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SCIENCE MEDICINES HEALTH

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Questions and answers on describing adverse events in the product information (summary of product characteristics (SPC) and package leaflet (PL))

These questions and answers (Q&A) were developed by the Pharmacovigilance Working Party (PhVWP-V) of the Committee for Veterinary Medicinal Products (CVMP) following the recent revision of the Quality of Review Document (QRD) template (version 9) to aid the writing or update of section 3.6 of the summary of product characteristics (SPC) and section 7 of the package leaflet (PL) to describe adverse events (AEs). This document aims to provide guidance for improving consistency and harmonisation for product information (PI) writing or updating, whilst it is acknowledged that a pragmatic approach should be taken to balance resource needed for this and the added value of any revised text. These principles were agreed by the Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMDv) and CVMP at their March 2022 meetings. Following a request from CMDv this document was further revised in July 2022 to include reference to 'Undetermined' adverse event frequency which may be used exceptionally (see Q&As 4, 7 and 8) and to provide further clarification of Q&A 1.

1. Which adverse events (AEs) should be listed in the product information (PI)?

Only AEs which have a potential causal association with the veterinary medicinal product (VMP) in question or same/similar VMPs, after recommended or unknown use of the product (i.e. excluding off-label use) should be listed in the PI.

These AEs are reported either from spontaneous or non-spontaneous reporting systems or sources. The potential causal association is determined based on findings from data submitted with the initial marketing authorisation application or/and through analysis of pharmacovigilance data and taking into account current scientific knowledge.

2. How should AEs be described in the PI?

AEs should be described using VeDDRA[1] low level terms (LLTs). VeDDRA is the agreed standard terminology for AE reporting in veterinary pharmacovigilance. The use of VeDDRA LLTs in the PI

[1] Veterinary Dictionary for Drug Regulatory Activities; Combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products (EMA/CVMP/PhVWP/10418/2009) and Guidance notes on the use of VeDDRA (EMA/CVMP/PhVWP/288284/2007).

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helps reporters use the correct terminology when reporting AEs. This, in turn, facilitates standardisation and harmonisation of the description of similar AEs across the Union. This will ultimately benefit and improve signal detection and evaluation of AEs. When clarification of VeDDRA terminology for veterinarians and animal owners is required, additional information can be annotated in footnotes under the adverse event table.

3. What if there is no appropriate VeDDRA LLT available to describe the AE?

When an appropriate VeDDRA LLT is not available to describe an AE, the marketing authorisation holder (MAH) should select the VeDDRA term that most closely reflects the AE, using an appropriate LLT synonym. The VeDDRA terminology is revised and improved regularly. Therefore, a request for a new LLT can be also made to the VeDDRA subgroup (via the process outlined in the VeDDRA Call for comments) as it is preferable that an appropriate VeDDRA LLT exists for all listed AEs to enable standardised and harmonised reporting of AEs within the Union.

4. How should the frequency of AEs be expressed?

The frequency of AEs should be described using the categories described in the QRD template and ranked so that the most frequently occurring clinical signs are listed first. Five standard frequency categories have been retained to maintain international harmonisation and to minimise confusion when comparing frequencies of AEs in PIs worldwide.

In each frequency category, AEs should be grouped in accordance with their VeDDRA system organ classes (SOC). In the examples below, LLTs are grouped under the SOC: Application site disorders and the SOC: Digestive tract disorders:

e.g. Application site alopecia, Application site lesion;
Vomiting, Gastric ulcer, Haematemesis.

Some VeDDRA LLTs in the VeDDRA standard list have associated text in parentheses providing VeDDRA coding guidance. This text should not be included in the PI e.g. 'Abnormal vision (see also impaired vision)' should be stated as 'Abnormal vision' in the PI.

NB. When updating older PIs where, for example, the frequency categories have not been used, e.g. 'vomiting occurs sometimes', the applicant should refer to the data on which the original PI statements were based and apply the frequency categories accordingly. Only when it is impossible to define a frequency for a specific AE, an additional frequency category called 'Undetermined frequency (cannot be estimated from the available data)' can be used. As soon as it becomes possible to define a frequency, the AE should be moved to the appropriate frequency category (see question 7).

5. Which frequencies should be published on the PI?

AEs that are observed in pre-authorisation studies (e.g. safety and/or efficacy studies) or post-authorisation (reported through the pharmacovigilance system) which have a potential causal association with the VMP should be included in the PI.

For AEs that are observed both pre-authorisation and post-authorisation, the highest frequency observed should be used in the PI.

6. Why is no longer any distinction made between AE frequencies related to controlled studies and spontaneous reporting?

The data source (controlled studies versus spontaneous reporting) of the AE is not considered useful information that can improve the safety or efficacy of a VMP. The requirement to indicate

the data source was removed with revision of the QRD template to version 9 to enable AE information to be presented more clearly and simply. This approach is generally considered as a simplification for users of VMPs.

7. Can I update the PI to change the frequency of AEs?

Yes, the frequency of AEs may be updated in the PI. If post-authorisation experience indicates reporting of an AE at a higher frequency compared with that observed in pre-authorisation safety/efficacy studies and described in the PI, it is strongly recommended to revise the frequency of that AE in the PI to reflect the higher frequency. Revision of PIs to reflect lower frequencies of AEs ('downgrading') is generally not permitted unless substantiated by appropriate scientific data from controlled studies.

When an AE has been put into the frequency category 'Undetermined frequency (cannot be estimated from the available data)' (see questions 4 and 8), it is expected that the MAH updates the frequency as soon as one can be defined.

8. What are the requirements related to AEs and AE frequencies for reference products and generics?

For initial authorisation of a generic, the AEs and frequency of active-substance related AEs in the PI of the reference medicinal product applies exactly i.e. 'copy and paste'. Where no frequency is expressed for a certain AE in the PI of the reference product, this AE can be included in an additional frequency category called 'Undetermined frequency (cannot be estimated from the available data)' in a row at the end of the table (see question 4).

Post-marketing experience should also be reflected in a consistent manner, so that when the PI of a reference product is updated with new information on active-substance related AEs, that of the generic should also be updated, and vice-versa. Other AEs, possibly arising from differences in excipient composition of the generic compared to the reference product, may be added to, but not replace, those on the product information, unless appropriate supporting data have been provided.

9. Is it a requirement to use a table to list AEs in the PI?

In section 3.6 of the SPC, it is a requirement to tabulate AEs. Tables present AEs in a clear and simple format and improve readability for product users.

The template includes approaches for further simplifying the tabular presentation of AE information e.g. presenting tables by animal species, using annotations in footnotes and deleting unused frequency rows.

In section 7 of the package leaflet (PL), tabulation is not a requirement, but the use of a single column table is encouraged. It is appreciated that there are practical constraints with lack of space and narrow line width when generating readable PLs. Irrespective of the format used, the information and sequence within section 3.6 of the SPC should be maintained in the PL.

10. How should additional information related to AEs be presented in the PI?

Additional information relating to AEs should be kept to a minimum and should be relevant for the VMP user and prescriber. The use of footnotes under the adverse event table to annotate information is preferred to provide a clearer and cleaner tabulated list of AEs. It is also permitted to place very brief additional information in parentheses after the relevant VeDDRA LLTs, but care should be taken to not affect the readability of the table.

11. What additional information related to listed AEs is permitted in the PI?

The use of additional information should be restricted to information that supports AE management or improves understanding of use of the VMP. Additional information on specific clinical signs may be added beneath the table of listed AEs. As stated previously, additional information should be kept to a minimum and should be relevant for the VMP user or prescriber, where appropriate.

Examples of permitted additional information:

- advice on whether and at what point to consult a veterinarian;

- specific measures to be taken – or to be avoided - by the animal owner or by the veterinarian, i.e. administration of an antidote, removing of a collar, washing of an application site;

- mention that vomiting will occur at the beginning of the treatment and will resolve as the treatment continues (e.g. cabergoline in dogs);

- expected severity, duration and any other precise and factual information providing further description of clinical signs, derived from the analysis of AE reports e.g. lameness (1-3 weeks following booster vaccination), vomiting (generally lasting 2 days), injection site oedema (up to 10 cm), to express duration, numeric values are preferred;

- the wording of the PI should clarify when an LTT may be associated with several kinds of AEs and pathophysiological mechanisms e.g. diarrhoea should be clearly associated either with anaphylaxis or to an enterokinetic action of an active substance or both if reported for both types of AEs.

Examples of additional information that should be avoided:

- imprecise statements: 'of short duration', 'transient', 'temporary';

- statements on frequency of AEs: 'occasionally', 'sometimes', 'in most cases';

- statements on the outcomes of the clinical signs: 'self-limiting' or 'spontaneous resolution' are generally not permitted unless accompanied by specific supporting evidence or timeframe.

The general guiding principle is that undefined or less precise statements on duration, severity and outcome of the AEs should be avoided unless considered concretely useful to aid the decision-making of the prescriber or VMP user.

References

- European Medicines Agency (2021) Quality Review of Documents veterinary product-information annotated template (English) version 9
- Committee for Medicinal Products for Veterinary Use (CVMP) (2021) Combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products (EMA/CVMP/PhVWP/10418/2009)
- Committee for Medicinal Products for Veterinary Use (CVMP) (2021) Guidance notes on the use of VeDDRA (EMA/CVMP/PhVWP/288284/2007)