Legal Framework

Recital (6) of the recently adopted Commission Implementing Regulation (EU) 2025/901 explains that (emphasis added):

> '*A substance only qualifies as an 'essential substance'* ***where no satisfactory alternative for the treatment or diagnosis of an indication is available*** *and where the condition would, if untreated, create unnecessary suffering for the animal. A substance only qualifies as 'bringing added clinical benefit'* ***where it provides a clinically relevant advantage based on improved efficacy or safety or a major contribution to treatment or diagnosis. This may be the result, inter alia, of different modes of action, different pharmacokinetic or pharmacodynamic profiles, different lengths of treatment or different routes of administration.***'

Furthermore, Article 2 of that Regulation provides for the following (emphasis added):

> '*1. Substances which are essential for the treatment of equine species may be used for the indications specified in the Annex to this Regulation,* ***where no veterinary medicinal product authorised for food-producing animals of the equine species or no medicinal product referred to in Article 113 of Regulation (EU) 2019/6 would yield equally satisfactory results*** *in terms of successfully treating the animal or avoiding unnecessary suffering for the animal.*
>
> *2. Substances which bring added clinical benefit compared to other treatment options may be used for the indications specified in the Annex to this Regulation and taking into account the alternatives listed in that Annex,* ***where they provide a clinically relevant advantage based on improved efficacy or safety or a major contribution to treatment compared to veterinary medicinal products authorised for food-producing animals of the equine species or to medicinal products referred to in Article 113 of Regulation (EU) 2019/6****.*

The above establishes that to be considered as essential or as bringing added clinical benefits for the purposes of being included in Commission Implementing Regulation (EU) 2025/901, a substance needs to be compared with substances contained in veterinary medicinal products authorised for food-producing animals of the equine species or in medicinal products referred to in Article 113 of Regulation (EU) 2019/6, i.e. substances listed in Table 1 in the Annex to Commission Regulation (EU) No 37/2010, as amended. Below, those substances are referred to as 'eligible alternatives'.

An important distinction needs to be made from the alternatives named in either Commission Regulation (EC) No 1950/2006 or Commission Implementing Regulation (EU) 2025/901 in respect of the substances listed therein. Those alternatives serve a different purpose, namely, to give the veterinarian a clinical choice in the settings of the exceptional use allowed under those two regulations.

Background

The Commission received input containing new elements, including additional bibliographic references, pointing to essentiality or added clinical benefits in respect of the following substances: midazolam; rifampicin; griseofulvin; ketoconazole; sevoflurane.

Request

The Commission would like the Committee on Veterinary Medicinal Products to consider the questions below, which pertain to the five substances above and their relevant indications. We invite

the Committee to take into account the legal framework and eligible alternatives as outlined above, and the additional elements provided to the Commission, which are summarised below and also attached to this communication, as well as further information.

MIDAZOLAM

Indication: premedication and induction of anaesthesia, mild tranquilisation with minimal cardiovascular and respiratory side effects

Question

The additional information received by the Commission underlined that, as the Agency's scientific advice (EMA/CVMP/159047/2023-Corr.2) established that '[*m*]*idazolam is a benzodiazepine whose effects can be compared to those of diazepam',* midazolam is expected to compare in the same way with the eligible alternatives as other benzodiazepines.

Could the Committee confirm if midazolam, being a benzodiazepine and due to its specific properties, compares favourably with the eligible alternatives in view of its mode of action at the GABA receptor level and tranquilisation without cardiorespiratory depression which cannot be produced by those alternatives, particularly α-2 agonists?

Alternatives for comparison

In approaching the question above, only eligible alternatives are to be considered for the comparison to determine the essentiality or added clinical benefits of midazolam. We also bring to the Committee's attention the additional elements, as per the additional input received by the Commission, which point to midazolam's intrinsic properties and activity, such as its mode of action (acts at GABA receptor), water solubility offering an additional route of administration, good local tolerance, faster onset and shorter duration of action, suitability for foals.

The Agency's scientific advice provides the following substances as examples: detomidine and xylazine, both of which are α-2 agonist sedatives contained in veterinary medicinal products authorised for food-producing horses. The advice also refers to other '*alternative treatments'* authorised for food-producing animals of the equine species without giving specific examples.

Propofol and diazepam are not eligible alternatives as neither are contained in veterinary medicinal products authorised for food-producing equids, nor are they listed in Table 1 in the Annex to Commission Regulation (EU) No 37/2010.

Overview of the additional information received by the Commission

As explained in Recital (6) of Commission Implementing Regulation (EU) 2025/901, added clinical benefits constitute clinically relevant advantages based on improved efficacy or safety. Those may be due to different modes of action, different pharmacokinetic or pharmacodynamic profiles, different lengths of treatment or different routes of administration.

The additional information highlighted some of those elements in respect of midazolam, such as safety aspects, as well as benzodiazepines' mode of action, midazolam's pharmacokinetic and pharmacodynamic profile, and the additional route of administration possible for midazolam within the benzodiazepines class.

Widespread use in the equine practice

The additional information highlighted that midazolam had well-established and well-documented use in equines. It is stated that '*midazolam is more suitable for maintenance of anaesthesia or sedation through CRI* (constant rate infusion) *and is well established for these uses*.' A national survey among equine practitioners further demonstrated that 90,5% of respondents have confirmed using midazolam in horses during anaesthesia.

Clinical properties

The additional information pointed to commonalities between benzodiazepines. It was highlighted that being benzodiazepines, diazepam and midazolam have '*similar properties in terms of sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant properties. Midazolam has also been described as more potent than diazepam, but has similar pharmacodynamic properties and is often used interchangeably in a clinical setting (Riviere & Papich, Veterinary Pharmacology & Therapeutics, 9th Edition, 2009)*'.

The Agency's scientific advice also acknowledges that '[*m*]*idazolam is a benzodiazepine whose effects can be compared to those of diazepam in terms of sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant properties (Nordt and Clark, 1997). Due to its lipid solubility, its onset is faster with a shorter duration of action due to its fast metabolism (Mason, 2004; Morant, 2004)*'.

Commission Regulation (EC) No 1950/2006, as amended, lists midazolam for the following reasons:

- It is '*similar to diazepam but water soluble, thus suitable for intravenous injection and essential for intravenous infusion in combination with anaesthetics. Shorter acting than diazepam. More suitable than diazepam for foals*'.
- It offers a '*mode of action (acts at GABA receptor) and unique tranquilisation without cardiorespiratory depression cannot be produced by the α-2 agonist sedatives (detomidine, romifidne and xylazine) or acepromazine*'.

Water solubility

The additional information pointed out the water solubility of midazolam as providing a safety benefit. It means that propylene glycol and ethanol are not used as part of the midazolam formulation. Propylene glycol has been associated with side effects affecting animal welfare, such as pain during intravenous or intramuscular administration. The additional information also pointed out that propylene glycol can cause shock reactions, as well as that: '*this vehicle can cause lysis of red blood cells*. *Large volumes or constant rate infusion may cause clinical haemolysis (Riviere & Papich, 2017) (Riviere & Papich, Veterinary Pharmacology & Therapeutics, 9th Edition, 2009). In human medicine, adverse events have been described in association with intoxications due to consumer products absorption or medicines containing propylene glycol when administered as a prolonged treatment and/or at very high doses in patients (Anonymous, 2017). Although such cases could not immediately be identified for veterinary medicinal products, adverse events with diazepam in horses are reported and further analysis could clarify the pharmacovigilance profile of products containing diazepam as well as midazolam.*'

Additional route of administration

The additional information highlights that midazolam also offers the intramuscular route of administration, as already acknowledged in the addendum (EMA/CVMP/35961/2025) to the

Agency's scientific advice: '*Midazolam is a short-acting benzodiazepine administered also as a water-soluble salt, and thus the main routes of administration are intravenous (IV) or intramuscular (IM) injection'*.

The clinical relevance of the intramuscular route of administration was also underlined in the additional information. That alternative route of administration preserves the jugular vein from trauma due to repeated injections, reduces pain and stress for animals and makes it possible to administer in foals, in uncooperative or fractious horses, in feral or wild equids, or in animals which are actively convulsing. It was acknowledged that the intravenous route is the preferred route of administration in equids. However, it was pointed out that '*if IV-administration is not possible, IM is the alternative route. Clinical settings in which this route is relevant are situations where an IV-catheter cannot be placed, but necessity to treatment is given (e.g. seizures, convulsions) (Ref 1.: Equine Pharmacology (Cole C, Bentz B, Maxwell L, eds), John Wiley & Sons, Ames, USA, Edition 1: pp 44-62 and 99-117, 2015;* https://app.plumbs.com*, Drug: Midazolam: „Seizure control in foals (extra-label): 2 – 5 mg/50-kg FOAL (NOT mg/kg) IM or IV*."). Further information also points to the clinical significance of the intramuscular route of administration (https://doi.org/10.1016/B978-0-7020-2484-9.50019-5).

Local tolerance

The additional information also pointed out that the local tolerance of midazolam reduces the risks of thrombophlebitis when the intravenous route is used thus providing a safety benefit. (https://app.plumbs.com, Drug: Midazolam: „*At usual doses, midazolam is well tolerated in veterinary patients. Midazolam IV CRIs may cause thrombophlebitis less often than diazepam CRIs.*"; https://app.plumbs.com, Drug: Diazepam; „*…the IV catheter should be flushed with fluids after administration to help prevent phlebitis. IM injection may cause pain at the injection site.*"; Ref 1.: Equine Pharmacology (Cole C, Bentz B, Maxwell L, eds), John Wiley & Sons, Ames, USA, Edition 1: pp 44-62 and 99-117, 2015; https://www.vetpharm.uzh.ch/Wirkstoffe/000000000043/9145_07.html)

Pharmacodynamics and pharmacokinetics

The additional information emphasises midazolam's faster onset and shorter duration of action indicating clinical benefits in terms of better controllable anaesthesia or sedation in general and for foals more specifically, for instance when CRI (constant rate infusion) is used.

The additional information supports the added clinical value for maintenance of sedation through CRI in horses undergoing cheek tooth extraction. It states that '*Even though in the first view one might come to the conclusion that ketamine is an equivalent option, the combination of midazolam, romifidine and butorphanole showed to be the significantly better option for reducing defence and chewing movements of horses compared to ketamine, romifidine and butorphanole. This property can be vital for the accomplishment of the procedure'* (Hopster et al. (2013), Müller et al. (2017), Müller at al. (2015)).

Mixability with other agents

It was also pointed out that midazolam can be mixed with other agents, like ketamine, in the same syringe. It was reiterated that '*midazolam is the preferred substance for the use in combined drips (e.g. 'triple drip')* […] *Due to midazolam´s higher solubility in water the risk of incompatabilities when mixed with other substances is much lower. Drips containing midazolam as component are therefore well established in equine medicine.*'

The additional information also highlights that '*„Benzo-Drips" are not only used as TIVA (Total IntraVenous Anaesthesia) and for sedation in the standing horse, but are also established for PIVA (Partial IntraVenous Anaesthesia) in combination with inhalation anaesthesia in order to reduce the dose of inhalant and with this to reduce adverse circulatory effects.*' It suggests that the drips contain midazolam '*because of the known aspect of pharmaceutical compatibility and controllability of sedative effect*' (Mosing et al. (2007); Huber (2009); Kushiro et al. (2005); Auer and Moens (2011); Ambrisko et al. (2017).

Indication: short-term anticonvulsant for treatment of seizures

Question to the Committee

The Agency's scientific advice acknowledges that (emphasis added) '[*m*]*idazolam is a benzodiazepine whose effects can be compared to those of diazepam in terms of sedative, hypnotic, anxiolytic,* ***anticonvulsant*** *and muscle relaxant properties (Nordt and Clark, 1997). Due to its lipid solubility, its onset is faster with a shorter duration of action due to its fast metabolism (Mason, 2004; Morant, 2004)*'.

The addendum to the scientific advice reiterates that (emphasis added) "*Midazolam exhibits similar pharmacologic actions as other benzodiazepines; subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS are depressed, which produces anxiolytic, sedative, skeletal muscle relaxant, and* ***anticonvulsant effects***."

Neither the scientific advice nor the addendum to it discuss the indication 'short-term anticonvulsant for treatment of seizures' in respect of midazolam.

However, the additional information recalled those anticonvulsant properties.

As outlined above, benzodiazepines have a common mode of action and similar clinical effects. The scientific advice and the addendum to it recognise that similarities exist between the effects of diazepam and those of midazolam, including in respect of their anticonvulsant properties.

Could the Committee confirm that the conclusions reached for diazepam with respect to the use as short-term anticonvulsant are equally valid for midazolam, that is to say that no satisfactory eligible alternatives to midazolam exist for the indication 'short-term anti-convulsant for treatment of seizures'?

In the affirmative, considering the specific pharmacokinetic profile of midazolam and use as CRI, could the Committee confirm if midazolam would also be essential for ensuring more prolonged control of seizure in foals?

Alternatives for comparison

As the indication 'short-term anticonvulsant for treatment of seizures' has not been discussed, no eligible alternatives to midazolam were specified in the Agency's scientific advice or the addendum to it.

The assessment of diazepam, another benzodiazepine with generally the same mode of action and similar effects as acknowledged in the Agency's scientific advice and the addendum to it, does not give examples of eligible alternatives either. Carbamazepine and primidone are not eligible alternatives as neither are listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010.

Overview of the additional information received by the Commission

The additional information, in relation to the intramuscular route administration referred to above, maintains that midazolam is important for treating seizures or convulsions (Ref 1.: Equine Pharmacology (Cole C, Bentz B, Maxwell L, eds), John Wiley & Sons, Ames, USA, Edition 1: pp 44-62 and 99-117, 2015; https://app.plumbs.com, Drug: Midazolam: „Seizure control in foals (extra-label): 2 – 5 mg/50-kg FOAL (NOT mg/kg) IM or IV.")'. That additional reference further discusses the benefits of the use of midazolam, as a safe sedative, for immediate short-term seizure control or as CRI for more prolonged control, as well as the significance of the possible intramuscular route of administration. Further information from a prospective clinical study in foals describes the effective use of CRI of midazolam for seizure control in foals with neonatal encephalopathy (Eather, AM, Russell, CM, Collins, N.M, Cudmore, LA (2017) Use of continuous rate infusion of midazolam for seizure control in foals with neonatal encephalopathy: 46 cases, Proceedings of the Bain Fallon Memorial Lectures, Australian Equine Veterinary Association, 39, 16).

As mentioned above, the additional input received by the Commission also refers to midazolam's shorter duration of action as an advantage for foals.

RIFAMPICIN

Indication: Treatment of [moderate to severe] *Rhodococcus equi* infections

Questions

The Agency's advice acknowledges that rifampicin is a '*broad-spectrum, concentration or time-dependent, bactericidal and/or bacteriostatic antibiotic, with activity mainly against mycobacteria, Gram-positive and facultative anaerobic organisms (Wilson et al., 1988). For example, rifampicin demonstrates bacteriocidal, concentration dependent activity against Mycobacterium tuberculosis (Yamori et al., 1992), whereas rifampicin demonstrates bacteriostatic, time-dependent activity against Rhodococcus equi (Giguère et al., 2012).*' The Agency's scientific advice further states that '*Rhodococcus equi infections, may be life-threatening in the severe form of the disease. The severe form of the disease can cause unacceptable suffering of the animal. It does pose a risk for public health since R. equi is considered zoonotic*.'

It is also worth noting that the World Organisation for Animal Health List of Antimicrobial Agents of Veterinary Importance of June 2024 lists rifampicin as a Veterinary Highly Important Antimicrobial Agent as '*Rifampicin is essential in the treatment of Rhodococcus equi infections in foals.*'

Could the Committee confirm that rifampicin, used in combination with a macrolide, remains a necessary component of the treatment of moderate to severe *Rhodococcus equi* infections in foals and provides an added clinical benefit in view of: its properties helping with better treatment outcomes due to mutant prevention thus improving efficacy; its route of administration preserving animal welfare by avoiding the need for repeated injections over the long periods of time required for treatment and associated side effects thus improving safety?

In the affirmative, could the Committee discuss the possible risk for consumers when the substance is used in food-producing animals of the equine species and a six-month withdrawal period is respected?

Alternatives for comparison

The Committee is reminded that in approaching the question above, only eligible alternatives are to be considered for the comparison to determine the added clinical benefits of rifampicin. The Agency's scientific advice refers to eligible alternatives, such as doxycycline, tulathromycin, gamithromycin, erythromycin.

The additional information points to '[o]*ther in vitro-sensitive agents against R. equi*', such as fluoroquinolones and gentamicin which would be considered eligible alternatives. However, it cautions that '[b]*ecause R. equi survives and replicates intracellularly, there is not always concordance between in vitro and in vivo antimicrobial efficacy*'.

The Agency's scientific advice also mentions a number of non-eligible alternatives, such as azithromycin, clarithromycin, minocycline, which, while clinically relevant for the successful treatment with antimicrobial combinations of moderate to severe *Rhodococcus equi* infections, including in combination with rifampicin, are not listed in Table 1 in the Annex to Commission Regulation (EU) No 37/2010 substances, or hyperimmune plasma.

Overview of the additional information received by the Commission

As explained in Recital (6) of Commission Implementing Regulation (EU) 2025/901, added clinical benefits constitute clinically relevant advantages based on improved efficacy or safety. Those may be due to different modes of action, different pharmacokinetic or pharmacodynamic profiles, different lengths of treatment or different routes of administration.

The additional information highlighted some of those elements in respect of rifampicin, such as safety aspects related to rifampicin's oral route of administration, as well as the fact the combination of rifampicin with a macrolide offers the additional advantage of reducing emergence of resistant mutants in the treated animals thus contributing to the treatment success.

Well-established use in the equine practice

The additional information highlighted that the combination of rifampicin with a macrolide remains the standard treatment for moderate to severe *Rhodococcus equi* bronchopneumonia in foals, stressing that this is a disease requiring prolonged therapy. The information underlines that '[t]*hese agents act synergistically and are lipophilic, enabling them to penetrate abscesses and accumulate within macrophages where the bacteria reside. Before this treatment became common in the 1980s, the survival rate for foals with Rhodococcus-pneumonia was as low as approximately 20%*.'

The additional information also underlines the existence of numerous scientific publications supporting the use of rifampicin and the well-documented field experience with that substance for the treatment of equine rhodococcosis, as well as the fact that there are no recent publications which argue that rifampicin is no longer relevant for its treatment.

While the eligible alternatives can also be used as monotherapy for *R. equi* pneumonia, the additional information points out that '[c]*ombination therapy with a macrolide and rifampicin is the recommended regimen for moderate to severe pneumonia. Monotherapy with either a macrolide or rifampicin promotes resistance*.' (https://doi.org/10.1111/eve.12870: '*Current evidence continues to support the combination of rifampin with a macrolide (azithromycin, clarithromycin or erythromycin) for treating clinical infections caused by R. equi despite recently described pharmacological interactions between these drugs. When infection with a macrolide-resistant isolate is confirmed, limited effective alternatives exist*.').

The additional information also demonstrates that in some European countries the use of rifampicin is strictly regulated and is permitted only for infections confirmed via culture or radiographic evidence of abscesses, thus ensuring prudent use and staving off the development of antimicrobial resistance.

Safety

The additional information warns that '[g]*entamicin has shown poor clinical efficacy, likely due to poor intracellular penetration. It requires daily intravenous injections, and nephrotoxicity has been reported in some foals. The remaining agents are either not permitted for use in food-producing animals or are associated with arthropathy in foals (e.g., enrofloxacin).' (https://doi.org/10.1016/j.vetmic.2015.05.019, https://doi.org/10.1111/evj.13567, http://dx.doi.org/10.1016/j.cveq.2016.11.002, https://doi.org/10.1111/evj.14135).*

The additional information highlights that when an eligible alternative (doxycycline) was used in combination with a non-eligible alternative (azithromycin) '[t]*hree out of thirteen foals treated with doxycycline/azithromycin developed hemolytic anemia.'* (https://doi.org/10.1111/evj.13211).

Further information also demonstrates that some of the eligible alternatives, or their routes of administration, may be associated with side effects in the treated animals thus affecting welfare.

For instance, tulathromycin, needs to be used intravenously as '*horses exhibited sweating, discomfort, and periods of recumbency*' following intramuscular and subcutaneous administration, with signs more pronounced in the latter case, suggesting tulathromycin may be more suitable for use in adult horses (https://vtechworks.lib.vt.edu/server/api/core/bitstreams/37125c04-7ff1-4bc3-b519-524a80f1c8fb/content).

Gamithromycin also needs to be administered intravenously, and diluted, as the intramuscular or subcutaneous administration was associated with '*severe local lesions likely caused by hyperosmolality of the injected solution*' and with '*markedly higher plasma exposure and better penetration into bronchoalveolar lavage cells but lower distribution into epithelial lining fluid*' (https://doi.org/10.1111/jvp.12402).

As seen, many of the eligible alternatives are to be administered intravenously over long periods of time with the side effects associated with that route of administration and its impacts on animal welfare.

In contrast, rifampicin's route of administration appears to offer safety benefits due to better tolerance. When rifampicin was used in combination with erythromycin, '[m]*ild diarrhea was sometimes noted, but was never severe enough to require the termination of therapy. No other adverse side effects were apparent*' (https://doi.org/10.1016/0378-1135(87)90121-0).

Route of administration

The additional information points out that '[f]*oals that receive treatment typically have moderate to severe Rhodococcus pneumonia requiring prolonged therapy, typically 4 to 12 weeks. Severe pneumonia with abscesses necessitates prolonged treatment, which must be manageable at the stable.*'

Based on the additional information and further to the safety aspects highlighted above, the oral route of administration of rifampicin avoids daily injections over extended periods which, apart from the possible side effects of intravenous administration, have an impact on animal welfare.

Against that background, the additional information stresses that rifampicin in combination with a non-eligible alternative is non-inferior to another combination of an eligible alternative with a non-eligible one: '*Treatment with doxycycline in combination with a macrolide (azithromycin) for mild to moderate Rhodococcus-pneumonia showed, in one study (one of few randomized clinical trials), nearly equivalent outcomes compared to the combination of rifampicin and a macrolide. Foals were treated for a minimum of 41 days'* (https://doi.org/10.1111/evj.13211).

GRISEOFULVIN

Indication: systemic antifungal use. Treatment of ringworm.

Questions

The Agency's scientific advice acknowledges that '[v]*irtually all dermatophytes of animal origin are inhibited by griseofulvin concentrations of 0.2-0.5 µg/ml.* […] *Actively growing fungi may be killed, but dormant cells are only inhibited, so that cure occurs when infected keratinized cells are shed. For this reason, treatment is prolonged.*'

Commission Regulation (EU) 1950/2006, as amended, lists griseofulvin for the following clinical benefits: '*griseofulvin given orally has good activity against trichophyton, microsporum, and epidermophyton*.'

Could the Committee provide information on whether there are any veterinary medicinal products authorised for food-producing animals of the equine species or substances listed in Table 1 in the Annex to Commission Regulation (EU) No 37/2010 which cater to the clinical cases of ringworm in equine animals which require systemic treatment?

In the negative, could the Committee confirm whether, due to its oral route of administration, griseofulvin would be considered essential for those cases of ringworm in equines which necessitate such systemic antifungal treatment?

In the affirmative, could the Committee discuss the possible risk for consumers when the substance is used in food-producing animals of the equine species and a six-month withdrawal period is respected?

Alternatives for comparison

The Agency's scientific advice lists enilconazole. It is an eligible alternative as it is listed in Table 1 in the Annex to Commission Regulation (EU) No 37/2010. That substance is allowed in food-producing animals for topical use only.

Overview of the additional information received by the Commission

Route of administration

The additional information received by the Commission underlined that '(t)*here is no equivalent treatment for managing extensive ringworm in horses:*

- *it is not possible to treat extensive ringworm with local treatments such as enilconazole;*
- *extensive ringworm is very painful and griseofulvin is therefore necessary to maintain the well-being of affected horses.*'

The Agency's scientific advice also acknowledges that '[o]*nly in very rare cases could a systemic antifungal agent be indicated*.'

As Commission Regulation (EU) No 37/2010 restricts the use of the eligible alternative referred to in the scientific advice to the topical route of administration only, it remains unclear if and what substances contained in veterinary medicinal products authorised for food-producing animals of the equine species or substances listed in Table 1 in the Annex to Commission Regulation (EU) No 37/2010 would meet the therapeutic needs of the clinical cases of equine ringworm which require systemic treatment.

The additional information cautions that less effective treatment of ringworm, being a zoonosis, may pose a risk to public health.

Efficacy

The additional information points to the '[d]*ual therapeutic effect of griseofulvin: on the development and reproduction of the fungus for elimination of systemic infection.*'

In terms of efficacy, further information underlines the activity and effects of griseofulvin in horse ringworm (https://doi.org/10.1016/j.jevs.2017.08.019) or refers to griseofulvin as '*the gold standard for the systemic treatment of animal dermatophytosis*' (https://doi.org/10.1007/s11046-008-9102-7).

KETOCONAZOLE

Indication: systemic antifungal use. Treatment of fungal pneumonia and guttural pouch mycosis.

Questions

Could the Committee confirm if ketoconazole, when used topically as an adjunctive therapy in the treatment of guttural pouch mycosis, brings added clinical benefits over the eligible alternatives?

If in the affirmative, could the Committee discuss the possible risk for consumers when the substance is used in food-producing animals of the equine species and a six-month withdrawal period is respected?

Alternatives for comparison

The Agency's scientific advice refers to enilconazole. As mentioned above, that substance is an eligible alternative and in food-producing animals is allowed for topical use only.

Overview of the additional information received by the Commission

The additional information is aligned with the Agency's scientific advice in stressing that ketoconazole is not used systemically in the case of guttural pouch mycosis. The information highlights that ketoconazole is used locally and after surgery, or as a substitute for surgery if the latter is not feasible. The information argues that as guttural pouch mycosis is a condition that can

lead to the death of the affected horses, local treatment with ketoconazole is beneficial in preventing mortality.

Indication: fungal pneumonia

Questions

The Agency's scientific advice acknowledges that the clinical significance of fungal pneumonia in equids in the Union is unclear but indicates that various fungal pathogens have been associated with pneumonia.

Could the Committee confirm if and what eligible alternatives exist to the systemic use of ketoconazole for treatment of fungal pneumonia in equids?

Could the Committee confirm if ketoconazole, when used systemically in the treatment of fungal pneumonia, brings added clinical benefits over the eligible alternatives, if any?

In the affirmative, could the Committee discuss the possible risk for consumers when the substance is used in food-producing animals of the equine species and a six-month withdrawal period is respected?

Alternatives for comparison

The Agency's scientific advice refers to trimethoprim-sulfonamide as treatment of choice for pneumonia caused by *Pneumocystis carinii,* a fungal pneumonia known in Europe. That substance combination is an eligible alternative, with MRLs established for trimethoprim in *Equidae*, and all sulphonamides in all food-producing species.

Amphotericin B is not an eligible alternative as it is not listed in Table 1 in the Annex to Commission Regulation (EU) No 37/2010.

It is unclear if and what eligible alternatives exist for cases of fungal pneumonia caused by agents which may be sensitive to ketoconazole, but not necessarily sensitive to trimethoprim-sulfonamide.

Further information

The additional information received by the Commission does not discuss the indication 'fungal pneumonia'. However, it is among the reasons for listing ketoconazole in Commission Regulation (EU) 1950/2006.

Further information suggests that ketoconazole may play a role in the treatment of systemic fungal infections in equines, particularly pneumonia, where the agent might not necessarily be sensitive to trimethoprim-sulfonamide (https://vetfolio-vetstreet.s3.amazonaws.com/mmah/81/24cca74a08405a89ecc8970eb989e6/filePVE_03_05_260.pdf; https://www.researchgate.net/publication/271535625_Update_on_Fungal_Respiratory_Disease_in_Horses; https://doi.org/10.1016/j.vetmic.2013.01.015).

SEVOFLURANE

Indication: inhalation anaesthesia for horses with limb fractures and other orthopaedical injuries and mask induction of anaesthesia in foals

Questions

Commission Regulation (EC) No 1950/2006 lists sevoflurane due the following added clinical benefits: 'sevoflurane is a *volatile anaesthetic with minor metabolism and fast excretion; while there is an MRL for isoflurane in the EU, isoflurane is not suitable for all equine anaesthetic cases due to its recovery characteristics where excitement may lead to the horse breaking a leg; sevoflurane is essential in certain equine surgeries where a smooth recovery is vital, as it has been shown to produce a smoother, more controlled recovery in horses; it is therefore selected in preference to isoflurane for horses with limb fractures and other orthopaedical injuries; sevoflurane is essential for mask induction of anaesthesia in foals as it is completely non-irritant as opposed to isoflurane, which is irritant and therefore causes coughing and breath holding*.'

Given that sevoflurane and isoflurane are comparable agents, could the Committee confirm that sevoflurane brings certain added clinical benefits in terms of control of anaesthesia and duration and quality of recovery in some clinical settings requiring rapid induction and recovery, or better controllability, and for certain populations, such as foals?

In the affirmative, could the Committee discuss the possible risk for consumers when the substance is used in food-producing animals of the equine species and a six-month withdrawal period is respected?

Alternatives for comparison

The Agency's scientific advice refers to isoflurane as it is listed in Table 1 in the Annex to Commission Regulation (EU) No 37/2010 for *Equidae* and there are veterinary medicinal products authorised for food-producing animals of the equine species.

Overview of the additional information received by the Commission

Efficacy and safety: recovery time, recovery quality and anaesthesia control

The additional information highlighted several advantages of sevoflurane over isoflurane:

- *'Sevoflurane has a lower blood-gas partition coefficient than isoflurane, leading to faster onset and recovery times, allowing for more precise anaesthetic depth adjustments, particularly crucial for foals and critical care patients.*
- *Sevoflurane is particularly a safer choice for young and compromised animals due to better maintaining cerebral perfusion and better cardiovascular stability.'*

Further information also emphasises the shorter recovery time with sevoflurane versus isoflurane and the better quality of recovery from sevoflurane and from sevoflurane followed by xylazine compared with that from isoflurane (https://doi.org/10.1111/j.1532-950x.1998.tb00160.x).

The additional information also highlights that horses '*under sevoflurane anesthesia may require less pharmacological support in the form of dobutamine than isoflurane-anesthetized horses. This could be due to less suppression of vasomotor tone*' (https://doi.org/10.1111/j.1467-2995.2005.00279.x).

Further information points out that '*administration of sevoflurane together with neuromuscular blocking drugs can provide stable and easily controllable anesthetic management*' (https://doi.org/10.2460/ajvr.2000.61.1430).

Suitability for mask induction in foals and for use in compromised patients

While evoked by Commission Regulation (EC) No 1950/2006, the Agency's scientific advice does not discuss specifically the significance of the use of sevoflurane in foals for the purpose of mask induction.

The additional information makes the case that sevoflurane is a safer choice for that population and, in addition, for compromised animals.

Further information would suggest that sevoflurane may have additional clinical benefits making it '*particularly useful for outpatient procedures, geriatrics, high-risk patients, prolonged procedures, and foals*' (Matthews, 2001, https://www.ivis.org/sites/default/files/library/aaep/2001/91010100426.pdf?utm), whereas other sources argue that there is no statistically significant difference in comparison with the eligible alternative although it should be noted that a different method of administration than mask use was studied (Read et al, 2002, https://doi.org/10.2460/javma.2002.221.393).