Disclaimer: The following document is intended to support a discussion with the national competent authorities. It has not been adopted by the Commission and therefore does not contain the official position of the European Commission.

Discussion Document:

Commission Implementing Regulation establishing a list of substances which are essential for the treatment of equine species, or which bring added clinical benefit compared to other treatment options available for equine species and for which the withdrawal period for equine species shall be six months

The Context

Regulation (EU) 2019/6 on veterinary medicinal products[1] ('VMP Regulation'), Article 115(5), requires the Commission to establish, by implementing acts, '*a list of substances which are essential for the treatment of equine species, or which bring added clinical benefit compared to other treatment options available for equine species and for which the withdrawal period for equine species shall be six months*'.

On 9 March 2023, the Commission tasked the European Medicines Agency ('EMA') with providing scientific advice on substances for inclusion. EMA submitted its advice on 19 July 2024. The advice underwent subsequent corrections, most recently on 21 February 2025, and is available on the Commission's website (link).

Following discussions at the Standing Committee on Veterinary Medicinal Products, the draft implementing regulation was open for public feedback from 15 January to 12 February 2025, receiving a total of 178 contributions, of which 163 valid entries.

At the 26 March 2025 Standing Committee meeting, Member States took note of the concerns expressed by the stakeholders. As a compromise, the Commission proposed keeping both lists—the new Commission implementing regulation and Commission Regulation (EC) No 1950/2006—in parallel for 24 months and using the Expert Group on Veterinary Medicines for steer from the Member States to identify the difficulties encountered in the equine veterinary practice and to explore possible approaches to addressing them, including by identification of potential data gaps.

Substances for which stakeholders expressed concerns

During the public consultation conducted as part of the legislative process, numerous stakeholders expressed concerns about substances not listed in the draft implementing regulation. The feedback falls into two main categories:

- Requests to retain substances currently listed in Commission Regulation (EC) No 1950/2006 and not included in the draft implementing regulation. The table

[1] Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products and repealing Directive 2001/82/EC, OJ L4, 7.01.2019, p.43

below shows only those substances that were mentioned in more than 10% of the valid contributions.

Proposed for retention		
Substance	**Times mentioned (n)**	**Share of valid contributions (%)**
Midazolam	139	85
Rifampicin	70	43
Sevoflurane	66	40
Griseofulvin	65	40
Technetium	58	36
Ketoconazole	53	33
Buprenorphine	33	20
Budesonide	24	15

General concerns of stakeholders:

- Substances with which experience has been gained may be preferable over those with limited clinical record.
- There is concern that decision-making around the molecule's status may lack sufficient input from field practitioners. Given the broad scope of the field, practical experience and empirical evidence are important components.
- In addition to bibliographic evaluations, input from veterinary practitioners, their associations, breeders, and other equine professionals provides valuable insight.
- Field experience and identified needs can contribute to the informed determination of appropriate treatment options.

MIDAZOLAM

Summary of concerns

An overwhelming majority of stakeholders who provided feedback express strong concerns about the proposed removal of midazolam from the list of substances for equids.

Overall, stakeholders indicate that midazolam cannot be substituted by the proposed alternative, diazepam. They emphasise its unique and clinically important properties, pharmacokinetics, compatibility, and regulatory approval in equids offering added clinical benefits over the proposed alternative which they consider as not suitable or satisfactory.

Stakeholders highlight the current experience with midazolam under Commission Regulation (EC) No 1950/2006: widely used, well-understood, and indispensable for equine anaesthesia and sedation, particularly in foals.

Specific aspects highlighted by the stakeholders

1. Clinical concerns

Stakeholders highlight the pharmacological and clinical benefits relevant in the equine practice:

- **Water solubility and administration**: Midazolam it the only benzodiazepine suitable for intramuscular injections due to its water solubility and physiological pH. Midazolam does not require solvents (e.g., propylene glycol, ethanol) which could cause pain and irritation upon intramuscular administration. Midazolam is well tolerated when administered intramuscularly and avoids the side effects of the proposed alternative, diazepam, by offering a route of administration which helps to preserve the jugular veins from repeated trauma due to injections, reduces pain and stress for animals and makes it both suitable and possible to use in foals, in uncooperative or fractious horses, in feral or wild equids, or in animals which are actively convulsing.

  Midazolam is associated with a lower the risk of thrombophlebitis during intravenous administration. Midazolam is not a tissue irritant upon accidental perivenous deposition which makes for a benefit when administered intravenously in needle-shy young foals compared to the proposed alternative.

  Midazolam's short action due to its rapid redistribution and short elimination half-life permits continuous rate infusion dosing, enabling a steady plasma concentration which is beneficial when treating repeated seizures. particularly for sick horses and neonates.

- **Compatibility with other drugs**: Midazolam is more versatile and can be safely combined with commonly used anaesthetics, including in the widely used *'triple drip'* (ketamine, alpha-2 agonist, and midazolam). In contrast, diazepam has limited compatibility due to its formulation and cannot be mixed reliably with other agents. By reducing the number of administrations necessary, midazolam helps maintain animal welfare. The mixability of midazolam with other drugs in the same syringe or bottle for induction or intravenous maintenance of anaesthesia contributes to a reduction of the use of volatile agents, also important for sustainability reasons even though not relevant to the criteria for inclusion.

- **Shorter duration of action**: Midazolam has a shorter half-life and is metabolised more rapidly than diazepam, making it more suitable and safer for use in neonates or foals with immature liver function, as well as for otherwise ill equids or for shorter procedures. The proposed alternative's active metabolites can prolong sedation, increasing the risk in these patients, and repeated administrations can be potentially risky in foals under the age of 21 days.

  Some stakeholders also note that as neurologic disorders are more and more prevalent in equids, midazolam due to its favourable pharmacokinetics, is more suitable for repeated injections to treat seizures.

2. Impact on patient safety

Veterinary anaesthetists and professional associations have pointed to midazolam's widespread use and safety record (in over 20 000 equids) and warned that it is indispensable for safe equine anaesthesia. Stakeholders point to the short elimination half-life of midazolam making it a potentially safer option, Unlike the proposed alternative, midazolam does not produce harmful metabolites, making it a preferable choice for patients with liver disease. They warn that its removal would:

- impair the ability to safely anesthetise foals and may result in their exclusion from the food chain at a very early age;
- complicate field anaesthesia protocols where intramuscular administration is critical;
- reduce options available for safely and efficaciously managing seizures, muscle relaxation, and induction of anaesthesia, especially in emergency or field settings.

3. Shortage considerations

Some stakeholders point out that midazolam is an alternative to guaifenesin for myorelaxation in the following situations: induction of anaesthesia followed by intravenous or volatile anaesthetic maintenance as well as total intravenous anaesthesia. It becomes the only possibility for total intravenous anaesthesia during times of guaifenesin shortage like has happened in 2024.

In this light, some stakeholders allude to whether there should necessarily be a choice made between midazolam versus diazepam.

4. Consumer safety considerations

Stakeholders also cite midazolam's shorter half-life and less harmful active metabolites compared to the proposed alternative diazepam.

5. Concerns about the evidence cited for not listing

Stakeholders claim that removing midazolam may inadvertently impair optimal patient care without clear justification or compelling reason. While admitting that there is a body of literature allowing for certain comparison between diazepam and midazolam, stakeholders point out that this data is limited and cannot be compared with the worldwide experience of veterinary anaesthesiologists.

Stakeholders also caution against using a single, limited study (Jarrett et al. 2018) to override extensive clinical experience and a broad body of literature[2] supporting midazolam's safety and efficacy. They point to several limitations of the study such as the very small sample size (n=6), the lack of blinding, the non-standard midazolam

[2] See Annex for references cited by the stakeholders.

dosing (double the authorised amount) and the fact that the study has been conducted under controlled experimental, rather than clinical conditions.

6. Regulatory status and practical implications

Stakeholders underline that midazolam is authorised for non-food-producing horses in multiple Member States. They point out that the products authorised for equids have been rigorously demonstrated as safe and efficacious in the target species and that no registration-standard studies have so far demonstrated the safety and efficacy of the proposed alternative which is currently not authorised for use in equids.

Stakeholders stress that excluding midazolam would not just preclude its use in food-producing equids in general but would also preclude its use in foals with serious impact on their veterinary care and possible loss of those patients so early on.

Stakeholders point out that retaining diazepam while removing the authorised midazolam also contradicts the principles of use outside the terms of the marketing authorisation laid down in Articles 112 and 113 of Regulation EU 2019/6 which prioritise authorised veterinary medicines over medicinal products for human use or non-authorised alternatives.

RIFAMPICIN

Summary of concerns

Stakeholders refer to rifampicin remaining indispensable for managing rhodococcosis in foals. The consensus among them is that rifampicin's clinical value justifies continued inclusion on the list, albeit with refined usage protocols. Given the risk of increased foal mortality and the limited alternatives, they see careful regulation rather than delisting as more prudent.

Specific aspects highlighted by the stakeholders

1. Clinical concerns

The stakeholders highlight that rifampicin is widely recognized as the reference treatment, when used in combination with a macrolide antibiotic, for equine rhodococcosis—a severe and frequently fatal respiratory disease affecting foals. This antibiotic combination therapy has been a cornerstone of efficacious clinical management in foals and has demonstrated consistent success. Stakeholders highlight that rhodococcosis is frequently fatal and it would result in even more fatalities without the use of rifampicin.

2. Role in addressing antimicrobial resistance

Apart from rifampicin's importance as an efficacious treatment in the light of numerous antibiotic-resistant bacteria, stakeholders refer to its role in minimising the

development of antibiotic resistance. Using rifampicin as part of a dual therapy reduces the selective pressure that can lead to resistant bacterial strains.

Practitioners and professional organisations advocate for maintaining rifampicin on the list due to its critical therapeutic role and the lack of equally effective alternatives.

They point out that the feedback to the survey preceding the advice for the list showed overwhelming support for rifampicin's continued use, as it remains a best practice standard, with calls for the need for controlled use—limited to no more than 15 days and only in conjunction with a macrolide.

3. Concerns about the evidence cited for not listing

Stakeholders disagree that there is no added clinical benefit in using rifampicin in combination with macrolides for *R. equi* in view of the abundant body of literature on the topic and good practices for the prudent use and limiting the risks of antimicrobial resistance.

SEVOFLURANE

Summary of concerns

Stakeholders express significant concern over the removal of sevoflurane from the list stating this would limit veterinarians' ability to provide safe, effective anaesthesia, particularly in critical and paediatric cases.

Apart from the clinical, they also cite environmental considerations which, despite being important, are not particularly relevant to the list of substances which bring added clinical benefits.

Specific aspects highlighted by the stakeholders

1. Clinical concerns

Stakeholders underline that sevoflurane is acknowledge by scientific and clinical evidence as a valuable and safe inhalant anaesthetic for use in horses, particularly in complex or emergency cases such as fractures and procedures involving foals. Sevoflurane offers several key advantages in terms of the quality of anaesthesia over isoflurane:

- It is less irritant to the respiratory tract.
- Due to its lower blood-gas partition coefficient and tissue solubility, sevoflurane allows for faster induction, better control of anaesthetic depth and rapid recovery making it a safer option, which is critical in foal anaesthesia.
- It might improve recovery quality in debilitated horses or foals, which is considered a critical and risky phase of equine anaesthesia.

- It may require less cardiovascular support during procedures and the perfusion of the brain is better maintained, which is especially important in foals or equids with brain trauma.

Stakeholders argue that the exclusion of this substance would disproportionately impact equine patients, especially very young foals.

2. Concerns about the evidence cited for not listing

Some stakeholders cite concerns with the use of one study to negate several publications and field experience which support sevoflurane's clinical benefits. Veterinary professionals also highlight that volatile and intravenous anaesthesia protocols are not interchangeable. Comparing them as alternatives, particularly for complex surgeries, is considered inappropriate.

3. Environmental impact

While not directly relevant to the list of substances bringing added clinical benefits, sevoflurane is also noted for having the lowest Global Warming Potential (GWP) among available options. Its atmospheric lifetime is shorter compared to isoflurane. This difference is sensitive, especially in large animal veterinary medicine, given growing awareness around climate impact.

GRISEOFULVIN

Summary of concerns

Stakeholders highlight the benefits of griseofulvin as a therapeutic option for equine ringworm, especially in cases where topical alternatives fail. Removing it from the list of authorised substances could significantly impair the ability to manage this common and contagious condition, with broader implications for animal and public health.

Specific aspects highlighted by the stakeholders

1. Clinical concerns

Stakeholders point to griseofulvin being the only systemically available antifungal medication for the treatment of ringworm in horses, a highly contagious and commonly encountered skin disease, particularly in stressful periods such as weaning or relocation.

Stakeholders consistently highlight that topical treatments stated as alternatives are often insufficient. They consider griseofulvin indispensable in managing extensive or persistent outbreaks where local applications are ineffective. Stakeholders signal that fungal infections have increasingly shown resistance to commonly used topical treatments like enilconazole, reinforcing the need for systemic therapy reducing the risk of contagion for the rest of the population.

2. Animal Welfare and Public Health Concerns

Stakeholders underline that ringworm is not only painful and distressing for affected horses but is also a zoonosis, meaning it can be transmitted to humans. Limiting access to effective treatment poses a risk to both animal welfare and public health. They recall the One Health principle as a critical consideration in this context.

TECHNETIUM

While nearly 40% or stakeholders supported the listing of Technetium 99, no specific concerns could be identified.

KETOCONAZOLE

Summary of concerns

Ketoconazole is considered useful in the treatment of fungal infections, particularly for local use. Stakeholders highlight that there are too few available antimycotic options, making ketoconazole a necessary component of current treatment protocols.

Specific aspects highlighted by the stakeholders

1. Clinical concerns

The application of ketoconazole is especially noted in the treatment of guttural pouch mycoses, where it is used via local instillation, typically following surgery or as an alternative when surgery is not planned. Practitioners emphasise that ketoconazole is often easier to source than alternatives like nystatin and yields better clinical outcomes in practice. Stakeholders advocate for its retention on the list, given its specific, practical applications and lack of viable substitutes.

2. Concerns about the evidence cited for not listing

Concerns have been raised over a misunderstanding of its actual mode of use, as it is not employed systemically in the treatment of guttural pouch mycoses.

BUPRENORPHINE

Summary of concerns

Stakeholders see buprenorphine as a well-supported and safe option for equine analgesia, with no readily available substitutes.

Specific aspects highlighted by the stakeholders

1. Clinical concerns

Stakeholders express concern over the potential withdrawal of buprenorphine as a valuable analgesic, particularly in managing severe pain such as that associated with laminitis and post-operative care. Its longer duration of action compared to alternatives like morphine or methadone is seen as a key clinical benefit. Stakeholders point out

that considerable research efficacy and safety data support its marketing authorisations for equids not intended for human consumption.

It is also used effectively in combination with constant rate infusion sedation during standing procedures, a practice that is becoming more common.

2. Concerns about the evidence cited for not listing

Concerns have been raised with the rationale for its proposed withdrawal, particularly the apparent lack of bibliographic references supporting the decision for its removal or stakeholder input in the decision-making process. Stakeholders argue that the absence of specific comments in the stakeholder questionnaire should not be interpreted as a lack of support or need for the substance.

3. Regulatory status and practical implications

Similar to midazolam above, stakeholders point to the existing marketing authorisations for veterinary medicinal products.

Stakeholders also highlight that buprenorphine is more accessible and practical, especially in certain EU countries where access to other opioids is restricted.

BUDESONIDE

Stakeholders have expressed concern over the removal of budesonide as it is widely regarded as an effective treatment for equine asthma, particularly mild to moderate forms, which is frequently encountered in racehorses and sport horses and is increasingly common.

Budesonide is commonly administered via nebulization, offering targeted respiratory treatment with fewer side effects compared to other general corticosteroids.

Given its effectiveness, safety profile, and frequent use in practice, stakeholders question the rationale for its exclusion.

- Proposals to add substances not listed in Commission Regulation (EC) No 1950/2006 and not included in the draft implementing regulation. The table below shows only those substances that were mentioned in more than 10% of the valid contributions.

Proposed for inclusion		
Substance	**Times mentioned (n)**	**Share of valid contributions (%)**
Phenylbutazone	65	40
Rifamycin	47	29

Tenoic acid	21	13

PHENYLBUTAZONE

Summary of Concerns

Stakeholders point to the effectiveness of phenylbutazone in comparison to other NSAIDs for managing pain in horses, particularly in severe or chronic conditions such as laminitis. Stakeholders claim that safety for consumers has been sufficiently demonstrated. Concerns have also been raised about the completeness of the evaluation process.

Specific aspects highlighted by the stakeholders

1. Clinical concerns

Phenylbutazone is regarded by equine practitioners as a useful analgesic and anti-inflammatory treatment, particularly for managing chronic and severe conditions. Stakeholders stress that phenylbutazone enables effective pain management in cases where alternatives may fall short, especially where ease of administration, rapid onset of action or a longer-lasting pain relief is required. Some practitioners note its utility in diagnostic protocols by helping distinguish pain-related conditions. Its practical use in the field, especially for long-term and palliative care, is emphasized by multiple veterinarians.

2. Consumer safety considerations

Stakeholders argue that concerns regarding consumer safety are addressed by existing data. They refer to the ANSES opinion alleging the safety of phenylbutazone residues after a six-month withdrawal period. Additionally, they refer to a joint EFSA/EMA risk assessment concluding that the probability of adverse effects in consumers from phenylbutazone exposure through horse meat was extremely low especially when administered under veterinary supervision and withdrawal periods observed.

3. Concerns about the evidence cited for not listing

Concerns are raised that some cited alternatives are not therapeutically equivalent in certain cases and that scientific and field-based evidence in favour of phenylbutazone has not been sufficiently considered. Stakeholders also inform that clinical studies—some already presented at international congresses—supporting these observations, as well as further evidence are in progress.

RIFAMYCIN

Concerns about the non-inclusion of rifamycin revolve around its use in topical ophthalmic treatments. Stakeholders argue that its topical application helps reduce the need for systemic antibiotics, thereby supporting efforts against antimicrobial resistance under the One Health framework.

Stakeholders are also concerned that the alternatives suggested—such as moxifloxacin and ofloxacin—are classified as highest priority critically important antimicrobials, while fusidic acid is limited to Gram-positive coverage.

TENOIC ACID

Stakeholders have raised concerns about the non-inclusion of tenoic acid, particularly in the context of combating antibiotic resistance and promoting the One Health approach. They describe tenoic acid as a complementary treatment for respiratory conditions in horses, with potential to reduce or enhance the efficacy of antibiotic use.

While literature remains limited, stakeholders cite clinical evidence supporting its use such as studies presented at international congresses, indicating both clinical interest and a lack of observed toxicity, and seem willing to provide additional detail.

ANNEX

Allison et al. (2017), [Allison A, Robinson R, Jolliffe C, Taylor PM. Evaluation of the use of midazolam as a co-induction agent with ketamine for anaesthesia in sedated ponies undergoing field castration. Equine Vet J. 2018 May;50(3):321-326. doi: 10.1111/evj.12759. Epub 2017 Sep 29. PMID: 28898439.]

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