



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Anthelmintic resistance

Status including feedback from the focus group meeting 13 June 2016 and presentation of the CVMP reflection paper on anthelmintic resistance

London. 16 March 2017



Background

- Anthelmintic resistance is an emerging threat for livestock production and animal health in general.
- Not only loss of efficiency of many products, but also limited introduction of innovative products/new substances
- Most problems linked to the development of resistance in small ruminants (sheep, goats), cattle and horses
- Interest of applicants to introduce treatment claims for helminth strains that are resistant to other active substances/classes

> > > EWP received the mandate from CVMP to prepare a reflection paper on anthelmintic resistance

CVMP Reflection paper on anthelmintic resistance

- Draft agreed by CVMP-EWP February 2014
- Adopted by CVMP for release for consultation 10 April, 2014
- Public consultation period 23 April – 31 July 2014
- Revised draft agreed by EWP 24 February 2016
- Revised draft adopted by CVMP for release for 2nd consultation 21 April 2016
- Second public consultation period 29 April – 31 July 2016
- **Focus group meeting 13 June 2016**
- Revised draft adopted by EWP February 2017
- Adopted by CVMP ...

Focus group meeting 13 June 2016

Scope:

To facilitate the exchange of views from regulators, industry, academics and veterinarians before revision of the reflection paper

Participants:

- EMA, CVMP and EWP-V members
- Academics
- Representatives of SCOPS, EGGVP, FVE, IFAH-Europe, Swissmedic
- Assessors from NCAs



Focus group meeting 13 June 2016

Four sessions (discussions and recommendations)

1. Anthelmintic resistance situation in Europe in main target species (cattle, sheep, horses) and factors influencing development of resistance
2. Prudent use: best practices, regulatory tools (SPC and product literature)
3. Development and authorisation of anthelmintics: Impact of VMPs on resistance development
4. Monitoring tools for resistance development: monitoring methods and systems, regulatory tools

Minutes published www.ema.europa.eu/



Scope of the reflection paper

- Overview of the current anthelmintic resistance situation in Europe for different helminths and anthelmintic classes
- Focus on food producing animals
- Reflection of current knowledge on known resistance mechanisms
- Monitoring systems and methods for detecting resistance
- Current management strategies to delay resistance development
- **Recommendations on measurements that might delay the selection of resistant helminth strains**



Reflection paper – current resistance situation in Europe

- Difficult to estimate because not systematically documented throughout Europe
- Resistance mechanisms in helminths are complex
- Suitable methods of detecting and evaluating resistance are limited



Reflection paper – current resistance situation in Europe



Fasciola hepatica (TBZ),
Cooperia spp. (IVM),



Parascaris equorum
Cyathostominae
(BZ, Pyr, MLs)

Reflection paper – current resistance situation in Europe

Teladorsagia spp.

*Haemonchus
contortus*

*Trichostrongylus
spp.*

Fasciola hepatica

Multidrug-resistant
(BZ, LVM, TBZ, MLs)



Reflection paper: Definition and mechanisms of resistance

- „*The ability of parasites to survive doses of drugs that would normally kill parasites of the same species and stage*“ (WAAVP, 2012), but there are other definitions
- Resistance mechanism are complex, include genetic mutations, changes in transport mechanisms/ metabolism of the drug within a worm species
- Different resistance mechanisms to the same anthelmintic within a worm species
- Cell-membrane transport proteins (P-glycoprotein) may lead to multi-drug resistance
- Resistance difficult to assess because no established thresholds (depending on helminth species and animal species), lack of standardised/validated tests



Reflection paper: Monitoring systems and methods

- Only few locally organised monitoring programmes, but no systematic surveillance programmes in any EU country
- Lack of practicable, standardised/validated methods
- Pharmacovigilance data of limited value (lack of efficacy underreported)
- *In vivo* tests: worm counts – not suitable (necropsy); FECRT – labour/cost intensive, low sensitivity, not species-specific, no established cut-off levels for resistance
- *In vitro* assays: e.g. egg hatch inhibition assay, larval development inhibition, molecular assays - very specific, only validated for some worm species/substances

Reflection paper: Management strategies

- Targeted selective treatment (treat on the basis of confirmed worm burden)
- Correct use of anthelmintics (dosing, selection of the appropriate anthelmintic substance/ timepoint of treatment)
- Concept of rotation of different anthelmintics with different modes of action – not proven
- Use of multiactive anthelmintic products – not yet sufficiently substantiated by data; risk of multi-resistance development?
- Maintenance of refugia of susceptible worm population (sheep, other species)
- Good nutrition, acquired immunity, quarantine protocols
- Biological control methods, e.g. vaccines, genetic selection of livestock



Reflection paper: Assessment of anthelmintic product applications

- Information on anthelmintic resistance is always requested
- More guidance needed on how to generate meaningful data to support efficacy against helminth strains with documented resistance
- Clearer guidance needed on how to address aspects of resistance/susceptibility of helminths in the product literature

Reflection paper – Recommendations (CVMP's responsibility)

- Promote targeted selective treatment
- Improve pharmacovigilance reporting
- Harmonise prudent use warnings
- Provide guidance on the resistance data that should be included in a dossier and on how to characterise and confirm suspected resistance in a helminth strain
- Promote increased availability of anthelmintics for minor species
- Sufficient number of different pack sizes to avoid left-overs that could be used inappropriately



Reflection paper – Recommendations (Responsibility of member states)

- Prescription only status is recommended for anthelmintics for food producing animals to avoid inappropriate use
- Sufficient number of different pack sizes to avoid left-overs that could be used inappropriately
- Encourage NCAs to establish systematic monitoring systems at national level or EU wide
- Encourage NCAs to control advertising for anthelmintic products

Reflection paper – Recommendations (research and education)

- Continue research on resistance mechanisms and develop suitable tests for detection of resistance, better monitoring tools
- Continuous validation of tests, e.g. by carrying out inter-laboratory ring tests
- Investigate resistance in companion and aquatic animals
- Continue research on management strategies and biological alternatives
- Educate and enhance awareness of anthelmintic resistance amongst veterinarians/animal owners
- Further explore the benefits and risks of multi-active anthelmintics
- Establish EU reference laboratory for anthelmintic resistance
- Develop more narrow-spectrum anthelmintics with short withdrawal periods



Thank you for your attention

Further information

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