the active substance strength should be expressed in IU/g product, since the assay is determined by means of a microbiological method. Based on historical batch data, a target potency of 552,000 IU/g apramycin was established and all references to 'g of apramycin activity' in the product information were replaced with the equivalent in IU/g product. Additionally, in some Member States a measuring device was authorised for the administration of Girolan. This was also not considered acceptable, as dosing by product weight was considered the most appropriate in terms of reproducibility of the dose and therefore any reference to the measuring device was deleted from the product information. Furthermore, taking into account the data provided and in line with the 'Note for guidance on start of shelf life of the finished dosage form (EMEA/CVMP/453/01)[1]', the shelf life period of the veterinary medicinal product as packaged for sale, which was 3 years, was reduced to 18 months.

**Pigs (weaned piglets)**

Pigs have been authorised as a target species for all products concerned by this referral procedure, as was the proposed indication, 'Treatment of bacterial enteritis caused by *Escherichia coli* susceptible to apramycin.' To support it, the marketing authorisation holder provided *in vitro* susceptibility data and clinical data including field studies.

$MIC_{90}$ values from a large pan-European study have been calculated for apramycin against *E. coli* from pigs as 16 µg/ml. These data are consistent with the published literature. A wild-type cut-off value of ≥32 µg/ml for *E. coli* of pig origin has been proposed. Recent data of clinical isolates from different European countries showed that resistance proportion of *E. coli* against apramycin is increasing. Some studies pointed out resistance percentages of 38% (MIC data) or even higher for disk diffusion (up to 82.1%).

[1] Note for guidance on start of shelf life of the finished dosage form (EMEA/CVMP/453/01) – link

With regard to field studies, twenty-three trials were provided using Girolan soluble powder for the treatment of post-weaning colibacillosis. These trials were conducted in Greece, Italy, Spain, the United Kingdom, USA and Canada. The studies analysed the effect of apramycin dosages between 3.45 mg/kg bodyweight (bw)/day and 75 mg/kg bw/day, via drinking water, during 3, 5 or 7 consecutive days. Apramycin was shown to be effective as measured by increased weight gain, improved feed efficiency, reduction of mortality rate, and the reduction in severity of diarrhoea and clinical signs. The daily administration of apramycin at a dose of 12,500 IU apramycin per kg bw (corresponding to 22.5 mg of product/kg bw), via drinking water, during seven days was shown to be an efficacious method to control the post-weaning colibacillosis in piglets.

It should be noted that in some Member States Girolan was also authorised for use against *Salmonella* in pigs, however the marketing authorisation holder decided to remove this indication, as it could not be supported. The CVMP accepted this deletion of *Salmonella*.

With regard to the withdrawal period, the residue depletion data indicated that apramycin is generally not well-absorbed from the gut after oral administration, which is consistent with the information available in published literature. Therefore the proposed withdrawal period of zero days for pig meat and offal was considered acceptable.

**Pre-ruminant calves**

Calves have been authorised in Denmark, France, Ireland, the Netherlands, Portugal, Spain and the UK. In support of the proposed indication, 'Treatment of bacterial enteritis caused by *Escherichia coli* and clinical outbreaks due to *Salmonella enterica* subsp. *enterica* serovar Dublin susceptible to apramycin', the marketing authorisation holder provided *in vitro* susceptibility data and clinical data including field studies.

$MIC_{90}$ values from a large pan-European study have been calculated for apramycin against *E. coli* from calves as 16 µg/ml. These data are consistent with the information available in published literature. A wild-type cut-off value of ≥32 µg/ml for *E. coli* of cattle origin has been proposed. Further data of clinical isolates from different European countries showed that resistance proportion of *E. coli* against apramycin is up to 12%.

While it was considered that *Salmonella* strains are generally susceptible to apramycin (MIC≤16 µg/ml) it should be noted that only *Salmonella* outbreaks with clinical signs (in the case of calves, caused by *Salmonella* Dublin) should be treated with apramycin. Additional data provided from 2014 indicate that *Salmonella* Dublin was mostly susceptible to apramycin (96.5% of isolates susceptible to all antimicrobials in the panel, including apramycin).

Seven trials were conducted as a blind study in Greece, Italy, Spain and the UK. These studies involved male calves of approximately one week of age naturally infected by *E. coli* and/or *Salmonella* spp. Apramycin was administered at a dose rate of 0, 20, and 40 mg apramycin activity per kg bw once daily for 5 consecutive days. All calves were subjected to a full clinical examination daily for at least the first week of each trial. Apramycin administered orally to calves once daily for five days at 20 mg apramycin/kg bw or 40 mg apramycin/kg bw was effective in reducing mortality. Surviving calves in the untreated control group failed to gain weight in the twelve days period whereas the survivors in the treated groups showed significant increases in average daily weight gain. The total clinical score in the 40 mg apramycin/kg bw group improved more rapidly than the 20 mg apramycin/kg bw group which improved more rapidly than the 0 mg apramycin/kg bw group. All the bacteria isolated from treated and untreated animals were sensitive to 16 µg/ml or less of apramycin. The oral administration of apramycin at 20 mg/kg bw or at 40 mg/kg bw during five consecutive days was shown to be efficacious for the treatment of colibacillosis and salmonellosis in young calves under field conditions.

With regard to *Salmonella*, a series of twenty-seven further experiments were conducted in calves, 15 of which therapeutic and 12 prophylactic. These studies involved one to three days old calves experimentally challenged with either *Salmonella* Dublin or *Salmonella typhimurium*, the most frequent serovars of *Salmonella* spp. in bovine species. The dosages of apramycin base or apramycin sulfate used were 0, 5.5, 11, 22 and/or 44 mg/kg bw/day during 5 or 10 consecutive days. Mortality was the principal criteria for efficacy. The results obtained from these trials showed that for both treatment and prevention of experimental salmonellosis in calves, apramycin sulfate and apramycin base perform equally. Treatment resulted in an almost linear dose/response in percent survival for apramycin dosages up to 22 mg/kg bw. It was demonstrated that 22 to 44 mg apramycin per kg bw during 5-10 consecutive days resulted in effective therapy against experimental salmonellosis in calves.

The CVMP considered that the use of antimicrobials in *Salmonella* would increase selective pressure and potentially promote antimicrobial resistance dissemination. Even host-adapted serovars (as *Salmonella* Dublin) might cause disease in humans (Evangelopoulou *et al*., 2014[2]; Singh, 2013[3]) so the use of antimicrobials in food producing animals should consider the zoonotic role of *Salmonella* and the consequences for public health (EFSA and ECDC, 2016[4]). Although it is acknowledged that *Salmonella* Dublin is an uncommon cause of salmonellosis in man, infection can be severe.

However, recent publications in the scientific literature indicate that the disease is present in cattle in Europe, e.g. in Ireland (O´Leary, 2014[5]) and the UK (Henderson and Mason, 2017[6]). Apramycin has been shown to be efficacious in the treatment of *Salmonella* infections in calves where its use reduced mortality and may therefore be justified on animal welfare grounds. In addition use of apramycin was considered preferable to the potential use of more critical antimicrobials such as fluoroquinolones. Therefore, the CVMP considered it justified to retain the indication for *Salmonella* Dublin for Girolan. In this respect, it was considered necessary to add the following sentence in section 4.5 of the summary of product characteristics (SPC) 'Special precautions for use in animals': '*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*.'

The agreed harmonised dose for both indications was 40,000 IU apramycin per kg bw (corresponding to 72 mg of product/kg bw), daily for 5 consecutive days.

With regard to the withdrawal period, of all the residue depletion studies provided, only one was considered adequate to be statistically analysed. The dosage, route and frequency of administration are those proposed in the product information. From this study, a withdrawal period of 28 days for calves meat and offal has been established, which is supported by the other references provided.

**Chickens**

Chickens have been authorised in Ireland, Italy, the Netherlands, Portugal, Spain and the UK. The proposed indication was 'Treatment of colibacillosis caused by *Escherichia coli* and not zoonotic *Salmonella* (*Salmonella* Pullorum and *Salmonella* Gallinarum) susceptible to apramycin'. To support this indication, the marketing authorisation holder provided *in vitro* susceptibility data and clinical data including field studies.

[2] Evangelopoulou *et al*. 2014. 'Pork Meat as a Potential Source of *Salmonella enterica* subsp. *arizonae* Infection in Humans' J. Clin. Microbiol., vol. 52 no. 3 741-744
[3] Vikash Singh. 2013. '*Salmonella* Serovars And Their Host Specificity.' J Vet Sci Anim Husb 1(3): 301. doi: 10.15744/2348-9790.1.301
[4] EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control), 2016. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2015. EFSA Journal 2016;14(12):4634, 231 pp. doi:10.2903/j.efsa.2016.4634
[5] O´Leary, C. 2014. '*Salmonella* Dublin in Irish cattle' Vet Ireland J 4:642-3
[6] Henderson, K. and Mason, C. 2017. 'Diagnosis and control of *Salmonella* Dublin in dairy herds' In Practice 39:158-168.

In various European monitoring programs, *E. coli* isolate from chickens were susceptible to apramycin. $MIC_{90}$ was 8 µg/ml or less. CVMP noted that data of clinical isolates from different European countries showed that resistance proportion of *E. coli* against apramycin is below 10%.

The marketing authorisation holder has provided twelve field trials in support of the efficacy for the indication against *E. coli*. These were conducted in Greece, Italy and Jordan, and involved 27-29 days old broilers from commercial farms with natural *E. coli* infection. In all trials, the animals were examined to confirm the diagnosis prior of to the initiation of treatment. Whenever possible, susceptibility testing and serotyping of bacterial isolates were carried out. The results obtained showed statistically significant difference on mortality between all the apramycin medicated groups and the unmedicated control groups. Dose/response was clearly observed for the mortality rate.

In this respect, it is to be noted that colibacillosis in chickens is essentially a systemic infection, involving a variety of organs, and its main entry route is the respiratory system. Although the respiratory route is considered a significant mode of entry, antimicrobials are expected to act at the site of infection. In this sense, it should be taken into account that the efficacy of the product was supported by various studies, where the veterinary medicinal product was administered for treatment and not for prevention. In those studies, the animals were examined to confirm the diagnosis prior to the initiation of treatment, bacteriologically and with lesions in different organs; treatment decreased mortality and carcases showed absence of lesions. In conclusion, the documentation provided supports the therapeutic use of Girolan for collibacilosis in chickens.

Regarding the indication in *Salmonella*, recent data were provided indicating good susceptibility to apramycin for *Salmonella* spp., however the only data specific to *Salmonella* Gallinarum was from Nigeria (Agbaje *et al*., 2010[7]) and Korea (Kang *et al.,* 2010[8]) and the epidemiological situation in Europe might be different. No data were presented for *Salmonella* Pullorum. No recent data about susceptibility of *Salmonella* Gallinarum or *Salmonella* Pullorum isolates obtained in clinical cases in Europe were available as salmonellosis caused by these serovars has not been detected in Europe since 2007.

The marketing authorisation holder provided one field trial including chickens artificially infected with *Salmonella* Pullorum. The objectives were to evaluate the efficacy of apramycin sulfate, administered in the drinking water for five consecutive days, at dose levels of 75, 150 and 225 mg/litre as treatment for these infections. From the study it could be concluded that *Salmonella* Pullorum infections could be controlled with apramycin. Again, no data for *Salmonella* Gallinarum was presented and in view of this it was not considered further for this indication.

*Salmonella* is one of the most frequent microorganisms causing foodborne zoonoses outbreaks and cases in Europe in humans (EFSA and ECDC, 2016[4]). European Control programmes of *Salmonella* in poultry in Europe have been focused on *Salmonella* Enteritidis, *Salmonella* Typhimurium, *Salmonella* Hadar, *Salmonella* Virchow and *Salmonella* Infantis, as the five most frequent serovars in human salmonellosis (Regulation (EC) No 2160/2003[9]). Colloquially, those five serovars are known as zoonotic in national control programmes established in poultry in Europe. According to Regulation (EC) No 1177/2006[10], antimicrobials should not be used as part of national control programs of *Salmonella* due to public health risks associated with development, selection and spread of resistance. Nevertheless,

[7] Agbaje, M. *et al*., 2010. 'Observation on the occurrence and transmission pattern of *Salmonella* gallinarum in commercial poultry farms in Ogun State, South Western Nigeria.' Afr. J. Microbiol. Res. Vol. 4(9), pp. 796-800
[8] Kang *et al.,* 2010. 'Characterization of antimicrobial resistance of recent *Salmonella enterica* serovar Gallinarum isolates from chickens in South Korea'. Avian Pathology Vol. 39(3), pp. 201-205
[9] Regulation (EC) No 2160/2003 of the European Parliament and of the Council as regards requirements for the use of specific control methods in the framework of the national programs for the control of salmonella in poultry – link
[10] Regulation (EC) No 1177/2006 implementing Regulation (EC) No 2160/2003 of the European Parliament and of the Council as regards requirements for the use of specific control methods in the framework of the national programmes for the control of salmonella in poultry – link

disease caused by *Salmonella* Pullorum is considered an exceptional circumstance that would require to treat (or slaughter) clinically affected flocks. This is stated in the Regulation (EC) No 2160/2003[9] and based on the EFSA Opinion (2004)[11].

However, the same EFSA document also states that:

- Any use of antimicrobials in poultry will increase the risk of emergence and spread of resistance in zoonotic bacteria such as *Salmonella* spp.
- In general, from a food safety/public health viewpoint, using antimicrobials to control *Salmonella* spp. in poultry has little justification. Any use in exceptional circumstances on animal health and welfare grounds must recognize the consequences for public health.
- The use of antimicrobials is never totally effective for the control of *Salmonella* spp. because it is not possible to eliminate all the organisms from an infected flock.
- If antimicrobials are used in breeding flocks or their immediate descendants there is a risk that any resistant bacteria which are selected may be disseminated to multiple flocks via contamination of hatching eggs and the hatchery environment.
- No specific advantages were identified for the use of antimicrobials in the case of meat-producing flocks. Antimicrobial treatment of meat-producing birds increases the risk of carcase contamination with resistant *Salmonella* spp. and *Campylobacter* spp. as well as resistant commensal bacteria, which may also transfer resistance genes to other bacteria.
- Should antimicrobial resistance be already present, develop or be acquired, then the use of antimicrobials for the treatment of clinically infected flocks, for the prevention of *Salmonella* infection, or for the treatment of infected flocks without clinical signs, will enhance the selection and spread of resistant bacterial strains throughout the production pyramid.

Moreover, Regulation (EU) No 2016/429 ('Animal Health Law')[12], that lays down rules for the prevention and control of animal diseases which are transmissible to animals or to humans, in Article 46 it is stated that the Member States may take measures concerning the use of veterinary medicinal products for listed diseases to ensure the most efficient prevention or control of those diseases, provided that such measures are appropriate or necessary. Those measures may cover, for example, prohibitions and restrictions on the use of veterinary medicinal products. Zoonotic *Salmonella* is listed in this Regulation. Furthermore, in this sense, the European Commission shall adopt delegated acts in accordance with Article 264 concerning amendments to the list referred. A disease shall be included on the list if it has been assessed in accordance with Article 7. In this sense, in a recent EFSA scientific opinion (June 2017)[13] *Salmonella* infection in poultry (*Salmonella* Pullorum, *Salmonella* Gallinarum and *Salmonella arizonae*) has been assessed according to the criteria of the Animal Health Law. According to the assessment performed, *Salmonella* can be considered eligible to be listed for Union intervention as laid down in Article 5(3) of the Animal Health Law. The main animal species to be listed are all species of domestic poultry and wild species of mainly Anseriformes and Galliformes. The report states that in developed countries antimicrobials are rarely used in commercial flocks for treatment of *Salmonella* Pullorum and *Salmonella* Gallinarum as they do not eliminate the infection from flocks and other control measures such as high level biosecurity, movement restrictions and depopulation are used instead.

[11] EFSA, 2004. Opinion of the Scientific Panel on Biological Hazards on a request from the Commission related to the use of antimicrobials for the control of Salmonella in poultry. The EFSA Journal (2004) 115, 1-76
[12] Regulation (EU) 2016/429 of the European Parliament and of the Council on transmissible animal diseases and amending and repealing certain acts in the area of animal health ('Animal Health Law') – link
[13] EFSA AHAW Panel (EFSA Panel on Animal Health and Welfare), 2017. Scientific Opinion on the assessment of listing and categorisation of animal diseases within the framework of the Animal Health Law (Regulation (EU) No 2016/429): Salmonella infection in poultry with serotypes of animal health relevance (S. Pullorum, S. Gallinarum and S. arizonae). EFSA Journal 2017;15(8):4954, 50 pp. https://doi.org/10.2903/j.efsa.2017.4954

Therefore, the CVMP concluded that the indication for the treatment of *Salmonella* in poultry could not be justified and should be deleted from the product information for Girolan.

With regard to the withdrawal periods for chicken meat and offal, a number of residues depletion studies have been presented by the marketing authorisation holder. All studies have been performed with the maximal dose proposed in the product information. Taking into account the available information the proposed withdrawal period of zero days for chicken meat and offal was considered acceptable.

**Rabbits**

Rabbits have been previously authorised in France, Italy and Spain. In support of the proposed indication 'Treatment and metaphylaxis of bacterial enteritis caused by *Escherichia coli* susceptible to apramycin', the marketing authorisation holder provided *in vitro* susceptibility data and clinical data including field studies.

The limited MIC data indicated a $MIC_{90}$ for apramycin of 3.5 µg/ml for *E. coli* isolates of rabbit origin and a proportion of <20% resistant strains.

A pivotal recently-conducted clinical field trial was provided. The study was conducted under the principles of Good Clinical Practice. In this blind, randomised trial Girolan administered at 20,000 IU apramycin per kg bw (corresponding to 36 mg of product/kg bw), daily for 5 consecutive days, was compared with a reference product containing colistin at a dose of 100,000 IU colistin/kg bw/day as the control group. The presence of *E. coli* was demonstrated by previous bacteriological or clinical results and was confirmed in samples taken from rabbits sacrificed or found dead after inclusion. The treatment period was initiated two weeks after weaning, when the signs of colibacillosis were clearly established. After the beginning of medication, the cumulative mortality increased similarly, with no-inferiority results in the apramycin group *versus* colistin group. Therefore, the CVMP concluded that the proposed indication was justified.

Concerning the withdrawal period, the residue depletion data indicated that apramycin is generally not well-absorbed from the gut after oral administration at the posology proposed in the product information. Therefore, the proposed withdrawal period of zero days for rabbit meat and offal was considered acceptable.

# 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 veterinary medicinal product Girolan. The referral leads to full harmonisation of the product information. This evaluation focuses on issues with regard to the harmonisation that may change the benefit-risk balance.

Girolan is a powder for use in drinking water/milk containing apramycin sulfate as active substance. Apramycin is a broad-spectrum aminocyclitol antibiotic produced by a strain of *Streptomyces tenebrarius*. Apramycin is bactericidal at minimum inhibitory concentrations and is effective against both Gram-negative and Gram-positive bacteria and some strains of mycoplasma.

**Benefit assessment**

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

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.

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.

**Pigs (weaned piglets)**

In support of the indication for treatment of bacterial enteritis caused by *E. coli* the marketing authorisation holder provided *in vitro* susceptibility data and clinical data including field studies.

$MIC_{90}$ of European isolates of *E. coli* for apramycin was demonstrated to be 16 µg/ml with a wild-type cut-off value of ≥32 µg/ml. The data provided also indicated that resistance to apramycin is increasing among *E. coli* isolates of pig origin, so the wording 'susceptible to apramycin' was added to the indication.

The provided clinical data demonstrated that Girolan was effective in the treatment of bacterial enteritis caused by *E. coli* when administered at 12,500 IU apramycin per kg bw (corresponding to 22.5 mg of product/kg bw), daily for 7 consecutive days.

**Pre-ruminant calves**

In support of the indication for treatment of bacterial enteritis caused by *E. coli* and clinical outbreaks due to *Salmonella* Dublin the marketing authorisation holder provided *in vitro* susceptibility data and clinical data including field studies.

$MIC_{90}$ of European isolates of *E. coli* for apramycin was demonstrated to be 16 µg/ml with a wild-type cut-off value of ≥32 µg/ml. The data provided also indicated that resistance to apramycin is not very common among *E. coli* isolates of cattle origin. *Salmonella* strains were considered generally susceptible to apramycin (MIC≤16 µg/ml) and <5% of *Salmonella* Dublin strains were shown to be resistant to apramycin.

The clinical data provided demonstrated that Girolan was effective in the treatment of bacterial enteritis caused by *E. coli* and clinical outbreaks due to *Salmonella* Dublin when administered at 40,000 IU apramycin per kilogram of bodyweight (corresponding to 72 mg of product/kg bw), daily for 5 consecutive days.

**Chickens**

In support of the indication for treatment of colibacillosis the marketing authorisation holder provided *in vitro* susceptibility data and clinical data including field studies.

$MIC_{90}$ of European isolates of *E. coli* for apramycin was demonstrated to be 8 µg/ml or less and the resistance proportion of *E. coli* of chicken origin against apramycin was below 10%.

The provided clinical data demonstrated that Girolan was effective in the treatment of colibacillosis when administered at 80,000 IU apramycin per kilogram of bodyweight (corresponding to 144 mg of product/kg bw), daily for 5 consecutive days.

With regard to the use of Girolan against *Salmonella* it was considered that in line with Regulation (EC) No. 1177/2006[10], antimicrobials should not be used for control and treatment of *Salmonella* in poultry except in exceptional circumstances. Moreover, Regulation (EU) No 2016/429 ('Animal Health Law')[12], states that the Member States may take measures concerning the use of veterinary medicinal products for listed diseases to ensure the most efficient prevention or control of those diseases. Furthermore, the European Commission shall adopt delegated acts concerning amendments to the list referred. A disease shall be included on the list if it has been assessed in accordance with Article 7. In this sense, in a scientific opinion (2017) of EFSA[13], *Salmonella* infection in poultry (*Salmonella* Pullorum, *Salmonella* Gallinarum and *Salmonella arizonae*) has been assessed according to the criteria of the Animal Health Law. According to the assessment performed, *Salmonella* can be considered eligible to be listed for Union intervention as laid down in Article 5(3) of the Animal Health Law. The main animal species to be listed are all species of domestic poultry and wild species of mainly Anseriformes and Galliformes. The report states that in developed countries antimicrobials are rarely used in commercial flocks for treatment of *Salmonella* Pullorum and *Salmonella* Gallinarum as they do not eliminate the infection from flocks and other control measures such as high level biosecurity, movement restrictions and depopulation are used instead. Therefore this indication was removed.

**Rabbits**

In support of the indication for treatment and metaphylaxis of bacterial enteritis caused by *E. coli* the marketing authorisation holder provided *in vitro* susceptibility data and clinical data including field studies.

The limited MIC data indicated a $MIC_{90}$ for apramycin of 3.5 µg/ml for *E. coli* isolates of rabbit origin and a proportion of <20% resistant strains.

The provided clinical data demonstrated that Girolan was effective in the treatment and metaphylaxis of bacterial enteritis caused by *Escherichia coli* when administered at 20,000 IU apramycin per kilogram of bodyweight (corresponding to 36 mg of product/kg bw), daily for 5 consecutive days.

**Risk assessment**

With regard to quality, a target potency of 552,000 IU/g of apramycin sulfate has been established for the medicinal product, based on the historical batch data provided. All references to 'g of apramycin activity' or measuring devices have been removed from the product information. Additionally, the shelf life has been reduced to 18 months.

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 summaries of product characteristics, 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.

Several residues depletion studies in the different target species were made available, which were variable in terms of reliability of the data, study design and reporting, and subsequently their outcomes. The harmonisation of withdrawal periods was based on the better conducted and most reliable studies.

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 Girolan 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 gantamicin and other substances of the aminoglycoside 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. Aminoglycosides are listed by WHO (2017)[14] as critically important for the treatment of certain zoonotic infections in humans (such as *Enterococcus* 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 harmonised product information of Girolan contains the necessary information to ensure the safe and effective use of the product.

**Evaluation and conclusions on the benefit-risk balance**

Girolan and its associated name Apralan has been shown to be efficacious in the indications in pigs (weaned piglets), pre-ruminant calves, chickens (broilers) and rabbits listed above.

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 subject to the recommended changes in the product information.

# 4. Re-examination procedure

Following the CVMP opinion of 5 October 2017 on this referral procedure, the marketing authorisation holders requested a re-examination of the CVMP opinion.

The marketing authorisation holders' grounds for the re-examination were submitted on 18 December 2017.

The scope of the re-examination was the shelf life of the product prior to first opening which was reduced from 3 years to 18 months. In the detailed grounds for re-examination the MAH requested a shelf life of 24 months based on stability data provided during the referral.

Data for 36 months was presented for 3 batches of finished product packaged in the final containers (bottles, bags and two different size sachets). Thus the data provided includes a sufficient number of batches in each of the container types for the full duration of the proposed shelf life. The testing time-points for these batches are not all in accordance with current guidelines but in all cases, data is provided for at last 5 time-points over the course of the stability study and trending of data is therefore possible. The assay results are presented as % of a target value of 552,000 IU/g. The results

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

show that the finished product is stable over 36 months with no significant change in active substance content. This is also supported by statistical analysis presented by the MAH which demonstrates that there is no change in assay over time. However, no storage conditions are provided for these stability studies and it is therefore not clear if they have been conducted at 25 °C/60% RH in accordance with the requirements of the 'Guideline on stability testing of existing active substances and related finished products (EMEA/CVMP/846/99-Rev.1)'[15]. Section 6.4 of the agreed SPC for the product states that no specific storage precautions are required for the product. This lack of storage precautions for the product is based on historical data, and was already approved in the individual Member States prior to the referral. No accelerated data have been provided during the referral procedure. Whilst it is not clear if the stability data was generated under controlled conditions or not, given the lack of significant change in active substance content and the fact that the product historically had a shelf life of 3 years, the data is considered adequate to support a 2 year shelf life for the finished product as proposed by the MAH.

**CVMP overall conclusions after re-examination**

Having reviewed the relevant information submitted during the initial assessment procedure and the detailed grounds for re-examination put forward by the MAH, the Committee concluded that the previous CVMP opinion should be revised as follows:

**SPC section 6.3**

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after dilution in drinking water/milk replacer according to directions: 24 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.

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

Whereas

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

the CVMP has recommended the amendment of the marketing authorisations for Girolan and its associated name Apralan as referred in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

[15] Guideline on stability testing of existing active substances and related finished products (EMEA/CVMP/846/99-Rev.1) – link

# Annex III

# Summary of product characteristics, labelling and package leaflet

# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

(Invented name of veterinary medicinal product)
Powder for use in drinking water/milk 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.
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.
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 6$^{th}$ to the 18$^{th}$ 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 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.

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:

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

## 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 beta-lactams, 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/milk replacer according to directions: 24 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.

Block bottomed laminated 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

*To be completed nationally.*

## 8. MARKETING AUTHORISATION NUMBER(S)

*To be completed nationally.*

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

*To be completed nationally.*

## 10 DATE OF REVISION OF THE TEXT

*To be completed nationally.*

## PROHIBITION OF SALE, SUPPLY AND/OR USE

*To be completed nationally.*

# ANNEX III

# LABELLING AND PACKAGE LEAFLET

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**

**Cardboard box (sachet)**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name>
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

## 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, use within 24 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

*To be completed nationally.*

## 16. MARKETING AUTHORISATION NUMBER(S)

*To be completed nationally.*

## 17. MANUFACTURER'S BATCH NUMBER

Lot:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Sachet**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name>
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, use within 24 hours.
Once opened, use immediately.

## 8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

# B. PACKAGE LEAFLET

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE - <u>COMBINED LABEL AND PACKAGE LEAFLET</u>**

**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: *To be completed nationally.*

Manufacturer responsible for batch release: *To be completed nationally.*

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name>
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:

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

## 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

*<DD/MM/YYYY>*
*To be completed nationally.*

## 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 $10^6$ 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 $10^6$ 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 $10^6$ 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 $10^6$ 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, use within 24 hours.
Once opened, use within 28 days.

## 21. MARKETING AUTHORISATION NUMBER(S)

*To be completed nationally.*

## 22. MANUFACTURER'S BATCH NUMBER

Lot:

*(sachet)*

**PACKAGE LEAFLET:**
**(Invented name of veterinary medicinal product)**
**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: *To be completed nationally.*

Manufacturer responsible for batch release: *To be completed nationally.*

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name>
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:

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

## 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 carton 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/milk replacer according to directions: 24 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

*<DD/MM/YYYY>*
*To be completed nationally.*

## 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 $10^6$ 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 $10^6$ 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 $10^6$ 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 $10^6$ IU apramycin and weight of 1,812 g of product.

Not all pack sizes may be marketed.