EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Focus group meeting the pilot project on dose optimisation of established veterinary antibiotics in the context of SPC harmonisation

Target Animal Safety

Focus group meeting, 12 October 2018, London

Presented by Helen Jukes
CVMP vice-chair, AWP chair

Approach for addressing risks to target animal safety due to changes in the dosing regimen

Data available

- Proprietary TAS studies (VICH GL 43)
- Proprietary clinical trials – field safety data (GCP)
- Proprietary dose determination studies, non-target laboratory animal safety studies
- Pharmacovigilance – PSURs
- Published literature: Journals, FoI reports, grey literature

Underlying principles

- PK/PD → increased dose ‘mg/kg’; duration of treatment generally unchanged
- Increased dose → reduced margin of safety (MOS)
- Additional risk mitigation measures may be possible
- Acceptable MOS depends on the ‘benefit-risk’ for the product

- Data can be pooled from different products providing that differences in formulation, pharmaceutical form and route of administration are taken into account

Seven steps

Progress through the steps until sufficient reassurance of the MOS for the new dose is obtained

Step 1: Review of classical TAS studies for products with same pharmaceutical form and route of administration

Aim

- Confirm target organs and toxicity profile for the active substance
- Estimate the MOS for the improved dose

Systemic, reproductive and local tolerance

Step 2: Safety in the target population - review of clinical/field studies for products with same pharmaceutical form and route of administration

- Safety in diseased animals
- Evidence of sensitive sub-populations

Step 3: Post-marketing pharmacovigilance

- Eudravigilance database

Step 4 (if needed): Published literature; Authorisations in 3rd (VICH) countries; SPCs

- May also include general safety for the active substance

Step 5: Conclude on the MOS for the increased dose for the pharmaceutical form and route of administration

Step 6: Product-specific considerations

- Excipients
- Indications

Step 7: Conclude on the benefit-risk for the dose increase for each specific product

Findings from case study 1

Amoxicillin in drinking water for treatment of SRD

(dose doubled from 10-20 mg/kg/d to 40 mg/kg/d)

AEs: Hypersensitivity. Gastrointestinal disturbances (microbiota). Rarely hepato- and renal toxicity.

Simple excipient formulations.

Available proprietary studies not to current GLP standards but, coupled with published and grey literature, sufficient evidence to support safety of the dose increase.

Findings from case study 2

Oxytetracycline injections to treat BRD

(dose remained within the original range of possible doses, but for some 10% formulations there would be an increase; for some 20% formulations the requirement for a 2nd injection at 36-48 h is new)

AEs: Renal toxicity, lower MOS

TAS studies showed that OTC → local injection site reactions → restrict the injection volume according to the formulation (SPC directions to be followed)

Thank you for your attention

Further information

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