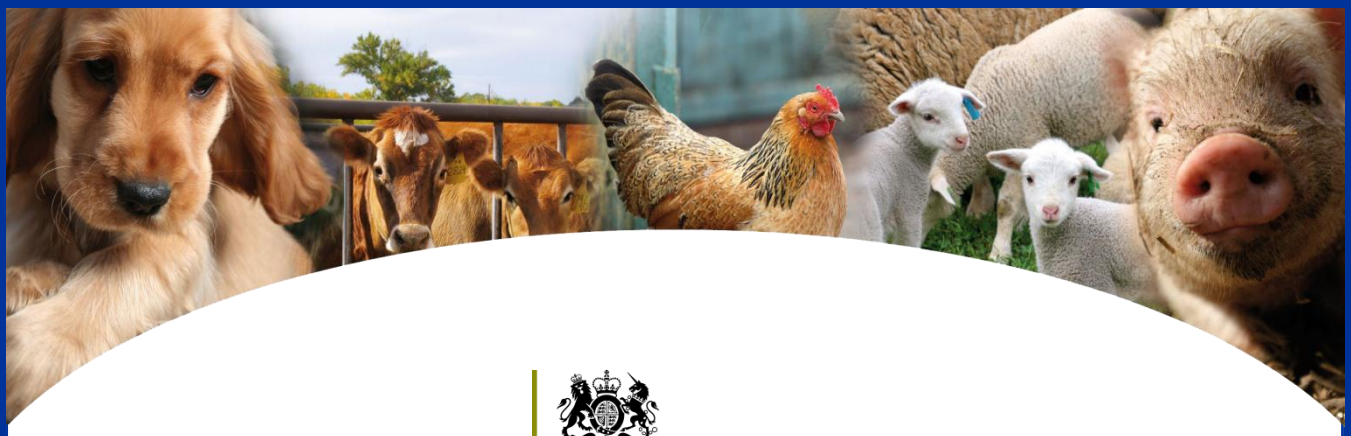

Veterinary Medicines Directorate

VETERINARY MEDICINES GUIDANCE NOTE

No 11

PHARMACOVIGILANCE

GUIDANCE ON ADVERSE EVENTS

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QUICK START GUIDE

This Veterinary Medicines Guidance Note (VMGN) is aimed primarily at Marketing Authorisation Holders (MAHs) and is intended to provide guidance on pharmacovigilance and the reporting of adverse events.

The quick start guide is a summary of the provisions of the Veterinary Medicines Regulations (VMR), detailed information is found in the body of the guidance note.

MAHs have a legal obligation to record any information which they receive about adverse events involving their veterinary medicinal products. Adverse events associated with veterinary medicines include adverse reactions in animals which occur after use in accordance with the advice on the label or following off-label use, and suspected lack of expected efficacy after use in accordance with the label, and adverse reactions in humans following exposure to a veterinary medicine or a treated animal.

MAHs must report any animal adverse events involving death, permanent disability, life-threatening illness or congenital abnormality, and all human reactions, to the relevant competent authority within 15 days of their receipt of the information. For adverse events which occur in the UK, the Veterinary Medicines Directorate (VMD) is the relevant competent authority.

The scope of pharmacovigilance includes incidents arising from exposure to a veterinary medicine present in the environment, and issues concerning the validity of withdrawal periods.

MAHs must include reports of all adverse events and other pharmacovigilance issues involving a veterinary medicine in the Periodic Safety Update Report (PSUR) for the product. PSURs should be submitted to the VMD at the intervals specified in legislation unless the VMD has agreed a deviation from the standard cycle, for example to allow participation in the Heads of Medicines Agencies' PSUR Worksharing Initiative. A scientific evaluation of the risk-benefit balance of the veterinary medicine is an important aspect of a PSUR, which should also include an estimation of exposure to the veterinary medicine and the incidence of adverse events associated with it.

The VMD should be informed immediately about any concerns relating to the safety of a veterinary medicine arising from pharmacovigilance or resulting from quality issues.

FURTHER INFORMATION

For more information on pharmacovigilance please contact the VMD's pharmacovigilance team on 01932 338427 or alternatively contact VMD reception on 01932 336911 and quote "pharmacovigilance".

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Introduction

1. This is one of a series of Veterinary Medicines Guidance Notes (VMGNs) explaining the requirements under the Veterinary Medicines Regulations (VMR). The VMR are revoked and replaced on a regular basis, so the references to them should be read as referring to the ones that are currently in force. Therefore, the date and number of the Statutory Instrument are not shown in this VMGN. This VMGN will be updated as necessary and the date of the most recent update is shown on the front cover.

2. The VMR set out the UK controls on veterinary medicines, including their manufacture, advertising, marketing, supply and administration. VMGN 1 Controls of Veterinary Medicines, which is published on the Veterinary Medicines Directorate's (VMD) website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx provides basic information about the scope of the Regulations and the requirement for Marketing Authorisations (MAs).

   The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problems are known as pharmacovigilance. Veterinary pharmacovigilance concerns the safety of veterinary medicines used for the treatment, prevention or diagnosis of disease in animals. This note concerns the provisions for veterinary pharmacovigilance in the UK. Further information, including guidance on reporting an adverse event (AE), can be found on the VMD website (www.vmd.defra.gov.uk) under Pharmaceutical Industry.

3. The VMR primarily place reporting obligations on marketing authorisation holders (MAHs). Under the VMR, failure to comply with the pharmacovigilance reporting requirements is an offence. As the competent authority in the UK, the VMD has established a dedicated team of experts to discharge its pharmacovigilance responsibilities. The pharmacovigilance team monitors adverse events to veterinary medicinal products (VMPs) in all animal species and in humans.

4. Guidance on pharmacovigilance is published by the European Commission in *The Rules governing medicinal products in the European Union, Volume 9B – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use,* which can be found on http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm. Complementary guidance to Volume 9B can be found on the EMA website at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000170.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002ddca&jsenabled=true. This VMGN is intended to supplement the European Commission guidance and should be read with it.

Qualified Person for Pharmacovigilance (QPPV)

5. The VMR require that each MAH must have permanently and continuously at their disposal an appropriately qualified person responsible for pharmacovigilance. The term "appropriately qualified" is not defined in the VMR. However, the VMD considers that any person who is capable of competently performing the following specific duties would meet the requirements:

- establish and maintain a system that ensures that information about all adverse events that are reported to the MAH is collected and collated in order to be accessible at least at one point within the Community;

- ensure that any request from the Secretary of State for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a VMP is answered fully and within any time limit imposed. Such information may include details of the volume of sales of the VMP concerned and, if available, details of prescriptions;

- provide the Secretary of State with any other information relevant to the evaluation of the benefits and risks relating to a VMP, including appropriate information on post-marketing surveillance studies.

6. Additionally, the QPPV may fulfil their duties for the whole of the EU and must reside in the Community. If the QPPV lives outside the UK, the MAH holds the legal responsibility for the UK obligations placed on the qualified person. The MAH also holds ultimate responsibility if the QPPV does not fulfil their duties.

7. The MAH must ensure that it is able to receive and investigate reports of adverse events that occur in the UK. An easily accessible telephone line must be available during working hours to take details of adverse events and to provide advice to product users. Alternative arrangements should be made for non-working hours.

8. The VMR do not specify how the QPPV discharges these responsibilities. In the absence of such guidance the VMD takes the view that he or she may delegate these functions to suitably qualified colleagues on a temporary basis or for management reasons. Within a company, one person may be the QPPV for all products or different people may handle different authorisations. Similarly, one person may be the QPPV for a product throughout the Community or there may be different ones for each national MA. All applications for national MAs should be accompanied by the following information:

- the name, business address(es) and contact details of the QPPV;

- the Curriculum Vitae of the QPPV, including the information relevant to their role (qualifications, training and experience) and a description of the back-up procedure to apply in their absence;

- the job description of the QPPV identifying the activities and responsibilities relevant to the role of QPPV.

9. The pharmacovigilance premises, records and documents used by a MAH may be inspected by the authorities at any time.

Adverse Events

10. The Commission guidance has adopted the term “adverse event” used in *VICH Guideline 24* instead of “adverse reaction”. (VICH is the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products).
An adverse event is any observation in animals, whether or not considered to be product-related, that is unfavourable and unintended and that occurs after any use of a veterinary medicine. Adverse events associated with veterinary medicines include adverse reactions in animals which occur after use in accordance with the advice on the label or following off-label use, suspected lack of expected efficacy after use in accordance with the label, and adverse reactions in humans following exposure to a veterinary medicine or a treated animal.

11. Two further situations are included in the scope of pharmacovigilance. These are:

- Adverse effects in animals of non-target species, humans or plants through exposure to a veterinary medicine present in the environment.

- Levels of veterinary medicine residues in tissues or food products of treated food producing animals above the maximum residue levels when the recommended withdrawal period of the given veterinary medicine has been respected.

12. Different types of reaction are defined as follows:

- A serious adverse event is an adverse event which:

    - results in death;

    - is life-threatening;

    - results in significant disability or incapacity;

    - is a congenital anomaly/birth defect;

    - results in permanent or prolonged signs in the animals treated.

  Life-threatening in this context refers to a reaction in which the animal was at risk of death at the time of the reaction.

- A human adverse event is a reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine.

- An unexpected adverse event is an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics (SPC).

Reporting Requirements for Adverse Events

Animal Adverse Reaction

13. The VMR require MAHs to record and report all adverse events to their products of which they become aware.

14. Non-serious adverse events should be reported in the relevant product's next PSUR, as described in paragraphs 33 to 42.

15. All serious adverse events should be reported electronically. EudraVigilance Veterinary (EVVet) is the European system for the electronic exchange, processing and evaluation of adverse events related to veterinary medicines. Reporting in EVVet may occur via a Gateway or using the EudraVigilance Veterinary Web Reporting Module (EVWEB). Further information about the EVVet system is given in the Commission guidance. Details of how to register with EVVet can be found on the EVVet website at http://eudravigilance.emea.europa.eu/veterinary/register.html. Tutorials on getting started and sending reports are also available to download at http://eudravigilance.ema.europa.eu/veterinary/Tutorials.html.

16. The correct use of the Unique Worldwide Case Registration Number is essential to avoid the creation of duplicate reports. The number should be a compilation of 'Country code - MAH or Competent Authority ID - Report number'. Each component should be separated by a hyphen.

    - The country code is the country of the primary source of the report.

    - The MAH or Competent Authority ID is a unique abbreviation or code for the sender organisation provided at the time of registration with EVVet by the registration team at the European Medicines Agency (EMA).

    - The report number is the sender organisation's case number.

    The Unique Worldwide Case Registration Number is assigned to the case by the first sender organisation, and must then remain unchanged in any subsequent transmission of the case report, such as a follow-up, regardless of whether the follow-up is made by the original sender or a different sender.

17. The Commission guidance provides advice on particular types of reports. However the classification of a report as a "serious" adverse event is often a matter of judgement, and some examples of non-fatal adverse events which are clinically serious and should therefore be expedited to the VMD are given in Annex 1. If doubt exists as to the seriousness of the event, the VMD pharmacovigilance team should be consulted, or a report submitted as for a serious adverse event.

18. In addition to a narrative description of the adverse event, all reports of serious adverse events should include a causality assessment using the "ABON" code (A - probable, B - possible, O - unclassifiable/insufficient data, O1 - Inconclusive, N - unlikely). A list of presenting signs should also be included, using terminology from the Veterinary Dictionary for Drug Related Affairs (VeDDRA), further details of which can be found on the EMA website via the following link:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000173.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002dea6&jsenabled=true

19. MAHs should report details of all serious adverse events occurring within the European Economic Area (EEA) to the national competent authority (NCA) in whose territory the incident occurred. These reports should be sent to the NCA within 15 calendar days of the MAH becoming aware of the adverse event.

20. MAHs should send reports of serious unexpected adverse events and suspected human adverse reactions occurring outside the EU involving products authorised within the EEA (Third Country reports) direct to the EVVet central database within 15 calendar days of the MAH becoming aware of the adverse event.

Human Adverse Reaction

21. A report of an adverse reaction in a human should include:

- details about the person who experienced the adverse reaction and the VMP involved;
- details of the nature and duration of the exposure to the product;
- information about the method of its administration and the animals being treated.

The occupation or status of the person should also be reported if it is relevant to the exposure, for example a veterinary surgeon, farm worker or pet owner. The personal details of the person who experienced the adverse reaction should not be sent electronically, but their initials and the first two characters of their post code should be provided to facilitate detection of duplicate reports.

Suspected Lack of Expected Efficacy

22. If an authorised product fails to have the expected effect in an animal, it should be reported as a suspected lack of expected efficacy. The assessment of such cases should take the following points into consideration:

- accuracy of diagnosis;
- the claims authorised for the product;
- the storage and handling of the product;
- whether the product was used in accordance with the manufacturer's instructions;
- other factors, such as, hygiene at the time of administration, the influence of stress from handling, and the possibility of immunosuppression.

23. MAHs should report all cases of suspected lack of expected efficacy involving death (including abortion) within 15 calendar days of the MAH becoming aware of the adverse event.

24. Suspected lack of expected efficacy which may indicate a defect in the product or batch should be reported to the VMD immediately. For details on how to report product or batch defects see this link: http://www.vmd.defra.gov.uk/mswd/pbr.aspx

Off-label Use/Misuse

25. Off-label use is the use of a veterinary medicine that is not in accordance with the SPC and includes misuse and abuse of the product.

26. MAHs should report all cases of off-label use involving death (including abortion) within 15 calendar days of the MAH becoming aware of the adverse event.

Reporting Requirements for other Pharmacovigilance Issues

Validity of Withdrawal Periods

27. The VMD should be informed of any cases where residues of an authorised veterinary medicine in tissues or food products of treated food-producing animals cast doubt on the validity of the withdrawal period of the veterinary medicine concerned.

28. Such reports may arise from a number of different sources, for example:

- reports of incidents from farmers or veterinary surgeons, e.g. residues in animal milk found through bulk milk tank screening tests;
- reports from other government agencies following the investigation of residues incidents identified through statutory programmes of surveillance;
- reports of individual incidents from public analysts or food producers who undertake the routine monitoring of foodstuffs;
- reports from doctors or hospitals of cases of ill health in humans suspected of having been caused by residues in food.

29. Reports that cast doubt on the validity of withdrawal periods should normally be included in the relevant product's next PSUR. However, incidents that could compromise food safety or public health should be recorded and reported immediately to the VMD Pharmacovigilance team. If necessary, advice should be sought from the VMD Pharmacovigilance team as to whether an incident should be reported spontaneously or in the next PSUR.

Environmental Problems

30. The following advice is provided as an aid to the reporting of environmental incidents.

31. When an authorised veterinary medicine is alleged to have caused an environmental problem, the MAH should collect as much information as possible including:

- identity of product, i.e. MA number;

- batch number;
- date of use of the product;
- date when alleged environmental problem occurred;
- details of reported problem;
- likely route of contamination;
- evidence that an environmental problem has occurred;
- initial steps taken by the MA holder.

32. Reports of environmental problems arising from the use of a veterinary medicine should normally be included in the relevant product's next PSUR. However, incidents which result in death of vertebrates or invertebrates, or with the potential to cause further environmental damage, should be recorded and reported immediately to the VMD Pharmacovigilance team. If necessary, advice should be sought from the VMD Pharmacovigilance team as to whether an incident should be reported spontaneously or in the next PSUR.

Periodic Safety Update Reports (PSUR)

33. Reports of all adverse events and other pharmacovigilance issues should be submitted in the form of a PSUR for each MA. Data relating to different formulations (either different dosage forms or different strengths) should normally be provided in separate reports. Combined PSURs might be acceptable provided that their format has been discussed and agreed with the VMD before their submission. Following the initial placing on the market i.e. after the first six month period in which sales are recorded, PSURs should be submitted immediately upon request or at the following intervals:

- 6-monthly for the first 2 years;
- annually for the subsequent 2 years;
- thereafter, at 3-yearly intervals.

34. If a veterinary medicine has not been marketed or distributed anywhere in a specific PSUR period, and no adverse events have been observed in any additional trials, an abridged PSUR containing a declaration signed by the QPPV confirming this should be sent to the VMD. The abridged PSUR should include the name(s) and MA number(s) of the product, the name and address of the MAH, the relevant Birth Date of the product, i.e. the European Union (EU) Birth Date (date of the first MA within the EU) of a veterinary medicine or its International Birth Date (date of the first MA for the product granted to the MAH in any country of the world), the chronological order of the PSUR and an estimated date for initially placing the product on the market.

35. If no adverse events have been reported in the period of the PSUR, a nil report should be submitted. This should follow the usual content and format (see paragraphs 37 to 41).

36. PSURs should be received within 60 days of the Data Lock Point (DLP) set according to the appropriate Birth Date, or as agreed between the MAH and the VMD.

37. The Commission guidance provides advice on the structure and content of PSURs. An important aspect of the PSUR is the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR. This provides the basis for a decision as to whether further investigation or changes to the SPC will be necessary.

38. Each adverse event report should include a company case reference number. An NCA report reference number, if known, should also be included, together with any unique Worldwide Case Registration Number.

39. Each adverse event reported in a PSUR should be line-listed. A summary of each incident should be provided and all presenting signs listed using VeDDRA terminology. The conclusions and comments of the MAH should include a causality assessment using the ABON classification (see paragraph 18).

40. In addition to a scientific evaluation of the risk-benefit balance of the veterinary medicine, a PSUR should include the following:

- the volume of the product sold in each calendar year covered by the report, calculated on an annual basis beginning 1 January;
- the number of adverse events for each calendar year of the report;
- the ratio of adverse events to volume of product sold, together with an explanation of the basis of the calculation;
- differentiation of data based on:
    - target species (if the product is authorised for use in more than one species);
    - event type (such as serious, non-serious, human, suspected lack of expected efficacy, unauthorised use or other);
    - the country of origin of the report.

41. If the product is indicated for more than one species, the information listed above should be broken down by species, so far as is practicable based on the estimated conditions of use of the product.

42. The VMD will consider requests from MAHs to amend the periods covered by PSURs in order to achieve harmonisation, providing gaps or overlaps in the data

are avoided. MAHs should be aware that for products concerning other Member States, changes to the PSUR submission cycle might require the submission of a suitable variation application. MAHs are advised to contact each concerned Member State to check for the necessity of a variation, before changing the PSUR cycle.

Release of Information by the MA Holder

43. Concerns arising from pharmacovigilance relating to the safety of a product for the target animal, operator, consumer or the environment should first be notified to the VMD before any information is made public. The VMD should also be informed of safety concerns resulting from quality issues. This includes notification or advice to veterinarians in the event of a product or batch defect, or the withdrawal of a product from the market for safety reasons. Further information about product defects can be found on the VMD website (www.vmd.defra.gov.uk) under Pharmaceutical Industry, Product Batch Recall.

44. It is not intended that this requirement should prevent or restrict the discussion of individual adverse events with the people who reported them or who are otherwise involved with the cases.

Change of MA Holder or Distributor

45. Following the sale of a MA for a veterinary medicine to another MAH, it is recommended that all available pharmacovigilance data for that product should be transferred to the new MAH.

46. If a VMP is distributed by someone other than the MAH, the VMD must be informed by submission of the appropriate variation. There must be suitable pharmacovigilance contracts in place to ensure that the MAH is made aware of all adverse events reported to the distributor, and if the change impacts on the content of the pharmacovigilance system description (DDPS) associated with the product, this will also require a variation.

Pharmacovigilance Obligations of ATC Holders

47. The holder of an Animal Test Certificate (ATC) is responsible for reporting adverse events to the VMD and must name a person responsible for pharmacovigilance in the ATC application form. ATC holders should keep appropriate records of adverse events, including those which are not serious, and report electronically any serious adverse event (i.e. any reaction involving a human or which has caused increased mortality or serious ill-health in treated animals) to any substance authorised by means of the ATC (i.e. test article, control or placebo) to the VMD within 15 days. For further guidance for ATC holders please refer to VMGN 6 Animal Test Certificates which can be found on http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

Exemption Scheme for Pet Animal Medicines (SAES)

48. Manufacturers, importers or retailers of medicines intended for use in minor species under the provisions of the SAES must keep records of all adverse events. These records must be kept for 3 years and should be made available to the VMD on request. Any serious adverse events must be reported to the VMD within 15 days of learning of the reaction. For further information please refer to VMGN 12 Exemption Scheme for Small Pet Animal Medicines which can be found on http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

Further Information

49. Further information is available from the Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3LS - Tel: +44 (0)1932 336911; Fax: +44 (0)1932 336618 or E-mail: VMGNotes@vmd.defra.gsi.gov.uk. Veterinary Medicines Guidance Notes and other information, including details of VMD contacts, can be found on the VMD website (www.vmd.defra.gov.uk).

ANNEX A

EXAMPLES OF SERIOUS NON-FATAL ADVERSE EVENTS BY ANIMAL SPECIES

Examples of Serious Non-Fatal Suspected Adverse Events

by Animal Species

The following are examples of non-fatal suspected adverse events which could be considered to be serious if they occurred in a time relationship with the administration of a veterinary medicine. The list is intended for guidance only.

General Conditions

- Anaphylaxis occurring within a few hours. Clinical signs may vary according to species. See Table 1.
- Blindness (partial, temporary or permanent) in all species.
- Collapse occurring immediately and lasting longer than 10 minutes in all species.
- Convulsions and/or other neurological signs occurring within a few hours in all species.
- Sarcomas at administration sites in cats.
- Severe epileptic fits and lethargy occurring within a few hours in all species.
- Severe respiratory distress occurring immediately in all species.
- Severe pyrexia occurring immediately in all species.
- Severe photosensitisation occurring within a few days in cattle and sheep.
- Severe gastro-enteritis occurring within a few days in all species.
- Severe injection site reactions with systemic involvement or reduced mobility in all species.
- Acute mastitis occurring within a few days in cattle, sheep and goats.
- Acute metabolic disorders, hepatic or renal failure occurring within a few days in dogs and cats.
- Significant reduction in physiological function occurring within one week and lasting for a longer period, e.g. persistent anorexia, circulatory collapse, reduced milk yield, reduced egg production, reduced growth rate, anaemia, blood dyscrasias.
- Birth defects with sequelae, e.g. deafness or blindness, in all species.
- Fish body deformities.

Table 1 - Clinical signs of Anaphylaxis in Different Species

Anaphylaxis is an acute, potentially life-threatening, Type 1 hypersensitivity reaction resulting from the generalised release of potent vasoactive substances from mast cells and basophils.

The clinical signs of anaphylaxis can vary depending on the major so-called 'shock organ' relevant to the species. The table below summarises the differences between species.

Species	Shock Organ(s)	Pathology	Clinical Signs
Dogs	Liver	Hepatic and intestinal engorgement, visceral haemorrhage.	Initially excitement, urticaria, angioedema and pruritus, then vomiting and defecation. Finally collapse, dyspnoea and convulsions.
Cats	Respiratory tract Gastrointestinal tract	Bronchoconstriction, pulmonary haemorrhage, oedema and emphysema, oedema of the glottis.	Initially angioedema and pruritus around the face, then salivation, dyspnoea, vomiting, incoordination and collapse.
Horses	Respiratory tract Gastrointestinal tract	Pulmonary oedema and emphysema, intestinal oedema and haemorrhage.	Initially shivering, sweating and incoordination. Possibly coughing, dyspnoea and diarrhoea. Finally collapse.
Cattle and sheep	Respiratory tract	Pulmonary haemorrhage, oedema and emphysema.	Initially urticaria, angioedema, pruritus and restlessness. Coughing, severe dyspnoea and cyanosis. Also defecation, urination and bloat.
Pigs	Respiratory tract Gastrointestinal tract	Pulmonary oedema and emphysema, intestinal oedema and haemorrhage.	Dyspnoea, cyanosis, pruritus and collapse.

List of Abbreviations

ABON	A, B, O and N system for causality assessment
ATC	Animal Test Certificate
AE	Adverse event
DDPS	Detailed Description of the Pharmacovigilance System
Defra	Department for Environment, Food and Rural Affairs
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EVWeb	EudraVigilance Veterinary Web Reporting Module
EVVet	EudraVigilance Veterinary
ID	Identity
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
SPC	Summary of Product Characteristics
VeDDRA	Veterinary Dictionary for Drug Related Affairs
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMGN	Veterinary Medicines Guidance Note
VMD	Veterinary Medicines Directorate
VMP	Veterinary Medicinal Product
VMR	Veterinary Medicines Regulations

VETERINARY MEDICINES GUIDANCE NOTE

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