NOTIFICATION TO THE EUROPEAN MEDICINES AGENCY OF A REFERRAL UNDER ARTICLE 82 OF REGULATION (EU) 2019/6

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This notification is a referral under Article 82 of Regulation (EU) 2019/6 to the European Medicines Agency (the 'Agency') made by Germany:

A range of veterinary medicinal products, all containing the same active substance	Veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection.
Target species	Cattle, horses, sheep, goats, pigs, dogs and cats
Route of administration	Intramuscular or subcutaneous
Active substance	Procaine benzylpenicillin
Applicant(s)/marketing authorisation holder(s)	To be identified

Detailed explanation of the matter involving Union interest:

This referral procedure concerns the treatment durations of veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection for use in food producing animal species and companion animals.

Procaine benzylpenicillin is a salt of benzylpenicillin which belongs to the group of natural, narrow-spectrum penicillins (β-lactamase-sensitive penicillins; AMEG category D). Veterinary medicinal products containing procaine benzylpenicillin have been widely used for decades in cattle, horses, sheep, goats, pigs, dogs and cats for the treatment of a variety of infections caused by bacteria susceptible to benzylpenicillin and affecting e.g. the urinary, respiratory or reproductive system.

During the recent decentralised procedures IE/V/0397/001/DC, DE/V/0337/001/DC, IE/V/0416/001/DC and IE/V/0649/001/DC submitted in accordance with Article 13(1) of Directive 2001/82/EC, it has been noticed that the treatment durations for procaine benzylpenicillin products are disharmonised across the EU.

Germany noted that for a number of veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection authorised in the EU a treatment duration of 1 to 3 days or 3 to 5 days with one injection every 24 hours is recommended. Procaine benzylpenicillin products authorised by means of purely national procedures in Germany require mostly a treatment duration of at least 3 days (injection every 24 hours), but for some products a treatment 2 days longer than clinical signs is recommended. This heterogeneity is further underlined by veterinary medicinal products that are authorised for a maximum treatment duration of 3, 4 or 5 days, while other products require a minimum treatment duration of 3 or 4 days.

Based on the available data, a treatment duration of 1 to 3 days may not be appropriate to treat all claimed indications effectively. Published literature (e.g. Smith *et al.* 1998; Scott *et al.*, 2013; Ordell *et al.*, 2016)[1] suggesting that 3 days is the minimum treatment duration necessary, but longer treatment durations may be required, adds to the serious concern that a treatment duration of

3 days or less could be insufficient. This is further supported by the fact that benzylpenicillin is a time-dependent antimicrobial substance, i.e. the driving factor for pharmacokinetic/pharmacodynamic (PK/PD) analysis is %T > MIC (fraction of time during which the concentration exceeds the MIC).

Furthermore, a number of publications[1] underline that a prolonged treatment duration of 5 days or longer for procaine benzylpenicillin may be necessary, e.g. to treat infections caused by *Leptospira* spp. (Ross and Rentko, 2000), *Clostridium* spp. (Greene, 1990; Staempfli and Oliver, 1999), or *Erysipelothrix rhusiopathiae* (Kunesh, 1999).

Therefore, Germany considers it important that the treatment duration is sufficiently long to ensure an effective use of veterinary medicinal products containing procaine benzylpenicillin as a single active substance and to avoid an unnecessary risk of antimicrobial resistance development.

On the other hand, Germany also considers it necessary to limit the maximum treatment duration to the therapeutically required minimum in order to avoid any unnecessary exposure of the animals to antibiotics, reduce the risk for adverse effects and prevent any unnecessary entry of penicillin into the environment leading to an avoidable risk of exposure for the environment as well as for the consumer.

In conclusion, Germany considers that a review of the treatment duration for veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection is necessary to ensure a safe and effective use of those veterinary medicinal products and to avoid an unnecessary risk of resistance development, for the environment and the consumer.

Questions to be addressed by the Agency's Committee for Veterinary Medicinal Products (CVMP):

The CVMP is requested to review the available data for veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection for food producing species and companion animals and to provide an opinion on the following questions:

- Considering the available data, what dosage regimen (i.e. dose rate and treatment duration in each species and for each indication) is required for the concerned veterinary medicinal products, to ensure optimal efficacy, to limit the risk of resistance to procaine benzylpenicillin and to minimise the risks for the target animal safety, environment and consumer?
- In case the need for a change to the dosage regimen is identified, then consideration should be given to establishing an adequate withdrawal period for food producing species and to potential impact on the target animal and environmental risk assessment of the concerned products. Any potential impact on the AMR risk to public health should also be taken into account.

In view of the elements described above and the necessity to take action at EU level, Germany considers that it is in the interest of the Union to refer the matter to the Agency and requests that the CVMP gives its opinion under Article 82 of Regulation (EU) 2019/6 as to whether the marketing

authorisations for the above-mentioned products should be maintained, varied, suspended, or withdrawn.

Signed [redacted] Date 08-Feb-2022

[1]References:

Billy I. Smith, G. Arthur Donovan, Carlos Risco, Ramon Littell, Colin Young, Larry H. Stanker, Jessie Elliott. Comparison of Various Antibiotic Treatments for Cows Diagnosed with Toxic Puerperal Metritis. Journal of Dairy Science Volume 81, Issue 6, 1998, 1555-1562.

Greene C., Appel M., Straubinger R. Lyme borreliosis in: Infectious diseases in the dog and cat (Greene C.). WB Saunders Company, Philadelphia, 2. edition: pp 282-293, 1990.

Kunesh J. Swine Erysipelas in: Current Veterinary Therapy 4. Food Animal Practice (Howard, J.). WB Saunders Company, Philadelphia (USA), 4. Edition: pp 395-396, 1999.

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Scott P.R. Clinical presentation, auscultation recordings, ultrasonographic findings and treatment response of 12 adult cattle with chronic suppurative pneumonia: case study. Ir Vet J. 66(1): 5, 2013.

Staempfli H., Oliver O. Tetanus, Botulism and Blackleg in: Current Veterinary Therapy 4. Food Animal Practice (Howard, J.). WB Saunders Company, Philadelphia (USA), 4. Edition: pp 383-386, 1999.