

Divergent position on a CVMP opinion on an Article 35 of Directive 2001/82/EC, as amended

Suanovil 20 and associated names, Captalin and associated names and generic products thereof (EMA/V/A/086)

On 12 September 2012, Germany presented to the European Medicines Agency a referral notification under Article 35 of Directive 2001/82/EC for Suanovil 20 and associated names, Captalin and associated names, and generic products thereof. The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to give its opinion on the indications, dosing regimens and withdrawal periods in cattle, calves and pigs, in order to ensure efficacious treatment and lower the risk of development of antimicrobial resistance to spiramycin and also to harmonise the withdrawal periods in cattle and pigs for the concerned products.

It is the opinion of the undersigned is that the indication: "Treatment of acute clinical mastitis in lactating cows caused by *Staphylococcus aureus* strains sensitive to spiramycin" cannot be accepted.

On the benefit,

Spiramycin is a macrolide antibiotic that is active against Gram-positive bacteria. Its mean residence time after i.m. administration is significantly longer in milk than in plasma and its concentrates up to 50 times higher in the mammary gland than in plasma (Ziv G & Rasmussen F 1975 *Distribution of labeled antibiotics in different components of milk following intramammary and intramuscular administrations. Journal of Dairy Science* 58 938–946; Franklin A et al., 1986 *Concentrations of penicillin, streptomycin, and spiramycin in bovine udder tissue liquids. American Journal of Veterinary Research* 47 804–807; Sanders P et al., 1992 *Pharmacokinetics of spiramycin after intravenous, intramuscular and subcutaneous administration in lactating cows. Journal of Veterinary Pharmacology & Therapeutics* 15 53–61). In lactating cows, it has a good distribution throughout the udder after i.m. administration for extended periods of time, e.g. >36 hours (Ziv G 1980 *Drug selection and use in mastitis : Systemic versus local therapy. Journal of the American Veterinary Medical Association* 176 1109–1115; Sanders et al., 1992).

On the risk,

There are major concerns that such veterinary medicinal products will not have adequate efficacy on field cases of acute mastitis due to *Staphylococcus aureus*. The main evidence used in support to maintain an "acute" mastitis indication is an experimental *S. aureus* mastitis study in cows (Ramage, 2013). A *S. aureus* challenge strain with a MIC of 4 µg/ml to spiramycin was used and cows were treated according to the authorised dose regime at 2 x 30 000 IU/kg in 24 hours interval in comparison with a placebo group. According to the Committee there were several deficiencies in the study design, but it was concluded that the efficacy of Suanovil 20 in acute *S. aureus* mastitis was demonstrated when injected i.m. twice at 30 000 IU/kg in 24 hours interval to lactating cows.

However, there appears to be a major difference between the results of the experimental study and field cases reported in the scientific literature. For example, mastitis cure rates reached after i.m.-injection of spiramycin in field cases of bovine *S. aureus* mastitis have been reported as poor: 20% (Pyörälä SH, Pyörälä EO, 1998 *Efficacy of parenteral administration of three antimicrobial agents in treatment of clinical mastitis in lactating cows: 487 cases (1989-1995). J Am Vet Med Assoc.*

212(3):407-12.), 33% (Taponen et al., 2003 *Efficacy of targeted 5-day combined parenteral and intramammary treatment of clinical mastitis caused by penicillin-susceptible or penicillin-resistant Staphylococcus aureus*. *Acta Vet Scand.* 44(1-2):53-62.) and <50% (Jánosi S et al., 2001 *Bacteriological recovery after intramuscular or intracisternal spiramycin-based drying-off therapy*. *Acta Vet Hung.* 49(2):155-62.), even though the frequency of treatments was higher than proposed for Suanovil 20 (3-5 injections instead of 1-2). The Committee further reports on a parallel study performed by Renard et al (1996). Renard et al. tried to predict the clinical efficacy of spiramycin in bovine mastitis from a PK/PD-model which was based on killing kinetics of spiramycin determined *in vitro* and on the pharmacokinetic properties of the compound in milk. Furthermore, a parallel clinical experiment performed by Renard et al. demonstrated that the *in vivo* success rates were much less than predicted from PK/PD-modelling. For example, with a single injection of 30 000 IU/kg only one out of 6 infected udder quarters was actually cured. The predicted cure rate for two injections at this dose rate in 48 hours interval interval was 3 out of 6 quarters. Reasons for the disparity between experimental and field cases could include:

- Bacteriostatic nature of spiramycin.
- Different spectrum of *S. aureus* field cases (e.g. acute, subclinical, and chronic).
- Different *S. aureus* strains involved in field cases.
- Potential immune cell inhibition from spiramycin (Hoeben D et al., 1997 *Influence of antimicrobial agents on bactericidal activity of bovine milk polymorphonuclear leukocytes*. *Vet Immunol Immunopathol.* 56(3-4):271-82.).

Similar poor efficacy of spiramycin against *Staphylococcus aureus* is backed up by other studies (Davey PG et al., 1987 *Comparative efficacy of clindamycin, erythromycin and spiramycin against Staphylococcus aureus in the rat croton oil pouch model*. *J Antimicrob Chemother.* 20(5):705-12.). Furthermore, adequate efficacy has only been shown in the scientific literature for spiramycin against *S. aureus*, when combined with other bactericidal antibiotics (Tarabla H, Canavesio V 2003 *Prevalence of intramammary infections by major pathogens at parturition in dairy cows after intramuscular antibiotic therapy at drying-off: a preliminary report* *Journal of Dairy Research* 70:233–235; Schällibaum M et al., 1981 *Treatment of chronic subclinical staphylococcal mastitis in lactating cows by administration of high doses of spiramycin*. *Schweiz Arch Tierheilkd.* 123(6):277-92.).

With these facts, the CVMP concluded to restrict the *S. aureus* indication to “acute” cases only, primarily based on an experimental challenge study provided. It is the opinion of the undersigned this restricted indication still represents a serious concern to animal health because the experimental study has not been confirmed by field studies. Maintaining this indication will likely lead to treatment failures. Treatment failures of acute *S. aureus* mastitis (a major contagious mastitis pathogen) will lead directly to chronic *S. aureus* mastitis, for which there are no efficacious treatment options and there is a need to cull the cow from the herd.

Furthermore, the same proposed indication states “...*Staphylococcus aureus* strains sensitive to spiramycin”. To state the indication as for strains sensitive to spiramycin is potentially misleading. For example, the interpretation of MICs for spiramycin is complicated because of the absence of valid veterinary medicinal breakpoints. Therefore, one marketing authorisation holder proposed to use a breakpoint of ≤16 µg/ml for susceptible bovine mastitis pathogens and a breakpoint of ≥32 µg/ml for resistant strains. However, this is not confirmed by scientific data.

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