Divergent position on a CVMP opinion on an Article 34 referral of Directive 2001/82/EC for

Baytril 10% oral solution and associated names (EMEA/V/A/067)

Introduction

Active substance: Baytril 10% oral solution contains, as an active substance, enrofloxacin, a fluoroquinolone carboxylic acid derivative. Fluoroquinolones are concentration dependent antimicrobials that are part of the quinolone group of synthetic antibiotics. It is the halogenated chemical groups (fluorine) that, when compared to quinolones, confer the increased effectiveness of enrofloxacin. This entails a broader spectrum of bactericidal activity across Gram + and Gram - bacterial types, including pathogenic and commensal bacteria within the same treated animals; this combined effect encompasses a high selection pressure in terms of exposure and dissemination of antibiotic resistance.

Enrofloxacins are indicated in veterinary medicine to be used responsibly.

Pharmaceutical form: Baytril 10% oral solution is administered via drinking water to rabbits.

Current situation: Baytril 10% oral solution is currently authorized for use in rabbits only in one member state for treatment of infectious diseases due to *Pasteurella spp*. and *Bordetella spp.*, and bacterial enteritis from Gram-negative organisms with a dose regimen of 5 mg/kg for 3 to 5 days and a withdrawal period of 15 days.

CVMP proposal: The CVMP proposes to reduce the indication of Baytril 10% oral solution to the treatment of infectious diseases due to *Pasteurella multocida*, and bacterial enteritis due to *E.coli* at a different dose regimen of 10 mg/kg for 5 days and a withdrawal period of 15 days.

Rabbit production: Rearing conditions which contribute to a high risk of resistance selection, development, and dissemination

Rabbits exhibit natural coprophagic behaviour and at the physiological level, this contributes to a caecotrophic effect since rabbits are hindgut fermenters. In terms of antimicrobial resistance pressure, this normal behaviour is expected to contribute to a cycling of sub-therapeutic enrofloxacin re-absorption in and amongst rabbits. Such cycling is considered as a complicating factor in this species for assessment of veterinary drug use. How it specifically impacts on resistance selection, development, and dissemination is, however, not clear.

Rabbits are mammals in close contact with their off-spring during the farrowing and lactating/suckling periods. Maternal contact facilitates vertical and horizontal transmission of bacteria (pathogenic and/or commensal). Does and finishing rabbits can be affected clinically by diseases such as pasteurellosis; therefore, oral treatments are potentially administered to both does and finishing rabbits. The commensal flora of does, where treated with enrofloxacin, would undergo selection pressure. Does may then transmit resistant bacteria to their off-spring. Though such resistance transmission has not been studied specifically in rabbits, it is documented in swine production (Belloc *et al.,* 2005) and expected to be present in rabbits since both swine and rabbits rear their young in close contact over a period of several weeks.

Potential use of enrofloxacin in nursing/lactating does creates other complicating factors. The ease

of penetration of enrofloxacin into milk should be considered when treating lactating does that continue to nurse (Fraile LJ, Martinez C, Aramayona JJ, *et al.* 1997). Therapeutic concentrations of enrofloxacin are reached in milk following a dose of 7.5 mg/kg bodyweight (Aramayona JJ, Mora J, Fraile LJ, *et al.* 1996). Furthermore, elimination of enrofloxacin is significantly less in neonates until at least sixteen (16) days of age compared with that in adult rabbits. The long-term effects on these neonates have not been fully assessed including the dissemination of resistant strains. Once the off-spring is separated from the does, treatments with enrofloxacin administered at the finishing stage may result in a specific selection of resistant bacteria population present in the digestive tract of rabbits. A vertical transmission of bacteria in poultry production, though it can occur, is limited. Different generations are physically separated and good hatching practices keep the egg, developing offspring and the mother hen independent of each other.

Therefore, it is expected that Baytril 10% oral solution would lead to increased selection pressures over time after repeated use in a given rabbit farm.

Current use of oral enrofloxacin in EU rabbits and level of resistance to enrofloxacin

At present, EU food rabbit production is concentrated in Mediterranean countries such as Italy, Spain and France which together account for 76.4% of total production. Although the total rabbit meat production is minor compared to other food animal species, by no means does this lessen the importance of rabbits to the food animal industry and thus rabbits deserve the same full consideration as all other food animal species in terms of risk.

Oral enrofloxacin for use in rabbits is authorised in some European countries. Some data on resistance exist: the sensitivity of enrofloxacin to *E. coli* isolated in rabbits is high in France (90%, RESAPATH 2009) whereas it is less sensitive in Member States using enrofloxacin-containing products authorised for rabbits *(e.g.* in Italy with respectively 78% in Camarda 2004, 62% in Pisoni 2007, 56% in Grilli 2009). The same pattern is observed for *Staphylococcus aureus* (89% sensitive in France versus 70% in Italy). However, in the latter publications there is insufficient information on methodology, and in particular on sample selection and interpretation criteria, to ascertain whether data are comparable or not.

It is noted that the risk characterization is incomplete.

The consequences of any antibiotic use on the level of resistance of pathogenic bacteria are widely acknowledged. On commensal and zoonotic bacteria, the consequence of use of oral enrofloxacin on the level of resistance is also assumed to be present, though it currently is not quantified.

Enrofloxacin in rabbits: Insufficient clinical data

The data provided in support of the claims “treatment of *Pasteurella multocida* and treatment of bacterial enteritis due to *E.coli”*, are not robust; neither the proposed dosage of 5 mg/kg/day, nor the proposed indications have been justified by the currently available data.

<u>*Pasteurella multocida* indication</u>:

The studies provided to support this indication were minimally reported and not performed according to current standards. Challenge studies suggested that a dose of 10 mg/kg would be more effective than the proposed 5 mg/kg, especially when treating acute cases of Pasteurellosis in rabbits. Moreover, there is a consensus that non-wild type *pasteurella* have good susceptibility towards enrofloxacin, but also first line antibiotics. For instance, RESAPATH (2009 data) shows that the susceptibility of *Pasteurella multocida* to first line antibiotics used to treat pasteurellosis is very good,

varying from 93% (for sulfonamides + trimethoprim), to 97 and 98% (for oxytetracycline and tilmicosin). The extra activity of enrofloxacin (up to 100%) is considered to be minimal when compared to other antibiotics and is not expected to be of any great clinical benefit.

E. coli indication:
Although enrofloxacin appears to be efficacious against experimental infections of *E. coli*, doses higher than the proposed dose rate for treatment of rabbits of 5 mg/kg were used in the experimental infection models. Therefore, the dose is not considered to be sufficiently justified. In addition, no clinical field study has been presented; therefore, this indication in this species has not been demonstrated.

It can be concluded that neither the current posology (5 mg/kg – 3-5 days) nor the CVMP proposed one (10 mg/kg – 5 days) are sufficiently substantiated for 2 reasons:

- The proposal from CVMP to increase the dosage to 10 mg/kg for 5 days with the commitment/condition to provide contemporaneous studies is not endorsed. For a highly critical antibiotics, it is not acceptable to anticipate the results.
- The proposed dosing regimen stems from Hipralona Enro-S, another authorised oral enrofloxacin in rabbits. it is deemed questionable if reference can be made to this dosing regimen which was justified and demonstrated for pasteurellosis only.

Specific incentives and risks linked to the pharmaceutical form

Oral enrofloxacins are incentives for the use in rabbit farms because the oral route of administration will facilitate the herd-level use of this antimicrobial when compared to injectable products. Indeed, treatment in water is easier for the farmer in terms of workload.

Oral enrofloxacin represents a high risk of selection of resistance because:

- It is acknowledged that the first risk posed by oral administration is immediate exposure to the intestinal flora. This risk may be amplified in this coprophagic species.
- Oral administration means mass treatment. Indeed, the treatment might be administered in drinking water to an entire batch of animals because, in most cases, only one drinking water system is available for each batch. Both diseased and healthy rabbits will be exposed, both as a treatment and prevention of spread of disease. Treatment is not likely to be individual.
- With administration in drinking water, there is variability of uptake among individual rabbits, especially sick rabbits; hence, each individual animal will not always receive the exact recommended dose. In severe cases of respiratory disease, it is probable that the water intake is reduced for the majority of rabbits in the batch. Here, underdosing with a concentration--dependent antibiotic will lead to higher selection pressure of resistance.

Benefit:risk

There are a number of incentives when oral enrofloxacins are used in rabbits farms that lead to increased use, and, given the particularities of rabbit farming, it is expected that Baytril 10% oral solution would lead to increased selection pressures over time.

The consequences of any antibiotic use on the level of resistance of pathogenic bacteria are widely acknowledged. On commensal and zoonotic bacteria, the consequence of use of oral enrofloxacin on the level of resistance is also assumed to be present, though it currently is not quantified.

Neither the current posology (5 mg/kg – 3-5 days) of Baytril 10% oral solution in rabbits nor the CVMP proposed one (10 mg/kg – 5days) are sufficiently substantiated.

Enrofloxacin being a critically important antibiotic (CVMP, 2011), the clinical benefit as demonstrated is not considered to outweigh the risks of resistance selection.

Consequently, despite the fact that rabbits are a MUMS species, the benefit:risk for the harmonization across the EU for this product and therefore inclusion in the SPC of the target species, rabbits, for countries where it is not yet authorized, is considered as unfavorable.

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References:

Ararnayana JJ, Mara J, Fraile LJ, *et al.* 1996 Penetration of enrofloxacin and ciprofloxacin into breast milk, and pharmacokinetics of the drugs in lactating rabbits and neonatal offspring. *Am J Vet Res* 57(4): 547-53.

Belloc, C. 2005. Effect of quinolone treatment on selection and persistence of quinolone-resistant *Escherichia coli* in swine faecal flora. J. Appl. Microbiol., 99, 954-959.

Camarda A. et al. Proceedings - Virulence Genes And Antimicrobial Resistance Patterns Of Enteropathogenic Escherichia Coli From Rabbits In Southern Italy - 8th World Rabbit Congress – September 7-10, 2004 – Puebla, Mexico - http://world-rabbit-science.com/WRSA-Proceedings/Congress-2004-Puebla/Papers/Pathology/P-Camarda.pdf

CVMP, 2011**. CVMP strategy on antimicrobials 2011-2015**
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109137.pdf

Fraile LJ, Martinez C, Aramayona JJ, *et al*. 1997 Limited capacity of neonatal rabbits to eliminate enrofloxacin and ciprofloxacin. *Vet Q* 19: 162-7.

Grilli G et al. - Profili di resistenza agli antibiotici ed individuazione di integroni di classe 1 e 2 in Escherichia coli isolati da lagomorfi. Osservazioni preliminari - Giornate di Coniglicoltura ASIC 2009 - http://www.asic-wrsa.it/documenti/giornate2009/11_Grilli.pdf

Pisoni A.M et al. -Osservazioni sulla sensibilità agli antibiotici di alcuni patogeni isolati da conigli da carne- Giornate di Coniglicoltura ASIC 2007 - http://www.asic-wrsa.it/documenti/giornate2007/12_Pisoni.pdf

RESAPATH 2009 *(French network on veterinary pathogens)* - http://www.resapath.anses.fr/SITE_RESAPATH_WEB%5Cuploadfiles%5Cfiles%5CDocuments%5C2009%20RESAPATH%20Annual%20Report%20GB%20%5Bid_doc=167%5D.pdf