



Responsible antibiotic use under the cascade

Summary Position Statement:

UK veterinary surgeons have raised concerns over a perceived tension in balancing the responsible use of antibiotics with the legislative requirement to use a UK authorised veterinary medicinal product (VMP) before applying the cascade.

The VMD supports and encourages the responsible use of antibiotics. Responsible use requires veterinary surgeons to take into consideration not only the most appropriate active substance(s) but also the most appropriate formulation, the posology, the current pattern of resistance in their locality, an awareness of how to reduce selection pressure (considering MICs and clinical breakpoints when available) and related factors (e.g. good biosecurity and husbandry/hygiene, avoiding surgical sepsis etc). If a veterinary surgeon can demonstrate that these steps have been taken, then cascade use of antibiotics is supported.

The VMD therefore considers that it is justified, on a case-by-case basis, to prescribe an antibiotic on the cascade in the interests of minimising the development of resistance, particularly where culture and sensitivity data indicate that a particular antibiotic active substance is effective against a bacterial pathogen and where knowledge of pharmacokinetics indicates that the selected product is likely to be safe and effective for the animal species and condition being treated; i.e. prescription of a narrow spectrum antibiotic on the cascade over a broad spectrum antibiotic that has a specific indication for that condition.

The VMD strongly urges professional bodies, veterinary schools, research institutions and other interested parties, to work together to aid veterinary surgeons by considering options and proposing measures to compile the necessary up-to-date evidence and guidance to enable them to make a more informed choice (based on current scientific finding and peer reviewed data) when prescribing medicines on the cascade. Veterinary surgeons are encouraged to maintain an awareness of guidance already provided by organisations such as the British Veterinary Association (BVA), British Small Animal Veterinary Association (BSAVA), British Equine Veterinary Association (BEVA), Pig Veterinary Society (PVS) and the Responsible Use of Medicines in Agriculture (RUMA) as well as discussions co-ordinated by the European Platform for the Responsible Use of Antimicrobials (EPRUMA), and the Federation of Veterinarians in Europe, (FVE).

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1. Background

- 1.1 Antibiotic resistance poses a significant threat to global human and animal health. Resistant populations exist and persist due to a variety of mechanisms and circumstances. It is accepted that the selection pressure that results from use of an antibiotic influences the rate of development of resistance. Discussion continues with regard to the influence and relationship between resistant organisms in man and in animals, however, it remains true that efforts to encourage responsible use of antibiotics are vital to preserve this therapeutic armoury for humans and animals.
- 1.2 The World Health Organisation (WHO) maintains a list of critically important antimicrobials (CIAs) by applying the WHO developed criteria to rank antimicrobials according to their relative importance to human medicine. The current list is the third revision: http://www.who.int/foodborne_disease/resistance/cia/en/. Fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides have been classified as those of the highest priority. The European Medicines Agency (EMA) is also working in collaboration with EU and international partners on a number of initiatives aimed to limit the development of resistance.
- 1.3 At the time of writing, the ability of veterinary surgeons to prescribe antibiotics is based on professional judgement but must be within the requirements of the Veterinary Medicines Regulations (VMR):

<http://www.legislation.gov.uk/ukxi/2013/2033/contents/made>.
- 1.4 The RCVS code of professional conduct states that veterinary surgeons must prescribe antibiotics responsibly, in a manner that minimises development of resistance.
- 1.5 The VMD supports clinical freedom in the interests of maintaining animal health and welfare but also has a responsibility to protect public health and the environment. However, the dynamic nature of antibiotic resistance has resulted in challenges for veterinary surgeons working within the established VMRs (as legislation is revised at greater intervals than changes in recommended clinical practice).
- 1.6 The VMD has held a number of engagement forums with stakeholders to discuss the challenges to the responsible use of antibiotics, within the current legislative framework. The purpose of this document is to provide an appropriate strategy that promotes and supports the responsible use of antibiotics but, does not compromise public or animal health.

2. The problem as defined by veterinary surgeons

- 2.1 Veterinary surgeons have identified that a conflict arises when trying to balance clinical judgement with legislative requirements. The key issue appears to be the perceived tension in some instances of balancing the responsible use of antibiotics with the legislative requirement to use a UK authorised veterinary medicinal product (VMP) as a first line treatment before applying the cascade.
- 2.2 An increasingly common challenge appears to be situations where there is an authorised veterinary antibiotic that is a CIA and/or is not narrow spectrum (in cases when targeted therapy is indicated); based on the legislative requirements this should be used as a first line treatment, in precedence over an unauthorised non-CIA product. By way of example;
 - 2.2.1 Poultry veterinary surgeons have reported that there are fluoroquinolone containing products authorised for use in turkeys which are therefore used as a first line treatment, despite the existence of narrow spectrum products authorised for use in turkeys in another EU Member State (MS).
 - 2.2.2 In small animal medicine there is a fluoroquinolone containing product authorised for use in “exotic” species which is often used as a first line treatment since it is currently the only antibiotic authorised for use in “exotic” species.

In both of these instances other antimicrobial products may be more appropriate first line choices, in accordance with scientific guidance on the responsible use of antibiotics. As a result, veterinary surgeons are of the opinion that greater clinical freedom in the selection of antibiotic therapy should be supported.
- 2.3 It is recognised that it is not feasible for the pharmaceutical industry to market antibiotics to cover all species and uses (especially minor species or minor uses).
- 2.4 It is not clear to veterinary surgeons why a product that is marketed in another MS is not authorised for use in the UK also.
- 2.5 Finally, it is acknowledged that antibiotic prescribing practices are known to vary between veterinary surgeons depending on experience, information available and degree of risk/responsibility considered acceptable to be taken. It has been reported that in some instances there is an inappropriate reliance on culture and sensitivity test results, without necessarily considering the responsible use of antibiotics (i.e. ensuring targeted treatment and considering the pharmacokinetics of the active substance as well as possible influences of the formulation).

3. VMD considerations

3.1 As previously stated, the availability of VMPs must be balanced with the protection of human health and the environment. This underpins the guidance provided for the VMRs, however it is recognised that this is not without its challenges.

3.2 The current guidance on the use of the Cascade (VMGN No. 13) states that:

In departing from the clinical particulars on the SPC the veterinary surgeon must balance the benefits against the risks of doing so and thus take responsibility for their clinical decision. The potential benefits of using the product are usually obvious but the risks may not be. Risk could relate to the animal, the owner or person administering the product, consumers (where veterinary medicine residues in food might be affected), the environment and even wider public health (for example where increased selection for antimicrobial resistance might be the outcome). Any departure from the SPC must be considered carefully as the advice and warnings given are there for good reason and based on assessed data. To ignore or disregard them without due care and thought would be inappropriate and, if something goes wrong with the treatment, could lay the veterinary surgeon open to litigation.

http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

3.3 The cascade permits veterinary surgeons the clinical freedom, on a case-by-case basis, to prescribe the most appropriate antibiotic for their patient(s). However, as highlighted in paragraph 3.2, when prescribing on the cascade, responsibility must be taken by the veterinary surgeon to ensure the safe and effective use of VMPs.

3.4 A report published by the Federation of Veterinarians in Europe (FVE) found that a number of factors influence prescribing practices amongst practitioners with some differences across Europe:

<http://veterinaryrecord.bmj.com/content/early/2013/09/25/vr.101454.full>

3.5 The decision tree guiding cascade use of VMPs takes into consideration the data gaps when the product has not been assessed by the VMD, or by another MSs' National Competent Authority (NCA) / Regulatory Agency, for use in animals. Formulations may be identical in terms of active substances, however, they can exhibit considerably different pharmacokinetic (PK) profiles. The PK profiles for a formulation can also vary widely between different species (variability may be even greater between ruminants and monogastrics as an example), including between animals and man (e.g. when a human preparation is used in animals). Variability of PK profiles will influence posology thus clinical decision making should be based on the research¹ done by the responsible veterinary surgeon, together with an awareness of the degree of risk being taken when using the antibiotic in question.

¹ In light of the current MIC and clinical end point data that are available from bodies such as the European Committee on Antimicrobial Susceptibility Testing (<http://www.eucast.org>) or the British Society for Antimicrobial Chemotherapy (<http://www.bsac.org.uk>).

- 3.6 It is noted that this clinical freedom is somewhat reduced when treating food-producing species. This is necessary in the interests of protecting public health and the environment (e.g. Maximum Residues Limits must have been set for the substance).
- 3.7 Due to the dynamic pattern of resistance to antibiotics, there is a move within the EU to state on a product's Summary of Product Characteristics (SPC) that the product is indicated for use when the bacteria are sensitive to the active substance(s). Therefore, it follows that although a product may be authorised for the treatment of respiratory disease, it may not be the appropriate treatment to use in a particular case of respiratory disease if the results of culture and sensitivity testing demonstrate that the pathogens are unlikely to be sensitive to the active substance in the authorised antibiotic. In such cases, prescribing an alternative antibiotic in line with the provisions of the cascade would be supported.
- 3.8 The specific indications for which any particular VMP is authorised are based on assessment of the supportive data that are provided by the pharmaceutical company (also known as the Marketing Authorisation Holder – MAH) submitting the Marketing Authorisation application. The design and selection of supporting studies are the responsibility of the MAH and unfortunately, are not necessarily driven by the requirements of practitioners. However, the RCVS code of professional conduct states that veterinary surgeons must prescribe antibiotics responsibly, in a manner that minimises development of resistance.
- 3.9 The VMD does not support the administration of antibiotics for the purpose of prevention of disease (i.e. prophylaxis), except under exceptional circumstances as such practice is not in line with the principles of responsible use. Antibiotics should not be used to compensate for poor hygiene or inadequate husbandry and biosecurity measures.
- 3.10 The VMD does support a principle of recognising the assessment of VMPs by other MSs. However, it should be noted that in instances where the VMP does not hold a Marketing Authorisation (MA) for the UK, granted either on a national-only basis or mutually recognised by a number of MSs in the EU, there may be little or no data available to the VMD about the product (i.e. limited or no information about the quality, safety and efficacy of the product). The VMD has historically approached pharmaceutical companies, on occasion, to encourage them to apply for a UK MA when one of their products is being imported by a significant proportion of veterinary surgeons. However, the pharmaceutical companies are not always necessarily in a position to do so.
- 3.11 Further to this, post marketing authorisation surveillance is necessary to monitor the safety and efficacy of antibiotics in the field. For products that are not authorised in the UK, these data are not always readily available, however if veterinary surgeons commit to reporting adverse events (including suspected lack of efficacy), this would help to better inform those dependant on such information when assessing or prescribing antibiotics.

4. Proposals

- 4.1 The VMD supports and encourages the responsible use of antibiotics. This however, requires veterinary surgeons to take into consideration, not only the most appropriate active substance(s) but also the most appropriate formulation, the posology, the current pattern of resistance in their locality, an awareness of how to reduce selection pressure (considering MICs and clinical breakpoints when available) and adjunctive requirements (e.g. good biosecurity and husbandry/hygiene, avoiding surgical sepsis etc). If a veterinary surgeon can demonstrate that these steps have been taken, then cascade use of antibiotics is supported.
- 4.2 As stated in paragraph 3.9, the VMD does not support routine preventative use of antibiotics.
- 4.3 The VMD considers that it is justified to prescribe an antibiotic on the cascade, on a case-by-case basis, in the interests of minimising the development of resistance, particularly where culture and sensitivity indicate that a particular antibiotic active ingredient is effective against a bacterial pathogen and where knowledge of pharmacokinetics indicates that the selected product is likely to be safe and effective for the species and condition being treated (i.e. a narrow spectrum antibiotic over a broad spectrum antibiotic, in place of one that has a specific indication for that condition).
- 4.4 As stipulated by the VMRs, appropriate withdrawal periods (meat, milk and eggs) must be set with cascade use of VMPs in food-producing species).
- 4.5 It is recognised that it may not be possible for every veterinary surgeon to do the research necessary to satisfy paragraphs 4.1 and 4.3 therefore, the VMD strongly urges the professional bodies, the veterinary schools, research institutions and other interested parties, to work together to aid veterinary surgeons by considering options and proposing measures to compile the necessary up-to-date evidence and guidance to enable them to make a more informed choice (based on current scientific finding and peer reviewed data) when prescribing medicines on the cascade.
- 4.6 It would be of great benefit if such a knowledge base (e.g. a list of essential antibiotics and formulations) was readily accessible to veterinary surgeons and the VMD, as it is likely that some of these antibiotics will need to be imported from other MSs, if there are no appropriate UK authorised VMPs. Such a database would have the potential to reduce data requirements and the timescales for importing necessary antibiotic products. The VMD may also then be able to liaise with the NCAs in other MSs to seek further data to support use of the product.
- 4.7 In instances where a particular product is being imported to fill a demonstrable gap in the market, the VMD will continue to approach MAHs to apply for UK authorisation of their products. Such applications would be subject to the usual data requirements and standards of assessment. For VMPs used in minor conditions and in minor species, alternative routes to obtaining MAs (e.g. Limited Marketing Authorisations) have been made available to promote such products on the UK market.

- 4.8 It should be noted however, that all decisions relating to the regulation of antibiotics will take into consideration the guidance provided by the European Medicines Agency (<http://www.ema.europa.eu>).
- 4.9 Antibiotics will remain subject to prescription in the UK. Due to the increase in internet sales of VMPs, those clients wishing to use internet retailers should be made aware of how to buy VMPs safely (e.g. the VMD Accredited Internet Retailers Scheme). Further to this, owner compliance is crucial to reducing the development of antimicrobial resistance and therefore client education is key.
- 4.10 The VMD will continue to engage with stakeholders to promote the responsible use of antibiotics and discuss specific concerns relating to antibiotic use in veterinary medicine. Veterinary surgeons are also encouraged to maintain an awareness of guidance provided by organisations such as the British Veterinary Association (BVA) and the Responsible Use of Medicines in Agriculture (RUMA) as well as discussions co-ordinated by the European Platform for the Responsible Use of Antimicrobials (EPRUMA), as well as the Federation of Veterinarians in Europe.

References

- British Society for Antimicrobial Chemotherapy - <http://www.bsac.org.uk>
- British Small Animal Veterinary Association - <http://www.bsava.com>
- European Platform for the Responsible Use of Medicines in Animals <http://www.epruma.eu>
- European Committee on Antimicrobial Susceptibility Testing - <http://www.eucast.org>
- European Medicines Agency - <http://www.ema.europa.eu/ema/>
- Federation of Veterinarians of Europe - <http://www.fve.org>
- UK Legislation - <http://www.legislation.gov.uk>
- Veterinary Medicines Directorate - <http://www.vmd.defra.gov.uk>
- World Health Organisation - <http://www.who.int>