Divergent position to a CVMP opinion on the procedure under Article 82 of Regulation (EU) 2019/6

For veterinary medicinal products containing procaine benzylpenicillin as a single active substance presented as suspensions for injection

Procedure number: EMEA/V/A/145

This referral procedure includes veterinary medicinal products containing procaine benzylpenicillin (as a single active substance) presented as suspensions for injection for cattle, pigs, sheep, goats, horses, dogs and cats for intramuscular/subcutaneous route of administration. The procedure was started with the aim to a review of duration of treatment for veterinary medicinal products to ensure a safe and effective use of those veterinary medicinal products.

Based on the data presented in the course of the procedure and the CVMP Assessment Report I hereby present my divergent position to the CVMP opinion:

According to the scope of the referral, CVMP was asked to review the dosage regimen (dose rate and duration of treatment), and in the notification submitted by the German National Competent Authority it was specifically highlighted that **a review of the treatment duration** of the concerned veterinary medicinal products is necessary to ensure safe and effective use of these veterinary medicinal products.

With respect to the aim of the referral the CVMP agreed to restrict the **minimum treatment duration to 3 days and the maximum treatment duration to 7 days** for all VMPs, which are subject to referral and administered at 24-hour intervals. VMPs characterised as "long acting" (dosing interval with possibility of the second dose administration at the interval of 72hrs) will not be affected by this decision.

In addition, the CVMP agreed as well on:

- minimum dosage limit to 10 mg/kg bw in cattle, sheep, goats and pigs,
- minimum dosage limit to 12 mg/kg bw in horses,
- minimum dosage limit to 20 mg/kg bw in dogs and cats, and
- deletion of 48h dosing intervals in all target animal species except horses and for horses if dosages are below 20 mg.
- further risk management measures including the deletion of some indications and several target pathogens and the inclusion of warnings in the product literature to indicate resistance or decreased susceptibility in specific target pathogens.
- rewording (or deleting, where relevant) indications and target pathogens which are not in line with the current nomenclature or current scientific standard.

The undersigned CVMP member would like to express the following comments towards the CVMP decision:

General comments:

The CVMP member highly values the effort and extensive work performed by rapporteur´s team as well as co-rapporteur´s team. Within the procedure also a number of Marketing Authorisation Holders (MAHs) of the concerned products replied to defined questions (two step) and delivered and commented the data (unfortunately data submitted differs in quality and some MAHs did not reply in a valid manner to justify sufficiently dosing schedules, based on which their VMPs have been authorised). The CVMP member would like to highlight, that based on Regulation (EU) 2019/6, Article 58 (4). "**The marketing authorisation holder** shall ensure that the summary of product characteristics, package leaflet and labelling **is kept up to date with current scientific knowledge**." The same was previously valid according the Directive 2001/82/EC. The CVMP member therefore recommends to ask Marketing Authorisation Holders for submitting (within certain time schedule) additional information that allows setting of evidence-based and fully justified dosing schedules (dose - frequency - duration) and also safe withdrawal period considering "worst case scenario" to ensure consumer safety fully.

Comment towards efficacy and risk mitigation targeted on AMR:

Being aware of the time dependency of the bacterial killing effect of penicillins as well as the fact that timely start of the treatment affects significantly the growing phase of the bacterial pathogens, involved as causative agents of the disease defined in the indications, the **CVMP member supports** setting the **minimum duration of the treatment for 3 days for VMPs**, whose composition is designed and adequate for dosing schedules at 24-hour intervals only.

With respect to ensuring efficacy of the VMPs concerned, the ability to reach/exceed the pathogen MIC for sufficiently long part of the 24h interval of dosing is of importance as well as timely start of the treatment.

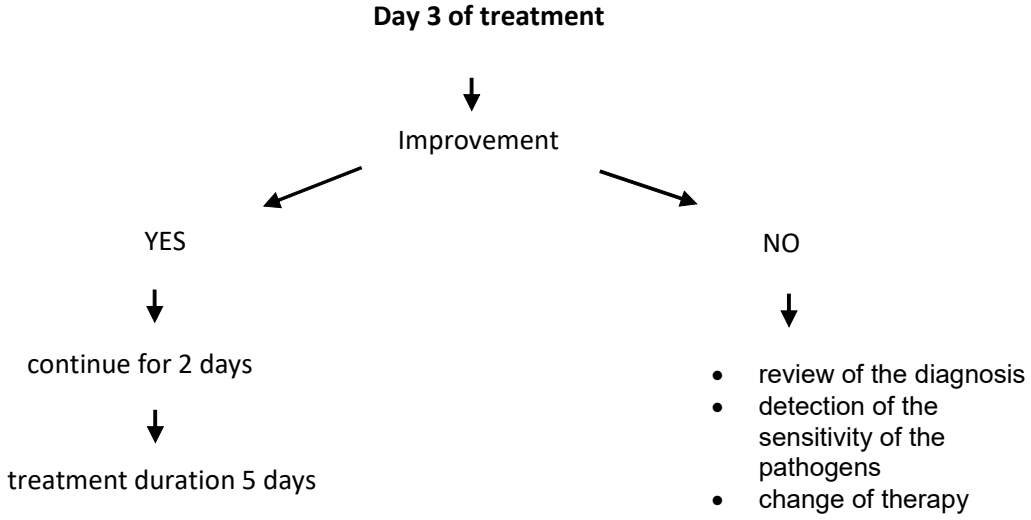
The wording of SPC section 3.9/4.9 of the VMPs concerned in this referral was reviewed to identify discrepancies in treatment duration. In summary, the vast majority of the VMPs are authorised for treatment duration of 3 and 3-5 days, only one VMP is authorised for treatment duration of 7 days. A minority of VMPs is authorised with undefined or unclearly defined treatment duration and 4 of these VMPs are authorised nationally in Germany, in which, in my opinion, treatment duration is expressed in a comprehensive manner – see below:

To illustrate that e.g. in four nationally authorised VMPs any unclear statement for treatment duration could be found, the English wording of the point 3.9/4.9 is presented:

At least 3 treatments at intervals of 24 hours.

If there is no clear improvement of the disease state after 3 treatment days, a review of the diagnosis and, if necessary, a change of therapy should be carried out. The detection of the sensitivity of the pathogens is recommended. After clinical symptoms have subsided, treatment should be continued for another 2 days.

In my opinion this instruction is clearly written, meaning, that the important decision point is the **3rd day** of treatment:



The terms used in the instruction which probably caused confusion/misunderstanding are:

"clear improvement of the disease" and "clinical symptoms have subsided"

According to the CVMP member's (medical) understanding, the two terms express essentially the same clinical situation as clear improvement of the disease may indicate, that the clinical signs can still be present but milder or the clinical signs resolve completely.

Generally, there can be a variety of clinical signs exhibiting various grade (e.g. mild, moderate, severe) depending on diagnosis, e.g. cough, loss of appetite or lameness … and in clinical practice, a clinical sign such as lower appetite may be the only symptom of the disease and may resolve completely very rapidly (e.g. lower appetite may resolve completely after one day of treatment). Other clinical signs need more time to improve (e.g. moderate cough may need a couple of days), but it does not mean, that the treatment is not effective. So, the wording of the abovementioned instruction has to be considered in the context of practise and specific situations arising from it.

Therefore, the proposal is to revise the wording of the section 3.9/4.9 of those VMPs, where confusion regarding treatment duration may arise with using the most appropriate terms to express the treatment duration clearly (see also proposals in CONCLUSION).

Regarding treatment duration this CVMP member would like to propose amendments of SPC section 3.9/4.9 **to allow flexibility within the range of the treatment defined** and **to avoid extension of the treatment duration to 7 days (or longer) becoming standard in <u>all</u> VMPs** concerned in this referral.

Moreover, recently, from human medicine come signals, that in uncomplicated infections in first line care, 5-day treatment with penicillins is sufficient for the majority of infections where etiological agent is susceptible and target tissue is accessible for the concentrations necessary to exceed MICs of the bacteria of concern (in fact it means that concentrations above MIC will remain approx. 6 days after the first administration, based also on exact MP composition). The exception with need of longer treatment exists in human medicine (e.g. *Erysipelothrix rhusiopathiae*, injectable for a longer time but in specific regimen (especially in recurrent infections) and with long acting <u>benzathine</u> benzylpenicillin, or orally dosed phenoxymethylpenicillin 5 - 7 days). There is a

growing body of evidence coming mainly from the human medicine pointing to the fact that long duration of treatment, which is not justified may be associated with risks, which have to be taken into consideration in the benefit risk analysis.

IN CONCLUSION as for the scope of this referral - duration of treatment,
the CVMP member supports:

- setting of the **minimum duration at 3 days** (VMPs with dosing interval 24h);

- keeping **the maximum duration of the treatment as already authorised** (those VMPs with maximum duration of the treatment set on **5 days or 7 days (1 VMP), where already authorised**);

- setting **maximum duration at 5 days for VMPs with unspecified or unclearly expressed treatment duration** - difficulties exist for such cases as for withdrawal period setting (please refer below to the comments related to consumer safety);

- once the **maximum duration is set at 5 days for VMPs with unclearly expressed treatment duration**, revising and precising the English/national languages wording of the text reflecting the above explained common approach in assessment of the clinical improvement and treatment algorithm is proposed;

- **amending of advice** (SPC point **3.9**) by exact wording as proposed below:

3.9 Administration route and dosage of the VMPs concerned (amended text in *italics*):

<The appropriate treatment duration should be chosen based on the clinical needs and individual recovery of the treated animal, but should not exceed 5 days (*7 days in one VMP, where already authorised*). Consideration should be given to *the timeliness of the treatment initiation,* accessibility of the target tissue and characteristics of the target pathogen.>

The undersigned CVMP member needs to express concerns related to the setting of the maximum treatment duration **to 7 days** (= prolongation of the total treatment duration in all VMPs, where has not been authorised yet) as it has **not been linked with any robust evidence** supporting the need for the upper limit of treatment duration range to **7 days. Moreover, the decision for the upper limit to be extended to 7 days will affect all authorisations** concerned by this referral **in the whole EU.** It is therefore recommended, rather to keep the maximum duration of treatment for individual VMPs as currently authorised and based mostly both on the data within the dossiers submitted or long-time broad use and experience and to allow veterinarians to critically assess individual cases of individual conditions to decide.

Risks (unjustified longer duration of administration = more antimicrobials consumed, consumer safety issue) linked to the setting of the upper limit of the range to 7 days without any data (= unjustified treatment duration extension) for all authorised VMPs of concern this referral (with different quantitative and qualitative compositions of the active ingredient and excipients) across the Europe cannot be omitted and **seem to outweigh the benefits.**

The CVMP member would like to highlight, that further effort is needed to ensure availability of authorised VMPs based on benzylpenicillin for the sake of effective national antibiotic policies as the first line VMP available for reasonable and justified treatment, using evidence-based approach and

therefore asks for an active approach of MAHs in line with Regulation (EU) 2019/6, with support of the European Commission programmes to find resources supporting in the sake of the public interest of ensuring essential antimicrobials useful and available on the market. MAHs consortia might be supported by such programmes to generate necessary data. Finally, it should be as well highlighted, that although it is acknowledged that PK/PD models can be used in the dose determination phase of the pre-clinical part, they have severe limitations and results generated by such modelling must be supported by dose confirmation studies and finally also sufficiently robust clinical (field) trials, once dosing schedules will be proposed to be authorised/subject of variation or referral. The reason behind is that the new dosing schedule (under this referral treatment duration) will be then used in clinical practice for the whole EU in a harmonised manner. In addition, the products may also be used as active comparators for development of new products. Thus, both referral decisions and any marketing authorisation should be based on robust scientific evidence, which is the only option how to avoid future errors in the system and ensure trust of stakeholders as well as public in the regulatory system. Unfortunately, up to now, no robust and validated model covering dose - frequency and especially duration is ready for use to set the right dosing for clinical indications, as the clinical infections are affected by a range of pathogen (e.g. virulence factors, diversity and variability of strains participating in the infection, differences of pathogens based on site of infection etc.), host (e.g. stress factors, genetics, health status / immune system interactions etc.), and environmental factors (e.g. co-infections), and only proper pre-clinical and clinical data can provide a robust evidence for safety and efficacy of the formulation under evaluation.

Another complication in this referral procedure is the fact that PK and PD data of sufficient quality obtained from target animal species and pathogens relevant for indications are not available for the performance of modelling.

Comment towards consumer safety and withdrawal period setting

The treatment duration in the submitted residue depletion studies, regarding residues in meat and offal as well as in milk, was **five consecutive days at a maximum** and therefore **none of the residue depletion studies submitted brings data adequate for robust establishment of withdrawal periods** regarding the proposed **treatment duration of up to seven days**.

CVMP has proposed and finally agreed that the withdrawal periods (for meat and offal) will be extended by 2 days based on the presumption that available evidence does not point towards a systemic accumulation of procaine penicillin G after repeated injections and no extra accumulation is therefore expected if the treatment duration is harmonised to 7 days. CVMP concluded as well that there is no need to extend the withdrawal period for milk in the case of extending the total treatment duration from 3 or 5 to 7 days.

The CVMP member does not agree with the outcome of the referral procedure for the following reasons in relation to serious deficiencies and lack of residue depletion data for 7 days duration of treatment, which do not allow setting of undoubtfully sufficient and safe withdrawal periods to protect consumer safety:

- A potential serious risk for the health of consumers is not excluded as the withdrawal periods (for meat and offal and milk) established by this approach taken by CVMP can lead to insufficiency of withdrawal periods.
- Regarding possible insufficiency of the withdrawal periods for milk a possible impact on human microbiome is not excluded. It has to in particular be highlighted that bovine milk is a sensitive commodity, which is very important for the nutrition of infants and children and

in this respect the withdrawal period for milk should be confirmed by depletion studies carried out for the worst case scenario of administration and proof that data would be relevant for the evaluation of the withdrawal period by statistical/alternative approach. (Sharing of data/ investments between (bio)equivalent products may be a possible approach, which could be developed at EMA level).

- Based on the depletion studies containing datasets for milk, which are available in one dossier submitted by a MAH, the trend of increasing of concentration of residues in milk during treatment has been detected. Although the authors (Li *et al.,* 2018) did not indicate systemic accumulation after repeated administration, it was explicitly mentioned that diseased animals´ certain conditions may lead to different distribution and elimination patterns of penicillin G. Therefore, the setting of a withdrawal period for milk should be judiciously considered. The CVMP used the pharmacokinetic data (half-life) in plasma to set the withdrawal period for milk (for duration of treatment of 7 days) and no safety factor was used. This approach for establishment of the withdrawal period is not agreed internationally and there is great uncertainty that the milk withdrawal period may be insufficient. Therefore, in this case the "precautionary principle" approach (Article 7, Regulation (EC) No 178/2002) should be followed and a safety span should be used to establish the withdrawal period. It should be once more noted that such decision will affect all authorisations for the whole EU of VMPs subject of this referral with updated maximum 7 days duration of treatment, which should be considered as the "worst case scenario" of the treatment duration. Based on recognised and valid EMA CVMP guidelines, the withdrawal period should be established based on the studies submitted for the individual VMPs representing the "worst case scenario" of administration of the product, which is not the case for even only one product within the whole referral procedure.

- It cannot be excluded that prolonged treatment duration might, in a formulation dependent way, affect residues´ levels of the active substance and excipients in edible tissues and milk. In this point of view the studies of residues depletion are recognised international "gold standard" that finally allows to establish withdrawal periods for veterinary medicinal products intended for food producing species. Such depletion studies should be performed with individual VMPs, which is of importance especially for suspensions for injections administered intramuscularly or subcutaneously. Performance of residue depletion studies and confirmation that these studies are representative/cover "worst case scenario" for the whole dosing schedule (dose-frequency-total administration duration-volume in injection site) is recommended by valid CVMP scientific guidelines. Breaking these rules, creates inconsistency in the documents approved by CVMP (GLs vs this referral outcome). It is therefore necessary to highlight, that both GLs and CVMP Opinion for this referral procedure should follow same principles leading to establishment of the safe, evidence-based withdrawal period, ensuring safety for consumers (including the most sensitive population - children).

- In most of the old studies, the tissue with the highest residue concentration was the injection site. However, there are also studies demonstrating highest measured concentrations in liver or fat as well as two residue studies (one with a short-acting (state-of-of-the-art) and one with a long-acting formulation), in which the residue concentrations reported in kidneys exceeded those in injection site. Concentrations in liver, fat or kidney may be higher in reality after 7 days of treatment (tissues, not plasma are discussed from the perspective of the consumer safety) and deriving adapted withdrawal periods might be necessary.

- In terms of injection site residues, there will be an increase in the number of injection sites (the product will be administered for up to 7 days), leading to possible crossover between injection sites and an increase in the injection site /surrounding of injection sites concentration of residues as the recommendation does not regulate the proper administration of the product. A critical assessment of the worst-case scenario of number of administrations (number of injection sites/day) was not performed, especially in heavy animals (cattle, horses, sows) for 7 days administration. This can have possible impact on the safety of consumers because the neck/or back are standard food commodities.
- For subcutaneous route of administration one depletion study for cattle and no residues study for sheep is available, although more products are authorised also for subcutaneous administration. In this point of view the relevance of the developed "new withdrawal period" for non-existing data is questionable.
- For goats and horses, no residue depletion studies were submitted during the referral procedure and depletion studies for treatment durations of 7 days for major species (cattle/pigs/sheep) are not available, therefore extrapolation of withdrawal periods for treatment of 7 days is not feasible, following the established rules for extrapolation. Setting a precedent with such an extrapolation may have consequences for future authorisation procedures.
- Input data are heterogenous and inconsistent, moreover coming from different depletion studies (for meat and offal as well as for milk). Products, for which studies are available, differ as for dose administered (6-30 mg/kg bw procaine benzylpenicillin), differ in the treatment durations (range of 1-5 consecutive days at 24h intervals), so these facts on their own created a high level of inconsistency. The design of the majority of the studies is not fully in line with the current valid guidelines and deficiencies were noted, e.g. low of number of animals /groups in the study, weight of inj. site/ surrounding, sampling times (e.g. one point study involved) and insufficient or no validation of data. Mixing the data gained by different methodologies (where historical studies, based on standards valid at the time of their performance, including differences in analytical methods and their sensitivity and accuracy) and with different quality of the data should be avoided to set any withdrawal period after the proposed increase of the duration of the treatment. Moreover, no input data are available for any product for 7 days treatment duration in major food producing animal species/category.
- Possible violation of EU rules on MRLs (in tissues and milk) once the newly adjusted dosing schedule with duration max 7 days cannot be ruled out, as the approach agreed by CVMP does not provide sufficient verification of the accuracy of the "new withdrawal periods". A possible negative impact on consumer safety can be expected in connection with a violation of MRLs. Economic impact on farmers or veterinarians cannot be excluded as well. Farmers and veterinarians are obliged by Regulation (EU) 2019/6 to follow conditions of authorisation (Art 106/1) and if the withdrawal period established in the SPC/PL would not be sufficient, it is questionable who is responsible for residues exceeding the MRLs.
- Disharmonisation of withdrawal periods: if the CVMP general approach "plus 2 days" is used, different withdrawal periods continue to be set for same individual product, as withdrawal periods differ currently across the EU (e.g. "product A" withdrawal period is 8 days (+ 2 days) in Czechia, the same "product A" withdrawal periods is 14 days (+ 2 days) in Germany). By this approach the disharmonisation will therefore continue further. The currently valid withdrawal periods differ among MSs based on the fact, that different studies were submitted at the time of the first approval, different datasets were available

for individual agencies once they authorised the VMP in the past, and different safety margin has been established, etc.).

- Not all concerned MAHs submitted detailed residue depletion studies and, in some cases, only summaries were provided lacking parts of the essential information needed for a thorough assessment. **It led to lack of certain data relevant to the evaluation and the conclusion of the referral could be therefore biased.**

IN CONCLUSION, as for the withdrawal period and consumer safety,
the CVMP member would like to express the following summary:

From the consumer safety perspective, according to the opinion of the undersigned CVMP members it is not possible to conclude that keeping the same withdrawal period **for milk** for VMPs with maximum 5 days duration also for VMPs with prolonged treatment duration to max 7 days without any data submitted and assessed will ensure both sufficient safety for consumer and will not lead to the violation of MRLs in milk, which could have economic consequences for farmers and veterinarians.

As for the **meat and offal**, establishing withdrawal periods artificially by assumptions without any robust scientific grounds by simple addition of 2 days is, together with the approach for milk not consistent with the rules and principles valid in the EU for establishment of safe withdrawal periods.

The only possibility for keeping the consistency of rules and decisions is keeping the maximum duration of the treatment and withdrawal period as already authorised, and only for the products which were authorised and are on the market with unspecified/unclearly defined maximum period of the treatment to establish maximum duration on 5 days.

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