Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, marketing authorisation holder in the Member States

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Virbac 1ere Avenue 2065M LID 06516 Carros Cedex France	Adjusol TMP Sulfa Liquide	Trimethoprim Sulfadiazine	16,65 mg/ml 83,35 mg/ml	Oral solution	Cattle (calves), sheep (lambs), pigs, rabbits, poultry (chickens, turkeys, ducks)	Oral use
Greece	Virbac 1ere Avenue 2065M LID 06516 Carros Cedex France	ADJUSOL TMP SULFA πόσιμο διάλυμα (1,665+8,335)g/100ml	Trimethoprim Sulfadiazine	16,65 mg/ml 83,35 mg/ml	Oral solution	Broilers	Oral use
Luxembourg	Virbac 1ere Avenue 2065M LID 06516 Carros Cedex France	ADJUSOL TMP SULFA LIQUIDE	Trimethoprim Sulfadiazine	16,65 mg/ml 83,35 mg/ml	Oral solution	Cattle (calves), sheep (lambs), pigs, rabbits, poultry (chickens, turkeys, ducks)	Oral use
Portugal	Virbac 1ere Avenue 2065M LID 06516 Carros Cedex France	ADJUSOL TMP SULFA LIQUIDO, solução oral para administração na água de bebida para frangos de carne	Trimethoprim Sulfadiazine	16,65 mg/ml 83,35 mg/ml	Oral solution	Broilers	Oral use

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

Overall summary of the scientific evaluation of Adjusol tmp sulfa liquide and associated names (see Annex I)

1. Introduction

Adjusol tmp sulfa liquid and associated names (thereafter called Adjusol) is a solution for use in drinking water/milk containing 83.35 mg/ml sulfadiazine and 16.65 mg/ml trimethoprim as active substances. The veterinary medicinal product is indicated for infections caused by bacteria susceptible to the combination of sulfadiazine-trimethoprim.

On 8 July 2019, the European Commission sent a referral notification under Article 34(1) of Directive 2001/82/EC, to the CVMP/European Medicines Agency for Adjusol tmp sulfa liquide and its associated names. The European Commission referred the issue due to divergent national decisions having been taken by the EU Member States resulting in discrepancies in the product information for Adjusol tmp sulfa liquide and its associated names.

The main areas of disharmony in the existing product information relate to target species, indications and posology.

2. Discussion of data available

To support the proposed indications in the target species (please see below), the marketing authorisation holder (MAH) provided a combination of *in vitro* susceptibility data, pharmacokinetic data, a pharmacokinetic/pharmacodynamic (PK/PD) modelling approach, and justifications from scientific literature including efficacy data with the proposed fixed combination or with other combinations associating trimethoprim and a sulphonamide.

A literature review was submitted to determine the relevant bacteria to be treated by the combination for each species, but was considered insufficient to support any indication.

Only scarce clinical data on the efficacy of the combination are available from the dossier of Adjusol as well as from scientific literature. Studies were usually old, with a small sample size, using different doses than the ones proposed, different animal subcategories and the administration route is not always via drinking water. In some studies, other sulfonamides than sulfadiazine were used. Therefore, the provided literature was considered by CVMP not as pivotal, but as supportive of the proposed indications.

In the absence of robust clinical data, the MAH presented a PK/PD model to justify the indications and dosage regiments for all target species.

Several bibliographic references were provided and summarised by the MAH to describe the kinetic behaviour of the compounds in all target animal species. The review is extensive and complete and well implemented in the information in the Summary of Product Characteristics (SPC) section 5.2 'Pharmacokinetic particulars'.

It is well described in scientific literature that sulphonamides and trimethoprim are bacteriostatic agents when each substance is used individually, whereas they exert a bactericidal effect when used in combination. These compounds have a synergistic action against susceptible bacteria.

The classical pattern of antimicrobial activity in which sulphonamides and trimethoprim are classified is time-dependant activity (concentration-independent killing), for which T > MIC (minimal inhibitory concentration) is considered as the appropriate PK/PD index (plasma concentration during the course of the therapy should not fall below a certain effective plasma concentration). The MAH did not perform

an assessment considering this approach and instead chose AUC/MIC as a PK/PD index. It has been demonstrated by Toutain *et al.* (2019)[1] using a semi-mechanistic *in silico* model that AUC/MIC is the most appropriate index when the terminal half-life is relatively long relative to the dosage interval. While this approach was considered acceptable by CVMP, it was also considered important to validate AUC/MIC as an index of efficacy to ensure not increasing the risk of promoting antimicrobial resistance when T > MIC is a relevant metric. Furthermore, it is well established that the three PK/PD indices (T > MIC; AUC/MIC and C_{max}/MIC) exhibit some co-linearity (Greko *et al.,* 2003)[2]. For these reasons, the CVMP would have favoured a PK/PD analysis based on both T > MIC and AUC/MIC.

With regard to the approach chosen by the MAH, the breakpoint value of the PK/PD index (AUC/MIC) to achieve a bactericidal effect was estimated at higher than 25 hours, based on the publication by Cheng *et al.*, (2009)[3]. The value was obtained in a specific population of humans (Thai individuals), on the basis of own time-kill studies (performed with isolates of *Burkholderia pseudomallei*) and was therefore not recognised by CVMP as a universal value. However, while the likely bactericidal effect is usually accepted to be achieved with values of around 100, in the framework of this referral under Article 34 the CVMP accepted the PD target value as proposed by the MAH.

In addition, the MAH made a number of extrapolations in the PK/PD model, e.g. considering a linear PK behaviour, a low variability in the concentrations and similarity in the pharmaceutical forms. In the context of this referral under Article 34, and taking into account that this antimicrobial combination has been used for several decades, and that there are few bibliographic references using drinking water and comparison is difficult, CVMP could accept those extrapolations in general.

Taking the above points into account, the CVMP noted that the structure of the numerical approach (with a direct extrapolation of AUC when the data to be compared were obtained with a different dose) and the formula were acceptable. The numerical calculations were considered to be correct and therefore the values above MIC determined by the MAH could be accepted.

It should be taken into account that a MIC value is obtained for each active substance and for comparison with the MIC values just one value (cut-off value) can be used (the value for the combination). For this reason, and considering the synergistic effect mentioned above, the MIC limiting value used for establishing predictive efficacy was the one for the sulphonamide.

Pre-ruminant calves

The proposed indication was: 'Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida* or *Mannheimia haemolytica*, and acute enteritis caused by *Salmonella* spp., and acute enteritis and arthritis caused by *Escherichia coli* or septicaemia due to the same bacteria species susceptible to trimethoprim and sulfadiazine.' To support it, the MAH provided data on the pharmacokinetics of sulfadiazine-trimethoprim combinations, a PK/PD justification and a bibliographic review for the target pathogens.

No clinical data was submitted to support the efficacy of the combination against these pathogens in clinical practice. A bibliographic review was provided but due to the differences in active substances, doses and/or route of administration, it was considered that this summary had a limited value.
A reference was provided by Roussel *et al.* (1991)[4]. In that review article a study is described by White

1 Toutain P.L. *et al.* (2019) VetCAST Method for Determination of the Pharmacokinetic-Pharmacodynamic Cut-Off Values of a Long-Acting Formulation of Florfenicol to Support Clinical Breakpoints for Florfenicol Antimicrobial Susceptibility Testing in Cattle. Front Microbiol.10:1310. doi: 10.3389/fmicb.2019.01310. PMID: 31244816; PMCID: PMC6581757.
2 Greko C. *et al.* (2003). Tissue Cages in Calves for Studies on Pharmacokinetic/Pharmacodynamic - Relationships of Antimicrobials. Doctoral thesis. Swedish University of Agricultural Sciences. Uppsala.
3 Cheng A. *et al.* (2009). Dosing Regimens of Cotrimoxazole. Trimethoprim-Sulfamethoxazole for Melioidosis. Antimicrobial agents and chemotherapy, p. 4193-4199.
4 Roussel J.A. *et al.* (1991). Treatment of diarrhea of neonatal calves. Veterinary of Clinics of North America: Food Animal Practice. Vol. 7, No. 3, November: 713-728.

et al. (1981)[5], in which experimentally induced salmonellosis of calves was treated with trimethoprim (4 mg/kg) and sulfadiazine (20 mg/kg) administered either intramuscularly or intravenously. However, this is a different formulation from Adjusol, different route of administration and different dose.

Susceptibility data extracted from the monitoring programmes Vetpath IV (years 2015 and 2016), from Resapath (from 2015 to 2018) and literature (from 1997 and from 2009 to 2012) are consistent with each other. For *E. coli*, *Salmonella enterica* non speciated and *S. enterica Typhimurium* (n=5) a susceptibility of 70%, 92% and 100% respectively was reported. In addition, for *M. haemolytica* and *P. multocida* a MIC_{90} of 0.5 and 0.25 µg/ml respectively was calculated.

According to the theoretical PK/PD analysis performed by the MAH (see general comment above), the recommended doses for calves of 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg body weight, every 12 hours for 4 to 7 consecutive days, allow to treat target bacteria presenting a MIC below 4.9 µg/ml for sulfadiazine. No data for trimethoprim were provided. Based on the available data, cut-off values of 0.25, 0.5, 0.25 and 1 µg/ml were calculated for *P. multocida*, *M. haemolytica, Salmonella* and *E. coli*, respectively.

Nevertheless, regarding *Salmonella*, it was considered that this indication and dose that have not been justified scientifically for a trimethoprim-sulfadiazine formulation in drinking water/milk for *Salmonella* infections in calves can lead to treatment failures and latent carriers that are a further risk for animal and public health. Treatment and metaphylaxis are questionable for *Salmonella* spp. infections in food animals. The use of antimicrobials for the treatment of clinical salmonellosis is controversial for two main reasons. The first is that treatment is only potentially useful in the early stages of infection, and with an antimicrobial with PK/PD characteristics that can be effective. Secondly, antimicrobial therapy comes with the risk(s) of inducing 'carrier' status in animals as well as encouraging resistant *Salmonella*. Similar conclusions have been drawn concerning antibiotic treatment of non-typhoidal *Salmonella* in man, where it was concluded based on several placebo-controlled studies that antibiotic treatment meant passage of the same *Salmonella* serovar one month after treatment was almost twice as likely (RR 1.96, 95% CI 1.29 to 2.98; 112 participants, three trials), which was statistically significant[6]. Also, non-clinical carrier *Salmonella* animals entering the food chain are a major concern for public health. Furthermore, as noted in the CVMP/CHMP advice on the Categorisation of antibiotics (EMA/CVMP/CHMP/682198/2017)[7], recent evidence shows that in general, oral antibiotic treatment causes more antimicrobial resistance than treatment with injectable antibiotics (Zhang *et al.*, 2013[8] and Zhou *et al.*, 2020[9]).

In addition, resistance to trimethoprim and sulfadiazine are well described in *Salmonella* spp*.* (e.g. *sul1, sul2*, *dhfr1* genes) that can be present on mobile genetic elements, as well as multi-resistant integrons (Randall *et al.*, 2004)[10]. Therefore, the CVMP concluded that the indication for *Salmonella* spp. could not be justified.

With regard to the withdrawal period, the MAH did not submit residue depletion studies in calves with the product Adjusol. To justify the proposed withdrawal period for calves' meat and offal, the MAH

[5] White G. *et al.* (1981). Use of a calf salmonellosis model to evaluate the therapeutic properties of trimethoprim and sulphadiazine and their mutual potentiation in vivo. Res Vet Sci 31:27 -31.
[6] Onwuezobe I.A. *et al*. (2012) Antimicrobials for treating symptomatic non-typhoidal *Salmonella* infection. Cochrane Database of Systematic Reviews, Issue 11. Art. No.: CD001167. DOI: 10.1002/14651858.CD001167.pub2.
[7] CVMP/CHMP advice on the Categorisation of antibiotics in the European Union (EMA/CVMP/CHMP/682198/2017) - link
[8] Zhang, L. *et al.* (2013) Antibiotic Administration Routes Significantly Influence the Levels of Antibiotic Resistance in Gut Microbiota. Antimicrob Agents Chemother. 57(8): 3659–3666.
[9] Zhou, Y. *et al.* (2020) Antibiotic Administration Routes and Oral Exposure to Antibiotic Resistant Bacteria as Key Drivers for Gut Microbiota Disruption and Resistome in Poultry. Front Microbiol; 11:1319.
[10] Randall LP*. et al.* (2004). Antibiotic resistance genes, integrons and multiple antibiotic resistance in thirty-five serotypes of *Salmonella enterica* isolated from humans and animals in the UK. Journal of Antimicrobial Chemotherapy 53(2):208–216. DOI: 10.1093/jac/dkh070.

presented publications on the depletion of sulfonamide and trimethoprim residues in this target species.

The presented information was considered insufficient in order to establish an adequate withdrawal period for calves. However, it should be noted that calves were only authorised as a target species in France and Luxembourg with a withdrawal period of 12 days for calves' meat and offal, and therefore no divergent decisions have been taken.

Considering the framework of Article 34 referral procedures, and taking into account that there has never been a report to the MAH on Adjusol with suspicion of an MRL violation, and to keep the continuous availability of veterinary medicines, it was concluded that maintaining the currently authorised withdrawal period of 12 days for calves meat and offal for Adjusol when given at the dose of 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg body weight every 12 hours for 4 to 7 consecutive days would guarantee adequate consumer safety.

Pre-ruminant lambs

No data were provided to support any indication in lambs. Nevertheless, in the frame of a referral under Article 34, an indication may be maintained on the basis of well-established use together with lack of evidence to show a risk, such as new pharmacovigilance information in relation to suspected lack of expected efficacy. Lambs have been authorised as a target species in France for decades with the same indications as calves. Therefore, an extrapolation of the indications from calves could be accepted for lambs.

With regard to the withdrawal period, the MAH did not submit residue depletion studies in lambs with the product Adjusol. To justify the proposed withdrawal period for lambs' meat and offal, the MAH presented publications on the depletion of sulfonamide and trimethoprim residues in this target species.

The presented information was considered insufficient in order to establish an adequate withdrawal period for lambs. However, based on the same considerations as for calves, it was concluded that maintaining the currently authorised withdrawal period of 12 days for lambs meat and offal for Adjusol when given at the dose of 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg body weight every 12 hours for 4 to 7 consecutive days would guarantee adequate consumer safety.

Pigs

The proposed indication was: 'Treatment and metaphylaxis of polyarthritis caused by *Streptococcus suis*, respiratory infections caused by *Pasteurella multocida* or *Actinobacillus pleuropneumoniae*, and acute enteritis caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.' To support it, the MAH provided data on the pharmacokinetics of sulfadiazine-trimethoprim combinations, a PK/PD justification and a bibliographic review for the target pathogens.

No clinical data was submitted to support the efficacy of the combination against these pathogens in clinical practice. A bibliographic review was provided but while it was accepted that the combination is widely used in the treatment of the proposed indications, due to the differences in active substances, doses and/or route of administration, it was considered that this summary had a limited value and could only be considered at supportive.

According to the PK/PD analysis performed by the MAH (see general comment above), the recommended doses for pigs of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg body weight every 12 hours for 4 to 7 consecutive days allow to treat target bacteria with a MIC below 4.6 µg/ml for sulfadiazine and 0.18 µg/ml for trimethoprim. Based on the available data, cut-off values of 4, 1 and 1 µg/ml were calculated for *S. suis, P. multocida* and *E. coli*, respectively. For *A. pleuropneumoniae*, a MIC_{90} of 0.25 µg/ml was reported.

In addition, data extracted from Vetpath IV, from Resapath and literature report a very low susceptibility for *E. coli* while for *P. multocida* and for *S. suis* the susceptibility remains high. On the other hand, trimethoprim/sulfadiazine are classified as category D antimicrobials and thus should be used as a first line of treatment whenever possible. In contrast, alternative choices for treating colibacillosis in pigs include aminoglycosides (category C), quinolones (category B), and colistin (category A). Therefore, CVMP considered it justified to accept the proposed indication (especially as it specifically concerns susceptible *E. coli* and since SPC section 4.5 'Special precautions for use' states that bacteriological sampling and susceptibility testing are especially important for *E. coli* due to resistance) and thereby retaining the possibility to use trimethoprim/sulfadiazine as a first line of treatment for colibacillosis in regions/farms where the susceptibility profile of *E. coli* allows it.

With regard to the withdrawal period, the MAH did not submit residue depletion studies in pigs with the product Adjusol. To justify the proposed withdrawal period for pigs' meat and offal, the MAH presented publications on the depletion of sulfonamide and trimethoprim residues in this target species.

The presented information was considered insufficient in order to establish an adequate withdrawal period for pigs. However, based on the same considerations as for calves, it was concluded that maintaining the currently authorised withdrawal period of 12 days for pigs' meat and offal for Adjusol when given at the dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg body weight every 12 hours for 4 to 7 consecutive days would guarantee adequate consumer safety.

Rabbits

The proposed indication was: 'Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida*, and acute enteritis caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine. Treatment of mastitis or skin disease caused by *Staphylococcus aureus* susceptible to trimethoprim and sulfadiazine.' To support it, the MAH provided data on the pharmacokinetics of sulfadiazine-trimethoprim combinations, a PK/PD justification and a bibliographic review for the target pathogens.

No clinical data or bibliographic reference was submitted to support the efficacy of the combination against these pathogens in clinical practice.

According to the PK/PD analysis performed by the MAH (see general comment above), it was established that the cut-off value was supposed to be higher than 1.8, however no cut-off values of reference were provided for the different pathogens and therefore, no conclusions could be made.

Data extracted from Resapath (from 2015 to 2018) show a very stable and high susceptibility to the combination of *P. multocida* (more than 91%).

For *E. coli* a very low susceptibility of 34% was reported in 2018. Nevertheless, trimethoprim/sulfadiazine are classified as category D antimicrobials and thus should be used as a first line of treatment whenever possible. In contrast, alternative choices for treating colibacillosis in rabbits include aminoglycosides (category C), quinolones (category B), and colistin (category A). Based on this, the CVMP considered it justified to accept the proposed indication (especially as it specifically concerns susceptible *E. coli* and since SPC section 4.5 'Special precautions for use' states that bacteriological sampling and susceptibility testing are especially important for *E. coli* due to resistance) and thereby retaining the possibility to use trimethoprim/sulfadiazine as a first line of treatment for colibacillosis in regions/farms where the susceptibility profile of *E. coli* allows it.

S. aureus has shown an improved susceptibility, from 50% in 2010 to 72% in 2018. However, the treatment claim proposed by the MAH for *S. aureus* was not considered acceptable, as the formulation of the product (product to be mixed into drinking water) allows only a claim for both treatment and metaphylaxis in the case of farm animals, according to the CVMP Guideline for the demonstration of

efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1)[11].

Despite the lack of data to justify the efficacy of the product in the proposed indications, the CVMP considered that in the frame of an Article 34 referral, an indication may be maintained on the basis of well-established use together with lack of evidence to show a risk, such as new pharmacovigilance information in relation to suspected lack of expected efficacy. Rabbits have been authorised as a target species in France for decades for the treatment of infections caused by bacteria susceptible to trimethoprim and sulfadiazine and in order to maintain the availability of Adjusol for treatment of important diseases in this minor species, it was concluded that the indications for rabbits, limited to infections caused by *P. multocida* and *E. coli* could be accepted based on the susceptibility data.

With regard to the withdrawal period, the MAH did not submit residue depletion studies in rabbits with the product Adjusol. To justify the proposed withdrawal period for rabbits meat and offal, the MAH presented publications on the depletion of sulfonamide and trimethoprim residues in this target species.

The presented information was considered insufficient in order to establish an adequate withdrawal period for rabbits. However, based on the same considerations as for calves, it was concluded that maintaining the currently authorised withdrawal period of 12 days for rabbits meat and offal for Adjusol when given at the dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg body weight every 12 hours for 4 to 7 consecutive days would guarantee adequate consumer safety.

Chickens

The proposed indication was: 'Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida*, infectious coryza caused by *Avibacterium paragallinarum*, and respiratory infections caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine. Treatment of arthritis or septicaemia caused by *Staphylococcus aureus* susceptible to trimethoprim and sulfadiazine.' To support it, the MAH provided data on the pharmacokinetics of sulfadiazine-trimethoprim combinations, a PK/PD justification and a bibliographic review for the target pathogens.

According to the PK/PD analysis performed by the MAH (see general comment above), the recommended doses for chickens of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg body weight for 4 to 7 consecutive days allow to treat target bacteria presenting a MIC below or equal to 1.8 µg/ml for sulfadiazine and 0.04 µg/ml for trimethoprim.

For *E. coli* a cut-off value of 1 µg/ml was calculated. *E. coli* shows a rather good recent susceptibility rate (80%) to the combination and stable over time.

For *Staphylococcus aureus,* the therapeutic efficacy of sulfadiazine-trimethoprim was investigated in an experimental model of induced arthritis in broilers by Mosleh *et al*. (2016)[12], showing that the fixed combination given for 5 days at a slightly lower dose is effective for the treatment of *S. aureus* infection. In addition, *S. aureus* is and remains very susceptible to the combination according to Resapath data. However, the treatment claim proposed by the MAH for *S. aureus* was not considered acceptable, as the formulation of the product (product to be mixed into drinking water) allows only a claim for both treatment and metaphylaxis in the case of farm animals, according to the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1)[11].

[11] CVMP guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1) - link
[12] Mosleh.N *et al.* (2016). Comparative evaluation of therapeutic efficacy of sulfadiazine-trimethoprim, oxytetracycline, enrofloxacin and florfenicol on Staphylococcus aureus–induced arthritis in broilers. British Poultry Science, Vol. 57, No. 2, 179–184.

In support of the indication for *A. paragallinarum* only one bibliographic reference from the U.S. (Crispo *et al*., 2019)[13] was provided and no other data were submitted, including no Resapath susceptibility data. This information was considered insufficient to accept the indication.

Regarding *Pasteurella multocida*, a clinical field study by *White et al.* (1983)[14] was provided which had been included in the initial marketing authorisation dossier, but this study was considered of limited value. None of the bibliographic references provided supported the use of sulfadiazine-trimethoprim combination at the proposed dose in chickens. No susceptibility data were reported by the MAH. Therefore, these data were considered insufficient to support the indication.

With regard to the withdrawal period, the MAH submitted a proprietary residue study in broilers, conducted prior to the establishment of the definitive MRLs for trimethoprim, according to the OECD-GLP guidelines. Broilers were treated with Adjusol tmp sulfa liquide via drinking water *ad libitum* during 5 days at a mean actual dose of 43.9 ± 12.0 mg/kg/day of sulfadiazine and 8.6 ± 2.3 mg/kg/day of trimethoprim.

The number of animals used in the study (35) and the collection time of samples were considered adequate to allow the evaluation of the data. It was considered that the dose received was representative of a normal administration of the product and in line with the dosage regimen in Greece and Portugal.

For sulfadiazine the statistical method can be used in case of skin, leading to a withdrawal period of 9 days, however the linearity criterion is not met. For the rest of the tissues, the statistical method cannot be used, since in the majority of slaughter times concentrations were found below the limit of quantification (LOQ) in the different tissues of the different animals under study. Therefore, the alternative method has to be used for the calculation of the withdrawal time. In this case, at day 10 all residues in all tissues are below the MRL for sulfadiazine and after adding a safety span of 20%, a withdrawal period for sulfadiazine of 12 days could be considered adequate.

For trimethoprim, because the LOQ for trimethoprim is the same as MRL (50 µg/kg), the behaviour of trimethoprim residues cannot be known and therefore a withdrawal period could not be established.

A major limitation is identified though regarding the information on the stability of active ingredients through freezing. Stability of trimethoprim in frozen tissues is not provided. Sulfadiazine seems not stable in frozen kidney tissues (indeed, residue concentrations are below the LOQ even just after the end of the treatment). The MAH did not provide an explanation on this observation. The depletion of sulfadiazine in kidney is thus considered as unknown from this study. Information on the applied storage period of the tissue residue samples at -20°C was also not provided. Due to these limitations no conclusions could be drawn from the presented residue depletion study.

Furthermore, the MAH provided supporting documentation on sulfonamide and trimethoprim residue depletion in this target species. This documentation consisted of different citations on residues within the trimethoprim Summary Report[15] and bibliographic references on sulfonamide and trimethoprim residues.

Taken individually, the presented data were considered insufficient in order to establish an adequate withdrawal period for chickens. However looking at the overall data provided in its totality and also considering the framework of an Article 34 referral, it was concluded that maintaining the currently authorised withdrawal period of 12 days for chickens meat and offal for Adjusol when given at the dose

[13] Crispo, M *et al.* (2019). Characterization of an Outbreak of Infectious Coryza (*Avibacterium paragallinarum*) in Commercial Chickens in Central California. Avian Diseases 63(3):486–494.
[14] White G *et al.* (1983). Evaluation of a mixture of trimethoprim and sulphaquinoxaline for the treatment of bacterial and coccidial disease of poultry. The veterinary record, Dec 24-31;113(26-27);608-12.
[15] CVMP MRL Summary report (2) for trimethoprim (EMEA/MRL/255/97-FINAL) – link

of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg body weight for 4 to 7 consecutive days would guarantee adequate consumer safety.

3. Benefit-risk assessment

Introduction

This benefit-risk evaluation is performed in the context of Article 34 of Directive 2001/82/EC, which is to harmonise within the EU the conditions of authorisation for the veterinary medicinal product Adjusol tmp sulfa liquide and its associated names. The referral leads to full harmonisation of the product information. This evaluation focuses on issues in regard to the harmonisation that may change the benefit-risk balance.

Adjusol is a solution for use in drinking water/milk containing 83.35 mg/ml sulfadiazine and 16.65 mg/ml trimethoprim as active substances. The veterinary medicinal product is indicated for infections caused by bacteria susceptible to the combination of sulfadiazine-trimethoprim.

Benefit assessment

The following indications for Adjusol can be supported based on the data provided:

Pre-ruminant calves and lambs:
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida* or *Mannheimia haemolytica*, and infections caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.
The presence of the disease in the group must be established before the product is used.

Pigs:
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida* or *Actinobacillus pleuropneumoniae*, and infections caused by *Streptococcus suis* or *Escherichia coli* susceptible to trimethoprim and sulfadiazine.
The presence of the disease in the group must be established before the product is used.

Rabbits:
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida*, and collibacillosis caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.
The presence of the disease in the group must be established before the product is used.

Chickens:
Treatment and metaphylaxis of collibacillosis caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.
The presence of the disease in the flock must be established before the product is used.

In support of these indications the marketing authorisation holder provided a combination of *in vitro* susceptibility data, pharmacokinetic data, a PK/PD modelling approach, and justifications from scientific literature including efficacy data with the proposed fixed combination or with other combinations associating trimethoprim and a sulphonamide.

The authorised dose regimen was justified for each of the target bacterial species, through a combination of a PK/PD approach, up-to-date MICs when available and reported efficacy data found in literature and supporting the proposed dose regimen.

Risk assessment

Since the dosing regimens recommended have not been increased and the indications have not been extended with regard to those already approved, the assessment of target animal safety, risk for the environment and user safety did not present new issues.

The harmonised warnings and precautions proposed in the product information are considered adequate to ensure the safety of the product to target animals and users. The information that trimethoprim is persistent in soils has been added to the product information.

One residue depletion study in chickens was made available, which was inconclusive in terms of reliability of the data and validation and consequently the outcome. The MAH also presented a number of bibliographic references to justify the proposed withdrawal periods for all target species. Based on the evaluation of the overall available information, the maintenance of the currently established withdrawal periods for all target species was considered safe for the consumer.

Information on the current situation regarding resistance against trimethoprim/sulfonamides combination has been provided by the MAH. The precautions for use in animals have been completed in the product information to take into account the current recommendations on prudent and rational use of antimicrobials. The information on pharmacodynamic properties has been updated with observed susceptibility percentages for *E. coli* in each target animal species.

Risk management or mitigation measures

The harmonised product information of Adjusol contains the information necessary to ensure safe and effective use of the product in the target animal species.

Adjusol includes warnings about the prudent use of antimicrobial substances according to the CVMP guideline on SPC for antimicrobials (EMEA/CVMP/SAGAM/383441/2005)[16].

Users are advised to take due precautions when handling the product to avoid exposure.

Withdrawal periods have been reviewed after evaluation of available data on residues depletion to ensure consumer safety.

Evaluation and conclusions on the benefit-risk balance

Adjusol has been accepted in the indications in pre-ruminant calves and lambs, pigs, rabbits and chickens listed above. The resistance situation for the target pathogens is considered favourable.

There is little evidence of serious adverse reactions, except use in animals suffering from severe liver of kidney disease, oliguria or anuria.

The risks to users were considered low and adequate information is included in the product information to ensure 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 MAH, the CVMP concluded that the benefit-risk balance of the product remains positive subject to the recommended changes in the product information.

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;

[16] CVMP guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/SAGAM/383441/2005) - link

- the CVMP reviewed the summary of product characteristics, labelling and package leaflet proposed by the marketing authorisation holders and considered all the overall submitted data;

the CVMP has recommended the amendment of the marketing authorisations for Adjusol tmp sulfa liquid and its associated names as referred in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

Summary of product characteristics, labelling and package leaflet

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

(Invented name of veterinary medicinal product) 83.35 mg/ml + 16.65 mg/ml solution for use in drinking water/milk

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Active substances:
Sulfadiazine 83.35 mg
Trimethoprim 16.65 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for use in drinking water/milk.
Light yellow solution, slightly viscous.

4. CLINICAL PARTICULARS

4.1. Target species

Pre-ruminant calves, pre-ruminant lambs, pigs, rabbits and chickens.

4.2. Indications for use, specifying the target species

Pre-ruminant calves and lambs
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida* or *Mannheimia haemolytica* and infections caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.

The presence of the disease in the group must be established before the product is used.

Pigs
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida* or *Actinobacillus pleuropneumoniae*, and infections caused by *Streptococcus suis* or *Escherichia coli* susceptible to trimethoprim and sulfadiazine.

The presence of the disease in the group must be established before the product is used.

Rabbits
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida*, and collibacillosis caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.

The presence of the disease in the group must be established before the product is used.

Chickens
Treatment and metaphylaxis of collibacillosis caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.

The presence of the disease in the flock must be established before the product is used.

4.3. Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use in animals suffering from severe liver or kidney disease, oliguria or anuria.

4.4. Special warnings for each target species

Severely diseased animals can have a decreased appetite and water consumption. If necessary the concentration of the veterinary medicinal product in the drinking water should be adjusted to make sure that the recommended dosage is being consumed.

Pigs, pre-ruminant calves, pre-ruminant lambs and rabbits: The uptake of medication by animals may be altered as a consequence of illness. In case of insufficient water uptake, animals should be treated parenterally instead using a suitable injectable product prescribed by the veterinarian.

4.5. Special precautions for use

Special precautions for use in animals
Due to the likely variability (time, geographical) in susceptibility of bacteria for potentiated sulfonamides, occurrence of resistance of bacteria may differ from country to country and even from farm to farm, and therefore bacteriological sampling and susceptibility testing are recommended. It is particularly of importance for *E. coli* infections where high percentages of resistance are observed (see section 5.1).

Use of the product should be based on susceptibility testing of bacteria isolated from the animal. If not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

Use of the product deviating from the instructions given in the Summary of product characteristics (SPC) may increase the prevalence of bacteria resistant to sulfadiazine and trimethoprim and may also decrease the effectiveness of combinations of trimethoprim with other sulfonamides due to the potential for cross-resistance.

Official, national and regional antimicrobial policies should be taken into account when the product is used.

To avoid deterioration of the kidneys due to crystalluria during treatment, it should be ensured that the animal receives sufficient amount of drinking water.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
This product contains sulfadiazine, trimethoprim and macrogol, which can cause allergic reactions in some people. Hypersensitivity to sulfonamides may lead to cross reactions with other antibiotics. Allergic reactions to these substances may occasionally be serious.

People with known hypersensitivity (allergy) to sulfonamides, trimethoprim or macrogol should avoid contact with the veterinary medicinal product.

This veterinary medicinal product may cause skin or eye irritation. During the preparation and administration of medicated drinking water, skin and eyes contact has to be avoided. Personal protective equipment consisting of waterproof gloves and safety glasses should be worn when handling the veterinary medicinal product. In case of accidental contact with the eyes or skin, wash the affected area with plenty of water, and if skin rash occurs, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

This veterinary medicinal product may be harmful if ingested. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6. Adverse effects (frequency and severity)

Reduced water intake has been reported in very rare cases in chickens.

Hypersensitivity reactions have been described in literature.

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

4.7. Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have shown evidence of teratogenic and foetotoxic effects.

Do not use during pregnancy and lactation, or lay.

4.8. Interaction with other medicinal products and other forms of interaction

Do not administer concomitantly with coccidiostats or veterinary medicinal products containing sulfonamides.

Do not associate with PABA (para-aminobenzoic acid).

Sulfonamides potentiate anticoagulants action.

4.9. Amounts to be administered and administration route

Administration route:
For oral use in drinking water/milk replacer.

Amounts to be administered:
Pre-ruminant calves and lambs
12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg body weight (corresponding to 1.5 mL of solution per 10 kg body weight), every 12 hours for 4 to 7 consecutive days, to be mixed with the milk replacer (when adding the water).

Pigs and rabbits
25 mg of sulfadiazine and 5 mg of trimethoprim per kg of live weight per day (corresponding to 3 mL of solution per 10 kg live weight per day in continuous), for 4 to 7 consecutive days, to be diluted in drinking water.

Chickens
25 mg of sulfadiazine and 5 mg of trimethoprim per kg of live weight per day (corresponding to 0.3 mL of solution per kg of live weight per day in continuous), for 4 to 7 consecutive days, to be diluted in drinking water.

Guidance for preparing product solutions:
To ensure the correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The intake of medicated water depends on the physiological and clinical condition of the animals. In order to obtain the correct dosage, the concentration of sulfadiazine and trimethoprim should be adjusted accordingly.

The dosage of the product to be incorporated should be established according to the following formula:

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

The medicated drinking water should be the sole source of drinking water for the treatment duration. Any medicated drinking water which is not consumed within 24 hours should be discarded.

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

Sulfonamides overdose causes renal toxicity. In this case, the administration of the product has to be stopped.

4.11. Withdrawal period(s)

Calves:
Meat and offal: 12 days.

Lambs:
Meat and offal: 12 days.

Pigs:
Meat and offal: 12 days.

Rabbits:
Meat and offal: 12 days.

Chickens: Meat and offal: 12 days.
Eggs: Not for use in birds producing or intended to produce eggs for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: anti-infectives for systemic use.
ATCvet code: QJ01EW10.

5.1. Pharmacodynamic properties

Trimethoprim and sulfadiazine have a broad spectrum of activity against gram-positive and gram-negative bacteria including *Streptococcus suis, Pasteurella multocida, Actinobacillus pleuropneumoniae, Mannheimia haemolytica* and *E. coli in vitro*. Sulfonamides block the conversion of para-aminobenzoic acid to dihydrofolic acid. Their effect is bacteriostatic.

Trimethoprim inhibits dihydrofolic acid reductase, which converts dihydrofolic into tetrahydrofolic acid.

The effect of trimethoprim in combination with sulfonamides is bactericidal. Sulfonamides and trimethoprim thus cause a successive blockage of two enzymes that play an important role in the metabolism of bacteria. Their effect is synergistic and time dependent.

Bacterial resistance to trimethoprim and to sulfonamides can be mediated via 5 main mechanisms: (1) changes in the permeability barrier and/or efflux pumps, (2) naturally insensitive target enzymes, (3) changes in the target enzymes, (4) mutational or recombinational changes in the target enzymes, and (5) acquired resistance by drug-resistant target enzymes.

A summary of available susceptibility data of *E. coli* from the Vetpath IV (years 2015 and 2016) and from the 2019 Resapath program report is presented below.

Susceptibility data presented showed high levels of resistance among *E. coli* isolated from pigs (39% classified as susceptible in the VetPath IV data - n=333 - and 51% in Resapath data - n= 1834).

For calves, the VetPath IV data (n=230) showed a susceptibility of 70%, while in the Resapath program for non-ruminant calves (n=4148) and lambs (n=334), the percentage of susceptibility was 60% and 61%, respectively. This observation has already been explained with the existence of a resistant population highlighted by a bimodal distribution.

For *E. coli* from rabbits, according to data taken from the Resapath program, the percentage of susceptibility was only 34% (n=227).

For chickens and turkeys, data taken from the VetPath IV program (n=65) showed a susceptibility of *E. coli* of 83%.

5.2. Pharmacokinetic particulars

The pharmacokinetic properties of sulfadiazine and trimethoprim are species dependent. With continuous administration in the drinking water, the steady-state concentrations are achieved in approximately 2 days.

Overall, sulfadiazine has almost complete and rapid oral absorption with very persistent plasma rates and oral bioavailability ranging between 80 to 90%, except in rabbits (29%). Its binding to plasma proteins varies between 28 to 80%, according to the species (28% pigs, 49% calves, 80% chickens). It presents a wide distribution in most tissues and organs in all species. Sulfadiazine is metabolised in the liver, and mainly excreted in the urine.

Trimethoprim is rapidly and well absorbed following oral administration with oral bioavailability ranging from 80 to 90%. Approximately 30% to 60% of trimethoprim is bound to plasma proteins, in percentages that vary according to the species (49% pigs, 57% calves, 77% chickens) and it presents a wide distribution in most tissues and organs in all species. Tissue concentrations, especially in lungs, liver and kidneys are often higher than the corresponding plasma concentrations. Trimethoprim is likely metabolised in the liver, and mainly excreted in the urine. The elimination rate of trimethoprim is generally faster than the one of sulfadiazine in all species.

Environmental properties
Trimethoprim is persistent in soils.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Macrogol 200
Sodium hydroxide (for pH adjustment)
Purified water

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 first opening the immediate packaging: use immediately.
Shelf life after dilution in drinking water according to directions: 24 hours.
Shelf life after dilution in milk according to directions: 2 hours.

6.4. Special precautions for storage

Store in a dry place.
Protect from light.

6.5. Nature and composition of immediate packaging

Polyethylene bottles or containers closed with a plastic screw cap.

Pack sizes:

Cardboard box containing one bottle of 100 mL, 250 mL, 500 mL or 1 L.
Container of 2 L, 5 L, 10 L.

Not all pack sizes may be marketed.

6.6. Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

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

7. MARKETING AUTHORISATION HOLDER

VIRBAC
1ère Avenue - 2065 m - LID
06516 Carros
France

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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE AND THE IMMEDIATE PACKAGE

Cardboard box and bottle of 100 mL, 250 mL, 500 mL or 1 L

Container of 2 L, 5 L, 10 L

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 83.35 mg/ml + 16.65 mg/ml solution for use in drinking water/milk

2. STATEMENT OF ACTIVE SUBSTANCES

Each mL contains:
83.35 mg of sulfadiazine
16.65 mg of trimethoprim

3. PHARMACEUTICAL FORM

Solution for use in drinking water/milk.

4. PACKAGE SIZE

100 mL
250 mL
500 mL
1 L
2 L
5 L
10 L

5. TARGET SPECIES

Pre-ruminant calves, pre-ruminant lambs, pigs, rabbits and chickens.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Calves
Meat and offal: 12 days.

Lambs
Meat and offal: 12 days.

Pigs
Meat and offal: 12 days.

Rabbits
Meat and offal: 12 days.

Chickens
Meat and offal: 12 days.
Eggs: Not for use in birds producing or intended to produce eggs for human consumption

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP {month/year}
Once opened use immediately.

11. SPECIAL STORAGE CONDITIONS

Store in a dry place.
Protect from light.

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

VIRBAC
1ère Avenue - 2065 m - LID

06516 Carros
France

16. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
<Invented name> 83.35 mg/ml + 16.65 mg/ml solution for use in drinking water/milk

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

Marketing authorisation holder and manufacturer responsible for batch release:
VIRBAC
1ère Avenue - 2065 m - LID
06516 Carros
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 83.35 mg/ml + 16.65 mg/ml solution for use in drinking water/milk
Sulfadiazine
Trimethoprim

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

Each mL contains:

Active substances:
Sulfadiazine 83.35 mg
Trimethoprim 16.65 mg

Light yellow solution, slightly viscous.

4. INDICATION(S)

Pre-ruminant calves and lambs
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida* or *Mannheimia haemolytica* and infections caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.

The presence of the disease in the group must be established before the product is used.

Pigs
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida* or *Actinobacillus pleuropneumoniae*, and infections caused by *Streptococcus suis* or *Escherichia coli* susceptible to trimethoprim and sulfadiazine.

The presence of the disease in the group must be established before the product is used.

Rabbits
Treatment and metaphylaxis of respiratory infections caused by *Pasteurella multocida*, and collibacillosis caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.

The presence of the disease in the group must be established before the product is used.

Chickens
Treatment and metaphylaxis of collibacillosis caused by *Escherichia coli* susceptible to trimethoprim and sulfadiazine.

The presence of the disease in the flock must be established before the product is used.

5. CONTRAINDICATIONS

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use in animals suffering from severe liver or kidney disease, oliguria or anuria.

6. ADVERSE REACTIONS

Reduced water intake has been reported in very rare cases in chickens.

Hypersensitivity reactions have been described in literature.

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

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

7. TARGET SPECIES

Pre-ruminant calves, pre-ruminant lambs, pigs, rabbits and chickens.

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

Administration route:
For oral use in drinking water/milk replacer.

Amounts to be administered:
Pre-ruminant calves and lambs
12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg body weight (corresponding to 1.5 ml of solution per 10 kg body weight), every 12 hours for 4 to 7 consecutive days, to be mixed with the milk replacer (when adding the water).

Pigs, rabbits
25 mg of sulfadiazine and 5 mg of trimethoprim per kg of live weight per day (corresponding to 3 mL of solution per 10 kg live weight per day in continuous) for 4 to 7 consecutive days, to be diluted in drinking water.

Chickens
25 mg of sulfadiazine and 5 mg of trimethoprim per kg of live weight per day (corresponding to 0.3 mL of solution per kg of live weight per day in continuous), for 4 to 7 consecutive days, to be diluted in drinking water.

Guidance for preparing product solutions:

To ensure the correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The intake of medicated water depends on the physiological and clinical condition of the animals. In order to obtain the correct dosage, the concentration of sulfadiazine and trimethoprim should be adjusted accordingly.

The dosage of the product to be incorporated should be established according to the following formula:

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

9. ADVICE ON CORRECT ADMINISTRATION

The medicated drinking water should be the sole source of drinking water for the treatment duration.

Any medicated drinking water which is not consumed within 24 hours should be discarded.

10. WITHDRAWAL PERIOD(S)

Calves
Meat and offal: 12 days.

Lambs
Meat and offal: 12 days.

Pigs
Meat and offal: 12 days.

Rabbits
Meat and offal: 12 days.

Chickens
Meat and offal: 12 days.
Eggs: Not for use in birds producing or intended to produce eggs for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Store in a dry place
Protect from light.

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 milk according to directions: 2 hours.

12. SPECIAL WARNING(S)

Special warnings for each target species:
Severely diseased animals can have a decreased appetite and water consumption. If necessary the concentration of the veterinary medicinal product in the drinking water should be adjusted to make sure that the recommended dosage is being consumed.

Pigs, pre-ruminant calves, pre-ruminant lambs, rabbits: The uptake of medication by animals may be altered as a consequence of illness. In case of insufficient water uptake, animals should be treated parenterally instead using a suitable injectable product prescribed by the veterinarian.

Special precautions for use in animals:
Due to the likely variability (time, geographical) in susceptibility of bacteria for potentiated sulfonamides, occurrence of resistance of bacteria may differ from country to country and even from farm to farm, and therefore bacteriological sampling and susceptibility testing are recommended. It is particularly of importance for *E. coli* infections where high percentages of resistance are observed.

Use of the product should be based on susceptibility testing of bacteria isolated from the animal. If not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

Use of the product deviating from the instructions given in the Summary of product characteristics (SPC) may increase the prevalence of bacteria resistant to sulfadiazine and trimethoprim and may also decrease the effectiveness of combinations of trimethoprim with other sulfonamides due to the potential for cross resistance.

Official, national and regional antimicrobial policies should be taken into account when the product is used.

To avoid deterioration of the kidneys due to crystalluria during treatment, it should be ensured that the animal receives sufficient amount of drinking water.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
This product contains sulfadiazine, trimethoprim and macrogol, which can cause allergic reactions in some people. Hypersensitivity to sulfonamides may lead to cross reactions with other antibiotics. Allergic reactions to these substances may occasionally be serious.

People with known hypersensitivity (allergy) to sulfonamides, trimethoprim or macrogol should avoid contact with the veterinary medicinal product.

This veterinary medicinal product may cause skin or eye irritation. During the preparation and administration of medicated drinking water, skin and eyes contact has to be avoided. Wear personal protective equipment consisting of waterproof gloves and safety glasses when handling the veterinary medicinal product. In case of accidental contact with the eyes or skin, wash the affected area with plenty of water, and if skin rash occurs, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

This veterinary medicinal product may be harmful if ingested. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy, lactation or lay:
Laboratory studies in rats and rabbits have shown evidence of teratogenic and foetotoxic effects.

Do not use during pregnancy and lactation, or lay.

Interaction with other medicinal products and other forms of interaction:
Do not administer concomitantly with coccidiostats or veterinary medicinal products containing sulfonamides.

Do not associate with PABA (para-aminobenzoic acid).

Sulfamides potentiate anticoagulants action.

Overdose (symptoms, emergency procedures, antidotes):
Sulfonamides overdose causes renal toxicity. In this case, the administration of the product has to be stopped.

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

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

Pack sizes:
Cardboard box containing one bottle of 100 mL, 250 mL, 500 mL or 1 L.
Container of 2 l, 5 l, 10 L.

Not all pack sizes may be marketed.