Proposed amendment to the Poisons Standard - 3.3 Meloxicam Oral Transmucosal Preparations

Submission of the Australian Veterinary Association Ltd

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The Australian Veterinary Association (AVA)

The Australian Veterinary Association (AVA) is the national organisation representing veterinarians in Australia. Our 8,500 members come from all fields within the veterinary profession, including companion animal and livestock clinical practice, and roles in government, public health, industry and academia.

Summary

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has submitted an application to create a new Schedule 6 entry for *MELOXICAM in oral transmucosal preparations containing 1 per cent or less meloxicam for pre-surgical treatment and pain management during routine animal husbandry procedures*.

The proposed change would mean that transmucosal meloxicam (currently S4, and thus prescription-only) would be available over-the-counter and online to the public, to be used without veterinary oversight.

The AVA **does NOT support** the amendment for several reasons:

- Unrestricted access to oral meloxicam provides opportunities for uncontrolled use of a potentially dangerous drug in a broad number of animal species, which may lead to significant harm.
- This product has the potential to be abused by humans, and thus poses a public health threat if available in an unrestricted manner.
- Inappropriate use without veterinary advice in target and non-target species poses risks not only to animal health and welfare, but also to human food safety, biosecurity, and public health.
- Incorrect administration without veterinary advice may negate the analgesic effects of the medicine, leading to poor animal welfare outcomes.
- Veterinary knowledge is important to meet label requirements to identify the presence of medical contraindications to use of the product, or any potential drug interactions, and to respond to adverse events including overdosage.
- Meloxicam is currently regulated as a prescription-only medication in Australia, the USA, Canada, New Zealand, UK, Ireland, and Europe due to safety considerations.
- It is noted that in 2005, the TGA introduced stricter measures around the prescribing of Cox-2 Inhibitors including meloxicam following the findings of a review into the safety of this family of medicines.
- The applicant has not demonstrated a persuasive need to reschedule transmucosal meloxicam to make the drug more accessible. There is no current impediment to supply through veterinarians.

These arguments are further expanded below.

Discussion

We address the relevant matters mentioned in section 52E of the *Therapeutic Goods Act 1989,* on which the TGA is likely to base their decision:

The risks and benefits of the use of a substance

Meloxicam is a potent short-acting nonsteroidal anti-inflammatory drug (NSAID) which is commonly prescribed in many species as an analgesic and anti-inflammatory. It is an excellent drug to manage inflammation and pain when given at the appropriate dose and duration to suitable patients.

However, there are known risks associated with its use in animals and humans, and for this reason meloxicam is currently regulated as a prescription-only medication in Australia, the USA, Canada, New Zealand, UK, Ireland, and Europe due to safety considerations.

Importantly, for animal patients, veterinary knowledge and oversight are required to prescribe appropriately and mitigate the known risks. The label for Ilium Buccalgesic OTM includes the following contraindications and precautions:

Contraindications:	This product is contraindicated for use in animals suffering from haemorrhagic gastrointestinal disorders, impaired hepatic, cardiac or renal function and haemorrhagic disorders, or where there is evidence of individual hypersensitivity to the product. This product is contraindicated for concurrent administration with glucocorticosteroids, other non-steroidal anti-inflammatory drugs or with anti-coagulant agents.

Precautions:	Use with caution in conjunction with other highly protein bound drugs. Overdose: In case of overdosing, a symptomatic treatment should be initiated.

It seems unrealistic to expect a non-veterinarian to establish that the medical conditions listed as contraindications are not present. Veterinary knowledge is also important to identify other highly protein bound drugs being administered, for example closantel which could be used concurrently in sheep.

In cases of overdose or adverse side effects, can the non-veterinarian be expected to provide appropriate symptomatic treatment?

It is therefore critically important that meloxicam remains a Schedule 4 (prescription only) medication so that veterinary oversight of its use can be maintained.

The purposes for which a substance is to be used and the extent of use of a substance

Meloxicam is used to reduce pain during husbandry procedures in animals and to manage inflammation and pain associated with disease processes or injury. It is commonly supplied by veterinarians in either injectable or transmucosal forms to farmers for use in sheep and cattle undergoing painful husbandry procedures. Veterinarians fully support and encourage increased use for this purpose, particularly when used as part of a multimodal analgesic plan for very painful procedures such as dehorning and castration. Injectable and oral formulations are also available to be dispensed by a veterinarian for the control of pain in dogs, cats, pigs and horses.

Note that transmucosal meloxicam will not be effective if administered inappropriately. For it to work effectively it needs to be administered onto the mucous membranes of the mouth. A common mistake is administration onto the tongue like a drench, which means the product is swallowed and not absorbed correctly, and pain relief is not achieved, resulting in poor animal welfare outcomes. This mistake can be avoided when a veterinarian's knowledge and advice are imparted to a farmer during the prescribing process.

The label for Ilium Buccalgesic OTM indicates that use in cattle for dehorning/disbudding *is to be in conjunction with a cornual nerve block*, while for castration use is *in conjunction with a local anaesthetic at the surgical site*. The concurrent medicine referred to is an S4 and will require veterinary intervention, therefore a veterinarian must be involved anyway. Rescheduling the transmucosal meloxicam to S6 will not change this requirement.

Claims:	Cattle: For the alleviation of pain associated with the routine husbandry procedure of disbudding (or dehorning) of calves, in conjunction with the administration of a cornual nerve block. For the alleviation of pain associated with the routine husbandry procedure of castration in calves, in conjunction with local anaesthetic at the surgical site to enhance pain relief and minimise tissue damage and distress. Sheep: For the alleviation of pain associated with the routine husbandry procedures of castration, tail docking and mulesing of lambs.

The applicant has not demonstrated a persuasive need to reschedule transmucosal meloxicam to make the drug more accessible. When use is considered appropriate, there is no impediment to supply through veterinarians. Whenever use is indicated, veterinarians can supply S4 medications such as meloxicam by telemedicine or other remote means, once an initial relationship with the client and knowledge of their flock or herd has been established. These preparations are used for routine procedures that are planned well in advance, allowing producers to obtain the correct amount of product from a veterinarian who has knowledge of the farmer's property and business. With effective transport services the rapid provision of product is possible even for the most remote properties.

The toxicity of a substance

Meloxicam dose rates vary from species to species. Administration at inappropriate doses can be associated with significant adverse effects in a range of body systems including the renal, gastrointestinal and haemopoietic systems. If meloxicam is given to diseased animals the risk of adverse effects is even higher. The literature provides copious evidence that these adverse reactions can be fatal. Given the toxicity risks, administration to animals needs to be under strict veterinary direction.

Further, there is potential for human toxicity if the product is accidentally or deliberately misused. According to the ARTG, there are currently 71 human products containing meloxicam (all S4 prescription-only). The associated Consumer Medicine Information documents summarise the safety and toxicity issues and the need for cautious use. These include potential adverse cardiovascular events, risks for children, people with liver and kidney problems, gastrointestinal ulceration, interactions with other drugs including antihypertensives, immunosuppressants, diuretics and alcohol, and use in pregnancy or while lactating.

It is noted and highly relevant that in 2005 the TGA introduced stricter measures around the prescribing of Cox-2 Inhibitors including meloxicam following the findings of a review into the safety of this family of medicines: https://www.tga.gov.au/media-release/regulator-takes-tough-action-arthritis-drugs-amended

For all of the above reasons, the AVA does not agree with the applicant that "*the acute toxicity profile of meloxicam is consistent with a Schedule 6 classification*". We maintain that S4 remains appropriate given the risks, and this is reinforced by the known regulation of meloxicam as prescription-only in other developed countries such as the USA, Canada, New Zealand, the UK, Ireland and Europe.

The AVA also notes the applicant's assertion that the APVMA "*has not received any adverse experience reports involving the product since its initial registration*". This may indeed be because the medicine has been prescription-only since it was first registered in 2015, consistently supplied with veterinary advice and labelling, as is appropriate. Equally likely is the reason that such reports are only obligatory of the registrant if they provide 'new' information that may change the product risk assessment and decisions on label statements. The need for caution is already evident in the label, adverse effects may already be occurring, but they may not constitute 'new' information. Furthermore, it is widely accepted in the pharmacovigilance community and also the subject of a number of publications in the human and veterinary literature, that only a very small percentage (ie less than 5%) of observed adverse experiences are ever reported. The longer the drug is on the market and the more experience with the use of a drug, the less likely reports will be made.

The dosage, formulation, labelling, packaging and presentation of a substance

It is essential that transmucosal meloxicam, given its potential toxicity and potential for misuse, is only prescribed by veterinarians, as this legally requires the addition of a specific label giving directions for use. This will mitigate the risks of accidental overdosage, use where it is contra-indicated, and misuse in other species, including humans. Labelling by a veterinarian of even a single-use dose for a livestock animal could prevent overdosing of a more susceptible species (eg cat or dog).

Furthermore, unlike the situation for use of S6 products, veterinarians must keep records of use of S4 medications, and this record can help in investigations of supply, appropriate use, and adverse effects.

The potential for abuse of a substance

Veterinarians must establish a genuine veterinary-client-patient relationship prior to supplying S4 medications. Supply of meloxicam by veterinarians requires them to have knowledge of the animals owned by the client. Supply under veterinary direction also ensures this product is not used inappropriately in other species, including humans.

Should this product be rescheduled to S6 however, it could be supplied to anyone over the age of 16 from any wholesale, retail, or online outlet, without the need to establish actual ownership of livestock, or any genuine justification for obtaining the medicine.

Potential for abuse in animals:

If rescheduled such that it is available over-the-counter, it is highly likely that it will be used inappropriately in other animal species:

- For example to treat sick or injured companion animals, with a high likelihood of **toxicity** due to incorrect dose calculation, or use in conjunction with other contraindicated medications.
- It may be used to **mask pain** in racing horses and greyhounds, or to mask pain in livestock that are otherwise unfit for transport – all of these pose unacceptable animal welfare risks.
- Misuse in **performance animals** without appropriate diagnosis by a veterinarian, particularly in the case of lameness or gait abnormalities in horses, poses a risk of serious injury to the rider if the horse has a catastrophic fracture of a masked prior injury, as has been reported in the past both in Australia and overseas.
- Inappropriate dose rates and withholding periods in both target and non-target food species poses an unacceptable risk of the **drug entering the human food chain** through residues in meat and other animal food products. Misuse to mask pain in livestock prior to transport to abattoirs for slaughter poses a similar risk. This could compromise Australia's food safety and impact our export industries worth billions of dollars to the economy.
- The medicine might be used to mask inflammation and clinical signs in animals suffering from **undiagnosed infections** – this poses a very real **biosecurity risk**, including the risk of serious **zoonoses** going undetected, and all the associated risks to public health.

Potential for abuse in humans:

The AVA does not support the applicant's claim that "*the potential for diversion of veterinary preparations of meloxicam to use in humans is low*". We believe the risk of rescheduling the veterinary product to S6 is that it will become a readily available and inexpensive substitute for the human prescription-only meloxicam products, because it would be obtainable without the inconvenience of arranging a medical consultation to procure via script.

There is increasing anecdotal evidence from the USA that some members of the public believe meloxicam is an opioid due to its description as a "prescription painkiller", and have taken excessive amounts in this belief. This has even led to a small black market for meloxicam in the US. To this end, the FDA has advised doctors against prescribing meloxicam, or its various brand name or generic counterparts, to patients who have demonstrated a risk for developing a psychological dependence on psychoactive medications.[23,24]

Thus, there is a very real possibility of this veterinary product being accessed by people for their own use – we have witnessed this behaviour only recently with abuse of another veterinary product ivermectin.

There could be significant risks to humans if used in combination with other NSAIDs and corticosteroids, as well as through continued use when signs of toxicity go undetected. Further, overdosage is possible in people unaccustomed to calculating dose rates, particularly when extrapolating from a veterinary preparation to take in oral form. Of course, the label contains no directions to the human consumer (no CMI or PI).

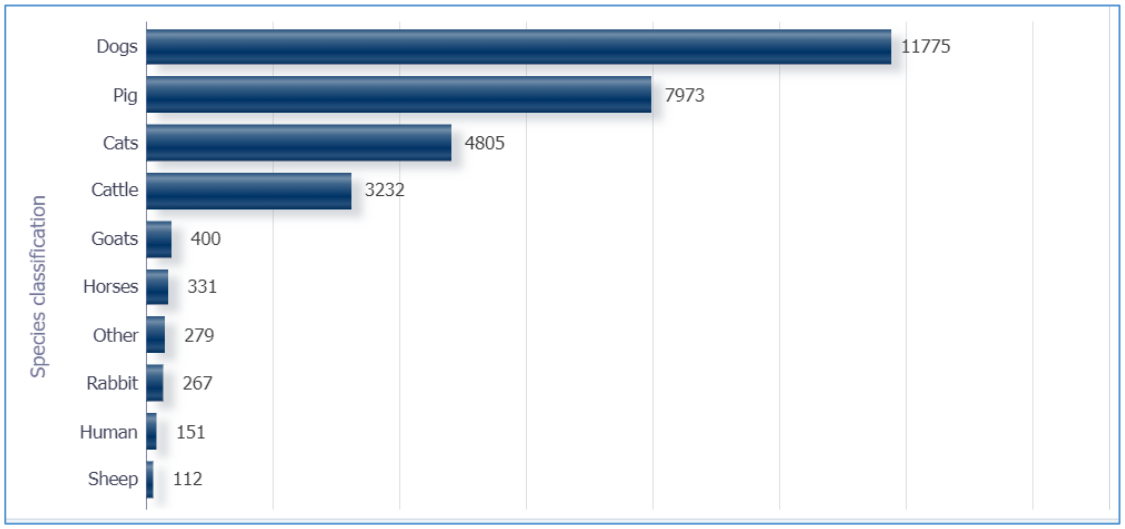
Given the risks outlined, the AVA does not believe the applicant's claims that "*appropriate labelling including safety directions, first aid and additional user safety statements, and packaging for single use prior to routine husbandry procedures*" will prevent intentional misuse of this product in the ways we have described.

Any other matters necessary to protect public health

A quick search of the European Medicines Authority pharmacovigilance database shows there are numerous cases (18,410 up to 26-09-2021) of suspected meloxicam adverse events in a range of species, including humans (see below).

European Medicines Authority pharmacovigilance database summary of reports of suspected meloxicam ADRs presented by species (including humans) as of 26-09-2021

Animal/Human	Species classification	Animals affected	% Animals affected
Animal	Dogs	11775	40.15%
Animal	Pig	7973	27.19%
Animal	Cats	4805	16.38%
Animal	Cattle	3232	11.02%
Animal	Goats	400	1.36%
Animal	Horses	331	1.13%
Animal	Other	279	0.95%
Animal	Rabbit	267	0.91%
Animal	Sheep	112	0.38%
Animal	Chicken	2	0.01%
Human	Human	151	0.51%



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