



Zoetis / SCOPS Workshop 9th September 2019
at
NFU Smith Square, London
11am – 3.30pm

Attendees:

Chair: Phil Sketchley

SCOPS

Lesley Stubbings

Fiona Lovatt

Dave Bartley

Sian Mitchell

Sophie Johns

Zoetis

Andrew Wylie

Dave Armstrong

Thomas Geurden

Adam Coomber

AGENDA

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| 1. Introductions around the table | Chair |
| 2. Zoetis objectives, issues to be discussed and new data | AW |
| 3. SCOPS objectives and technical discussion points for the day | LS |
| 4. Identify the main areas of agreement from the introductory sessions | ALL |
| 5. Work through the technical areas raised: | |
| ▪ Evidence available | DB/SM/TG |
| ▪ Gaps in our knowledge | |
| ▪ Identify any contentious issues – review the evidence | |
| 6. Review and agree a way forward – identify any barriers to progress | ALL |
| 7. What next? | ALL |
| ▪ Summary of the meeting | |
| ▪ Actions | |



Section 1 – Points of General Agreement

It was agreed that:

1.1 The overriding objective of all parties is to sustain the efficacy of moxidectin as an anthelmintic (and also as a parasiticide against sheep scab).

1.2 The prevalence of moxidectin resistance in the UK is increasing and is of concern, underlining the need for responsible use of this active using SCOPS guidelines.

1.3 The use of 2% as an anthelmintic *per se* is not 'against SCOPS principles' providing the SCOPS principles, in particular reference to refugia, are actively promoted and adopted.

1.4 There is a danger that the adverts used to farmers last winter promoted mox 2% LA as an easy way to control worms without reference to responsible use. The use of 2% LA in a proportion of ewes for control of the spring rise can be an appropriate strategy and Zoetis will continue to advertise its use but with more emphasis on responsible use messages.

1.5 There should be a much stronger message around the need to avoid over-use of mox 2%. It should not be promoted for use more than once in any one year and farmers advised not to use year on year in any flock. We need emphasis on the 5 'Rs' (right animal treated with the right dose of the right product at the right time and in the right way) rather than 'rotation' *per se*.

1.6 It is important to differentiate between the use of mox 2% as an anthelmintic where the partial treatment messages are vital versus those when it is used against sheep scab. This is potentially confusing. Zoetis are to propose OP dip as the first line treatment for sheep scab, particularly where 2% LA has been used in the spring for worm control. However if plunge dipping is not possible then the most potent and persistent ML injectable maybe appropriate with risk mitigation such as an exit drench*. In this case the use of moxidectin next lambing would not be appropriate.

1.7 We should not directly equate persistence of an anthelmintic with a longer tail (definitions below) without further evidence. This to be amended/qualified within the SCOPS Manual. All products (except LV which is cleared from the host very quickly) have a tail to a greater or lesser extent. The question regarding mox 2% is whether one 'tail' is better than several 'tails' where treatment is more frequent and this requires further work.

1.8 There has been misinformation in the field and both parties will work to address this, ensuring that all those involved always promote responsible use via application of the SCOPS principles.

1.9 It was agreed that in future private veterinary surgeons would be provided with the more detailed technical information that Zoetis provide to SQPs.

*The use of exit drenches in this situation needs more work- see below.



Section 2 – Technical information, positioning and advertising

2.1 Zoetis / SCOPS concerns regarding information to prescribers and farmers

2.1.1 Zoetis raised concerns regarding perceived increase in incorrect and potentially misleading comments in the market, in digital format and verbally, and cited several examples. Zoetis believe it is imperative that SQP's are provided with up to date information regarding product use and SCOPS guidelines as SQP's are obliged by the code to prescribe within SCOPS guidelines.

2.1.2 SCOPS raised concerns that CYDECTIN® 2% was being pushed for the 'Spring Rise' in an aggressive way as a 'silver bullet', when SCOPS was trying to encourage farmers to consider responsible use and not blanket treatment. There is also evidence of mis-information in the field via some account managers. This was acknowledged by Zoetis, who confirmed that the education and training provided is in line with SCOPS guidelines and re-affirmed commitment to ensuring messages are presented in line with Zoetis approved content.

2.2 Technical Positioning of Moxidectin 2% LA (Zoetis)

2.2.1 Zoetis presented the technical positioning of Moxidectin 2% LA sheep and supporting studies conducted by Zoetis to provide an evidence base for this position.

Kerr et al 2017 Small Ruminant Research 151 98 – 103

Kerr et al 2018 A practical farm-based trial to compare ewe nematode control strategies in periparturient ewes (currently under peer review)

2.2.2 Zoetis confirmed the Kerr work was based on moxidectin 2% LA not being used more than once per year in a flock and it is important to decide where it (mox 2%) is best placed and most beneficial for the farm. If used for worm control it should be aimed at a proportion of periparturient ewes, not all ewes and should **not also be used** in lambs for worm control. It has been proven to reduce the spring rise leading to the potential to reduce lamb treatments. For worm control, treat ewes or lambs, not both. Treating both is potentially over use of anthelmintics. If used to treat lambs, they should be dosed on risk.

2.2.3 If used for scab control, every sheep in the group must be treated (and it should be noted that this will have unintended consequences in the selection of worm resistance). For scab control the persistency and potency are important features which differentiates it from other products. With a non-persistent product sheep need to be treated and moved to scab free pasture. Note that it is misleading to use the term "clean grazing" with respect to scab. It should be 'pasture that has been sheep free for at least 3 weeks' Zoetis perceive this message is not widely understood and that it needs to be explained given more emphasis to all parties (vets, SQPs and farmers).



2.3 Advertising 2018/19

2.3.1 CYDECTIN 2% LA Sheep advert in NSA: SCOPS confirmed the positioning of the advert in the e-newsletter, adjacent to a SCOPS article on reducing ewe treatments was a key concern (though adverts in general were also of concern). It potentially gave the impression of blanket use which is not in-line with SCOPS principles.

2.3.2 In response Zoetis presented the technical studies as reference above, the wide collection of marketing communications, including technical articles, detail aids and AMTRA accredited CPD material which demonstrates Zoetis alignment with SCOPS principles. It is acknowledged that from a single advert this is not always highly prominent, and Zoetis have agreed to upweight the responsible use message in communications to all. Zoetis also reiterated the evidence base for the technical positioning.

Section 3 - Technical Discussions

The section below details the technical discussion and comments/ references found subsequently. There was discussion about various terms and these are defined below:

- **Persistency:** How long the active in a treatment is detectable in a site of action, which includes therapeutic and sub-therapeutic (tail) concentrations
- **Potency:** a measure of activity expressed in terms of the amount required to produce an effect of given intensity
- **Efficacy:** Is a measure of the treatment's capacity to produce an effect e.g. kill roundworms
- **Tail:** Time that the active in a treatment is at its site of action at a sub-therapeutic concentration

Other abbreviations used:

AI- active ingredient

MPC- Minimum Parasitocidal Concentration

3.1 Is there a positive advantage with moxidectin 2% in terms of the development of AR?

3.1.1 Moxidectin resistance has clearly been identified in the UK, (WAARD report) (http://hccmpw.org.uk/farming/projects/anthelmintic_resistance_project McMahon et al, Vet Para (2013) 195, 122) however Zoetis stated that most testing has been conducted with the oral formulation. The questions remain as to

- whether MOX LA would be more effective against these populations,
- whether MOX LA is more or less likely to select for resistance compared to oral MOX and
- more importantly, if the extra potency proves to make the product more effective, how long will that advantage remain?

Zoetis' position is that this formulation provides higher potency, longer persistency without a longer tail and the opportunity for less frequent treatments. The discussion on this is summarised below:



3.1.2 There was concern from SCOPS that this position by Zoetis is being used to promote the use of Mox 2%. Zoetis confirmed that they do promote the 2% injection rather than the drench for the PPRI.

3.1.3 While the higher potency of mox 2% is accepted, the impact this may have in terms of delaying the increase in AR is **not sufficiently understood** and is dependent on, for example, the allele frequency for AR in the worm population on an individual farm. Its relative potency may also vary with worm species and life cycle stage. But moxidectin has some unique characteristics differentiating it from other MLs (Pritchard and Geary 2019).

Nevertheless, Zoetis pointed out that moxidectin has been shown to be more effective in farms with avermectin resistance compared to any other avermectins *at least in the short term*. We support this with reference to the following *T. circumcincta* in sheep (Bartley et al 2004 and 2005) and *Cooperia oncophora* in cattle (Bartley et al. 2012). But how long this is sustainable is not known.

Also, SCOPS have found Lawrence et al., (2006) which reports a cross sectional study on farms to test for associations between an ML resistance (ivermectin) and management practices. One factor identified as associated was the use of long acting formulations in ewes pre-lambing. Leathwick et al (2006) and Leathwick et al (2009) and summarized in Leathwick 2014, also state that treatment of ewes at lambing time especially with long acting formulation (not specifically mox 2%) is a risk factor for developing AR.

3.1.4 Further insight into the potential benefits based on these characteristics was provided by Zoetis. However, these concepts are based on research into managing resistance in heartworms in dogs and SCOPS felt it was not proven that these principles also apply to GI nematodes in ruminants. It is stated in the reference presented by Zoetis that the use of a long acting formulation of moxidectin “can be useful in preventing production losses from parasitism where avermectin resistance is present, but this utility can be lost by misuse/over use” (Pritchard and Geary 2019).

3.1.5 Zoetis presented information on the tail selection period of mox and IVM. The group accepted that longer persistency does not always equal longer tail but that the shape of the PK profiles differed between products (NB the data presented was curtailed before the full extent of the tail could be evaluated). Multiple tails are created with multiple treatments. It is not known if one longer tail is more or less selecting than multiple shorter tails. (see below).

3.1.6 Recommendation: mox 2% has been put forward as an anthelmintic with increased potency and duration of effect which has benefits in the management of anthelmintic resistance by Zoetis with reference to Pritchard and Geary 2019. It is agreed that mox is different from other MLs and can be used in the face of avermectin resistance. It may have benefits in the removal of avermectin resistant GI parasites and produce some production benefit but this utility can be lost by misuse/overuse of moxidectin (also stated in Pritchard and Geary 2019). The group agreed that at this stage, there was insufficient evidence to support a statement regarding any positive effect of the 2% formulation on the speed of development of AR.



Research required:

- *What is the prevalence of MOX LA resistance in UK ?*
- *What are the concentrations of drug in parasites following treatment with MLs?*
- *Determining the efficacy of MOX LA or higher dose rates of MOX against isolates of parasites that are ML resistant to currently administered dose rates*
- *Determining the efficacy of MOX LA or longer durations of exposure of MLs against isolates of parasites that are ML resistant to currently administered dose rates*
- *The use of exits drenches as a resistance mitigation strategy require further investigation.*
- *What is the impact of using MOX LA annually on parasites epidemiology and AR development*

3.2 Control of the Peri-parturient Rise (PPR)

3.2.1 The Zoetis position is that mox 2% is used to suppress the pasture contamination associated with the peri parturient relaxation of immunity (PPRI) in ewes and therefore there is a lower challenge for lambs and a reduced need for treatments for lambs. This means that in the situation where farmers are carefully monitoring their lambs, they may use fewer doses of anthelmintic in a flock where ewes are treated around lambing.

3.2.2 While SCOPS agreed that mox 2% suppresses the pasture contamination associated with PPR in ewes, there are significant concerns with respect to widespread use for this purpose. (see specific items below). In particular we need to identify the minimum number /proportion of ewes to be treated to gain the maximum benefit while minimising risks of developing AR, in particular there are concerns regarding the risks posed by the presence of mox in the milk of treated ewes (see below).

3.2.3. SCOPS referred to Crilly et al (2015) showed a reduction in persistency (return to egg output earlier than expected) in ewes treated with moxidectin 2% injection in the UK. Such a reduction in the period before egg reappearance may be a measure of decreased duration of anthelmintic efficacy and can be a precursor / early indication of AR. Experience in horses has described shorter Egg Reappearance Period (ERP) for both IVM and MOX, but the shorter ERP does not immediately lead to treatment failures straight after treatment.

3.2.4. Also SCOPS referred to work with treatment of periparturient ewes with oral moxidectin. This has been associated with a shift in the pattern of ewes' faecal *T. circumcincta* egg shedding towards the mid-summer period. (Sargison et al., 2012) It is not clear whether the marked rise in faecal egg output that was observed 7–12 weeks after treatment was attributable simply to the intensity of challenge at the time when the persistent activity of moxidectin declined, or whether it was attributable to an enhanced susceptibility to infection as a consequence of limited host/parasite contact during the period of moxidectin persistence. (Sargison et al., 2012)

3.2.5 The evidence supporting an increase in performance of lambs suckling ewes treated with mox 2% was discussed. Zoetis cited the Kerr work in lambs prior to weaning (data presented as a poster at Sheep Vet Soc. but currently undergoing peer review). In contrast SCOPS cited Learmount *et al* (2016) Vet. Par. **226** (116-123) which reports a 3-year evaluation



of best practices guidelines for nematode control on 16 commercial sheep farms in the UK and in which it was demonstrated that there was no performance penalty nor increased level of worm infection in lambs associated with fewer anthelmintic treatments in ewes. Also Learmount (2018) which was an observational study which showed no significant benefit in early infection levels in lambs when ewes were treated with a long acting v short acting anthelmintic at lambing.

Research required:

- *What is the impact on species composition, life history traits and fitness of larvae on pasture following different ML based PPRI control strategies*

3.3 The 'tail' effect of 2% compared to other actives / preparations

3.3.1 The question is 'Is one 'tail' of mox 2% better than several 'tails'? where treatment is more frequent. There was a lot of discussion and Zoetis presented some more detailed studies on the pharmacokinetics of mox. compared with other ML injectables. These varied and require further analysis to assess what effect the different profiles may have on resistance development. However, the data presented was curtailed before the full extent of the tail could be evaluated, so there remains a question regarding what happens when these products dip below the MPC line – how long are they in the animal's system and therefore risking a sub-optimal level of exposure for nematodes?

3.3.2 The Zoetis response was that through modelling we can predict the decline of the active ingredient (AI) in plasma and that below the level presented it is not possible to detect the AI in the laboratory.

3.3.3 Recommendation: The consensus was that more work is required to assess the impact of sub-therapeutic concentrations (tail) selection between 2% mox and other actives in terms of the anthelmintic resistance development.

Research questions:

- *Impact of a single tail versus multiple tails on phenotypic expression of sensitivity/resistance to MLs*
- *The levels of mox in animals once the MPC is reached – how long can it still be detected and therefore is the tail in effect longer?*

3.4 Use of other actives when 2% has been used.

3.4.1 It was agreed that there should be a much stronger message around the need to avoid over-use of mox 2%. Simply advising 'rotation' was not sufficient, we need emphasis on the 5 'Rs' rather than 'rotation' *per se*. Mox 2% should not be used more than once in any one year and farmers advised not to use it consistently year on year in any flock. Zoetis position is to treat ewes or lambs on risk and not both. The role of the prescriber and the private veterinary surgeon in this is key (see below).



3.5 The effect of mox in the milk of treated ewes.

3.5.1 SCOPS raised two specific concerns in respect of the presence of mox in milk:

a) The development of AR – in this context is there sub-optimal exposure of worms in lambs via milk that is selecting for resistance (as proposed by Dever and Kahn 2015 and Leathwick et al., 2015).

and

b) The acquisition of immunity in the suckling lambs given this exposure and their ability to withstand a challenge later in the season post-weaning. Work to date presented by Zoetis has not looked at this, lamb weights being recorded only up to weaning.

3.5.2 The presence of mox in milk was agreed. Zoetis acknowledged that due to the lipophilic nature of the AI moxidectin in milk is likely. However, they state that the practical implications are not known as sucking lambs are not ingesting high volumes of worm larvae.

3.5.3 Zoetis also state that the study by Leathwick et al., (2015) artificially infected lambs with larvae which is not representative of practical situation and therefore more work is required. Furthermore, they state that in the discussion of the paper, assumptions are made that need to be further confirmed.

3.5.4 SCOPS pointed out that young lambs are ingesting significant numbers of larvae. Multiples in particular graze from an early age (2 weeks), indeed the ingestion of *Nematodirus battus* L3 and subsequent disease risk underlines the fact that they are taking in significant quantities of herbage from an early age. Kerr et al (2017) referred to by Zoetis earlier measured faecal egg counts (Trichostrongyle-type and *N. battus*) in lambs from the start of the experiment when lambs were 6 and 7 weeks old, indicating ingestion at least 3 weeks earlier. Leathwick et al (2015) detected moxidectin in the plasma of lambs from treated ewes until 60 days (> 8 weeks). Leathwick's work also showed that lambs receiving treated ewes milk preferentially supported ML resistant parasites. Dever and Kahn (2015) state that lambs are receiving a sub-therapeutic dose via the milk of treated ewes and that this will increase the selection for AR. Moxidectin is highly lipophilic – more so than the other ML endectocides and its partitioning into milk is higher than for ivermectin (Pritchard and Geary 2019)

3.5.5 It was agreed that more work on the extent of the risks posed is required. SCOPS urged the need to be cautious due to the potential risk associated with sub therapeutic doses of MOX in milk going into lambs.

Research required:

- *Extended study to look at the effects on lambs post-weaning and over successive years on 2% mox treated ewes (see above)*
- *More information on the ewes that should be treated – how to identify them and optimise the proportion left untreated.*



Section 4 – Future Actions Agreed

- 4.1 Increased emphasis of partial flock/mob treatment when worming ewes.
- 4.2 The role of the SQP and vets – we should work together to help SQPs and vets to ask farmers the right questions and provide them with good advice. AMTRA are key to this aspect with regards to SQP training. Sheep vet society and BVA are important dissemination to vets.
 - a. SCOPS guidelines – make these clear and practical
 - b. Prescription – encourage the development of a check list of questions and recorded information at the time the prescription / sale is made (already under development).
 - c. Training needs
- 4.3 Account Manager Training
- 4.4 Advertising to farmers – Focus groups? Zoetis to increase presence of responsible use message on advertising and other material.
- 4.5 Zoetis to share the full FAI study (Kerr paper-in review) draft manuscript
- 4.6 Which animals / groups will benefit the most – SCOPS to consider how we improve these messages and encourage contamination mapping etc.
- 4.7 Communication of the key outputs of this workshop to Vets, advisers, SQPs and Zoetis technical managers.
- 4.8 Review advice regarding the use of mox 2% in the light of additional evidence as it becomes available.
- 4.9 Strengthen communication to, and the role of vets. Both SCOPS and Zoetis to ensure positive engagement with vets so they have the same information when talking to their farmer clients.
- 4.10 SCOPS to encourage AHDA to develop a 'Code' for their members with respect to the responsible promotion of POM-VPS animal health products to customers.
- 4.11 Zoetis to share the internal technical information they have (in confidence) with the SCOPS team at the meeting.
- 4.12 SCOPS to remind stakeholders the importance of communicating accurately on what is or isn't within the guidelines. Zoetis will raise directly with SCOPS in future.