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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

Withdrawal assessment report for Equidormin (EMEA/V/C/006593/0000)

INN: midazolam

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant CP-Pharma Handelsgesellschaft mbH submitted on 25 November 2024 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Equidormin, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 18 July 2024 as no other marketing authorisation had been granted for the veterinary medicinal product within the Union.

At the time of submission, the applicant applied for the following indications:

Intravenous co-induction of anaesthesia (especially) with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia. Other combinations are possible, e.g. with thiopental and alfaxalone.

As part of partial intravenous anaesthesia (PIVA) and total intravenous anaesthesia (TIVA) for maintenance for medium duration processes.

Anti-convulsant, for treatment of seizures.

The active substance of Equidormin is midazolam, a derivative of the imidazobenzodiazepine group, which exhibits similar pharmacologic actions as other benzodiazepines. The subcortical levels (primarily limbic, thalamic, and hypothalamic), of the CNS are depressed through an enhancement of the GABAergic neurotransmission at inhibitory synapses, thus producing anxiolytic, sedative, skeletal muscle relaxant, and anticonvulsant effects. The target species is horse (non food-producing).

Equidormin solution for injection contained 5 mg/ml midazolam and was presented in vials of differing volumes.

The applicant submitted the dossier under Article 23 of Regulation (EU) 2019/6 – an application for limited markets.

On 9 September 2025, CP-Pharma Handelsgesellschaft mbH withdrew the application during the clock-stop at day 120 of the procedure. In its letter notifying the Agency of the withdrawal of the application, the applicant stated the reason for the withdrawal was based on a commercial decision.

Limited market status

The applicant requested classification of this application as limited market by the CVMP.

The Committee confirmed on 16 March 2022 that limited market status would apply as horse (non-food-producing) is not listed in Article 4(29)(b) of Regulation (EU) 2019/6, which provides that: "'*limited market' means a market for one of the following medicinal product types: (b) veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats*". Based on the information available at the time, the CVMP also considered that the application could qualify to be submitted under Article 23 of Regulation (EU) 2019/6 (limited market), as the benefit of the availability on the market of the veterinary medicinal product to the animal or public health was expected to outweigh the risk inherent in the fact that certain documentation would not be provided. The CVMP further considered that the data requirements in the relevant CVMP guideline(s) for applications for veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 would be applicable when assessing the application. However, prior to withdrawal of the application the applicant had been requested to provide (updated) evidence that the conditions of Article 23 of Regulation (EU) 2019/6 continued to be met as the validity

of the legal basis must be assessed and confirmed by CVMP at the time of the final opinion and considering the final approved indication.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant provided a summary of the pharmacovigilance system master file which fulfilled the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF), has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

Manufacture, quality control, primary and secondary packaging, storage and/or distribution of the active substance midazolam were proposed to take place outside the EEA. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an audit performed in July 2022.

Finished product

Manufacture, sterilisation, quality control testing (microbiological, chemical/physical), primary and secondary packaging of the finished product were proposed to take place within the EEA. The site had a valid manufacturing authorisation issued. GMP certification, which confirmed the date of the last inspection and shows that the site is authorised for the activities indicated above, had been provided too.

Quality control testing (chemical/physical), of the finished product were proposed to take place within the EEA. The site had a valid manufacturing authorisation issued. GMP certification, which confirmed the date of the last inspection and showed that the site was authorised for the activities indicated above, was provided.

Secondary packaging and batch release of the finished product were proposed to take place within the EEA. The site had a valid manufacturing authorisation issued. GMP certification, which confirmed the date of the last inspection and showed that the site was authorised for the activities indicated above, was provided.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file was considered to be in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites was satisfactorily established and in line with legal requirements.

Part 2 - Quality

Composition

The product was a sterile solution for injection containing 5 mg/ml of midazolam as the active substance, together with several excipients. The product was proposed to be packaged in vials of differing volumes. A 20 mm bung size was used for all vial sizes. At the time of withdrawal of the application, a number of amendments to the declaration of the product composition in the dossier were outstanding.

Containers and closure system

The product was a colourless to slightly yellowish solution which was proposed to be packaged in type I glass vials with a rubber stopper and a closure system. The glass vials comply with Ph. Eur. 3.2.1 glass containers for pharmaceutical use. The rubber stopper complied with the requirements in the European Pharmacopoeia (Ph. Eur. 3.2.9). In-house specifications and certificates of analysis for the packaging materials had been requested. The dossier did not include any reference to outer containers, although it appeared that the vials were packaged in an outer cardboard box. Details of the outer box were requested to be included in the dossier in Parts 2A and 2C.

Product development

The product formulation development was based on publicly available information from a number of sources including the British Pharmacopoeia (BP) and United States Pharmacopoeia (USP) monographs for "Midazolam injection", information available in public domain related to another midazolam injection product which is authorised in several MSs and in the USA and information related to human midazolam containing products. The excipients used in the formulation were widely used in parenteral preparations. Publicly available information on the authorised midazolam injection product allowed the applicant to determine the quantitative composition of that product with respect to the active substance i.e. 5.0 mg/ml midazolam and the preservative. The remaining quantitative details were deduced from some limited analytical comparative data and reference to full qualitative and quantitative details available on the label of a US authorised midazolam injection product for human use. The information provided on elaboration of the qualitative and quantitative formulation of the product was limited. Very little qualitative data was provided. Despite the limited data provided, the derivation of the formulation was clearly based on publicly available information on existing products, and provision of additional information was not considered necessary.

Data was presented demonstrating that the sterilisation process had no detrimental impact on the quality of the product. The proposed packaging is routinely used for this type of product. Whilst no rationale was provided for the selected rubber stopper, it was presumably used to minimise any potential sorption or leaching. The suitability of the packaging was demonstrated in development stability studies and in the stability data presented in Part 2F of the dossier which includes vials stored in the inverted position.

The proposed SPC included information on use of the product in combination with ketamine and a statement that the 2 products can be administered in the same syringe. The applicant therefore investigated the compatibility of the product and ketamine when used in the ratio referenced in the SPC. The 2 products were mixed in a syringe and tested. No changes are observed in any of the tested

parameters and the data presented was considered to support the statements in the SPC regarding use in combination with ketamine.

Description of the manufacturing method

The manufacturing process was a standard manufacturing process involving the sequential addition and mixing of the components and sterilisation.

Mixing times and speeds were stated where appropriate and in-process controls were provided. A number of discrepancies in the in-process controls were noted and a question had been raised, but otherwise, the information provided in the dossier was considered to be acceptable for this simple standard process.

Process validation data was presented for batches filled into different the vial sizes. Testing was conducted before filtration, after filtration and during filling. Testing was also conducted to support hold times. The process validation data was acceptable to demonstrate that the product could be routinely manufactured to the desired quality. With reference to the process validation guideline, the provision of process validation data was considered adequate for a sterile solution formulation that is sterilised according to standard conditions i.e. the Ph. Eur. reference conditions. Nevertheless, a process validation scheme in accordance with Annex I of the guideline remained to be provided for the maximum batch size.

Control of starting materials

Active substance

The active substance, midazolam, is monographed in the Ph. Eur. The active substance is supplied from one manufacturer and supporting data was provided in the form of a Ph. Eur. Certificate of Suitability (CEP). A copy of the current Ph. Eur. CEP was provided.

The active substance specification includes tests for appearance, identity, appearance of solution, assay, impurities, sulfated ash, loss on drying, and microbiological quality. The test methods used are all validated are as per the Ph. Eur. monograph or standard Ph. Eur. methods and neither a description of the methods nor their validation are required in the dossier. Prior to withdrawal of the application, a question had been raised on the quality of water used in the last step of the synthesis of the active substance.

The CEP for the active substance includes a retest period when stored in a double polyethylene bag, placed in an aluminium bag.

Excipients

All excipients are well known pharmaceutical ingredients, and their quality is compliant with their respective Ph. Eur. monographs. Sample certificates of analysis, demonstrating compliance are provided for each excipient. There are no novel excipients used in the finished product formulation. The absence of microbial control on the excipient specifications was accepted as by virtue of their intrinsic properties, they will not support microbiological growth. A question had been raised regarding the control of residual solvents in one excipient.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests on the finished product

The specification proposed at release was generally appropriate to control the quality of the finished product. However, some questions had been raised.

A single analytical method was used for the identification and assay of midazolam and its related substances and the preservative. The method is validated in accordance with VICH GLs 1 and 2.

The potential presence of elemental impurities in the finished product was assessed on a risk-based approach in line with the CVMP guidance on risk management requirements for elemental impurities in veterinary medicinal products.

Batch analysis results were provided for three batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

The specification applied during shelf-life is similar to that at release.

Batches were placed on stability under real time and accelerated conditions and different batches of active substance were used in the batches. Testing of inverted vials stored under real time conditions and in-use testing was also included in the study. A bracketing design means that the smallest and largest vials sizes are tested which is acceptable in line VICH GL45. For the in-use studies the largest vial size was tested as this is considered to represent worst case scenario. Data up to 6-months was available for two of the batches and 3-month data was available for the third batch. The stability study design was generally acceptable. However, no clear stability protocol was included in the dossier and one needed to be provided which included clarification on the proposed duration of the study, justification for the length of the inverted vial studies and justification for any proposed skip testing.

All results for all parameters remained within specification at all times in the stability study.

An in-use stability study including repeat challenge preservative efficacy studies was presented. However, a number of issues regarding the study required to be addressed and additional data were required before an in-use shelf life could be agreed.

A photostability study in line with VICH GL5 was conducted on two pack sizes. Section 5.3 of the SPC included a precaution to 'Keep the vial in the outer carton in order to protect from light.'

Based on the data available prior to withdrawal of the application, a 12-month shelf-life with a storage precaution of 'Keep the vial in the outer container in order to protect from light' was considered appropriate. Further details were required before an in-use shelf-life could be agreed for the product.

Overall conclusions on quality

The information provided on elaboration of the qualitative and quantitative formulation of the product was limited and largely based on publicly available data. Very little qualitative data was provided: only results for a small number of parameters for a batch of another midazolam injection product which is authorised in the EU and the osmolality of a single trial batch of the proposed formulation. A question had been raised regarding the relevance of osmolality testing conducted. Despite the limited data provided, the derivation of the formulation was clearly outlined, and provision of additional data, other than that requested above was not considered necessary.

Manufacture of the final product is a simple process, involving sequential addition, stirring and dissolution of the components. A number of minor corrections to Part 2 B of the dossier had been required prior to withdrawal of the application, but otherwise the data provided was satisfactory. The process was satisfactorily validated.

The active substance is supported by a current CEP. The applicant's specification complies with the Ph. Eur. monograph and the CEP and was considered acceptable. Additional batch data from the dosage form site was outstanding. The excipients are commonly used in parenteral pharmaceutical forms, and all comply with their respective Ph. Eur. monographs. Some updates had been requested to the preservative specification to include control of potential residual solvents. The information provided regarding the container-closure system was generally acceptable although specifications from the dosage form site were outstanding.

Control of the finished product was well described. A number of updates to the finished product release specification were outstanding. The analytical methods were satisfactorily validated in line with VICH GL 1 and GL 2. Three batches had been placed on stability under real time and accelerated conditions and the data available supported a 12-month shelf life. Some additional data had been required before the proposed in-use shelf life could be accepted. Data provided in Part 2.A.4 of the dossier showed that the product is unstable in light and an appropriate warning was included in the SPC, but the dossier required updating in this respect.

Part 3 – Safety documentation (Safety and residues tests)

This application was submitted in accordance with Article 23 of Regulation (EU) 2019/6 (limited markets). The application was made through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

Equidormin contained the active substance midazolam, a derivative of the imidazobenzodiazepine group, which exhibits similar pharmacologic actions as other benzodiazepines. The subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS are depressed through an enhancement of the GABAergic neurotransmission at inhibitory synapses, thus producing anxiolytic, sedative, skeletal muscle relaxant, and anticonvulsant effects.

The target species for the candidate veterinary medicine product was horses (non food-producing).

The applicant applied for the following indications for the candidate VMP:

"*Intravenous co-induction of anaesthesia (especially) with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia. Other combinations are possible, e.g. with thiopental and alfaxalone.*

As part of partial intravenous anaesthesia (PIVA) and total intravenous anaesthesia (TIVA) for maintenance for medium duration processes.

Anti-convulsant, for treatment of seizures."

Equidormin solution for injection contained 5 mg/ml midazolam and was presented in different pack sizes.

Note: In their submission, the applicant provided bibliographic references in support of safety and efficacy of the candidate VMP, and the applicant also made frequent reference to an authorised VMP containing 5 mg/ml midazolam and presented as a solution for injection with which equivalence was claimed. The VMP in question is currently authorised in accordance with Article 12(3) of Directive 2001/82 (that is, a full dossier) in 27 member states by Mutual Recognition.

In assessing the dossier provided for the current MAA, the CVMP considered the submitted bibliographic data in support of safety of midazolam/the candidate product. Any direct references to the marketing authorisation referenced above, and the safety data underpinning that authorisation, were not considered. The criteria for 'well-established veterinary use', as detailed in IV.5.3.1 of Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 were considered relevant to this assessment, and the data were assessed according to these criteria.

Safety tests

The candidate *VMP*, Equidormin, was a solution for injection containing the active substance midazolam at a concentration of 5 mg/ml.

The formulation also contained the excipients that are well-known in the veterinary pharmaceutical industry and are currently in use in the manufacture of a wide range of veterinary medicinal products.

It was noted that the preservative may produce hypersensitivity reactions, including local irritation and skin reactions.

The proposed excipients were discussed by the applicant in detail in Part 3 of the dossier. All excipients were of European Pharmacopoeial standard. It was accepted that the excipients used can generally be considered safe at the concentrations used in the candidate product. The main risks posed to the user in relation to the formulation related to the active substance midazolam, and the preservative (primarily effects on cardiorespiratory function for midazolam, and risk of hypersensitivity reactions for both substances).

Pharmacology

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicology

The applicant presented a summary of general toxicology data extracted from published literature (Schlappi, 1983)[1].

The applicant claimed that the safety of the active ingredient was supported by its history of use in human medicine for similar indications, and well-established use in the target species horses (and also cats and dogs). Evidence for well-established use in horses was presented in Part 4.

Single-dose toxicity

LD_{50} values of approximately 1600 mg/kg (oral administration) were determined for midazolam in the rat and the mouse. For intravenous administration, the reported values were 75 mg/kg (rat) and 50 mg/kg (mouse).

Repeat-dose toxicity

Subchronic oral studies over 13 weeks in doses of 5, 15 and 45 mg/kg/day in the dog and 50, 100 and 200 mg/kg/day in the rat demonstrated minimal toxicity for midazolam, as for other benzodiazepines.

High doses produced increased liver weight in the rat and the expected increases in alkaline phosphatase in the dog (species-specific reaction). Detailed blood and urine analyses as well as histological examination of organs produced no indication of changes relevant for man.

Subchronic parenteral studies (i.v. and i.m. for five weeks) using up to 6 mg/kg/day in dogs and rats showed the compound to be systemically and locally well-tolerated.

Tolerance in the target species

See Part 4.

Reproductive toxicity, including developmental toxicity

Studies on reproduction indicated that midazolam was neither embryotoxic nor teratogenic and that it had no effect on the fertility and post-natal development of animals.

Genotoxicity

In the AMES test and the AMES fluctuation test, midazolam had no mutagenic effect.

Carcinogenicity

No proprietary data was provided. The cited published literature gave no final conclusion on carcinogenicity for the active substance (the cited publication simply states, "*Carcinogenicity studies are in progress*.").

Overall conclusion on the toxicity data provided

The toxicity data submitted by the applicant relating to midazolam were based on a single article from published literature (Schlappi, 1983). This paper presents a high-level summary of the findings of acute, subchronic, reproductive/developmental and mutagenicity studies. The source of the information included in the paper is unclear (the paper does not cite any other publications) and there is no information on the GLP status of the various studies, nor the extent to which they complied with relevant (current) guidance, etc. Based on the limited published data provided, it was not possible to conclude on the toxicological profile of the active substance. The single publication provided was not considered to meet the very basic requirements for what would be considered appropriate bibliography (section IV.5 of Commission Delegated Regulation (EU) 2021/805).

[1] Schlappi, B. (1983). Safety aspects of midazolam. British Journal of Clinical Pharmacology, (16) pp.37-41

The applicant had been requested to provide updated toxicity data based on review of more recent scientific literature, with particular attention to information on reproductive/developmental effects and the potential for genotoxicity or carcinogenicity.

Other requirements

Observations in humans

The active substance midazolam is used in human medicine as a short-acting sedative and sleep-inducing agent. The applicant referred to the SmPC of the authorised human medicinal product, '*Midazolam 5 mg/ml Solution for injection or infusion*', which has the following therapeutic indications in both adult and paediatric patients: Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia, premedication before induction of anaesthesia induction of anaesthesia, and sedation in intensive care units. It is also indicated as a sedative component in combined anaesthesia in adults only. The most dramatic reported adverse drug reaction following administration of midazolam to human patients is cardiac arrest, particularly after parenteral administration. The SmPC contains a comprehensive list of reported adverse effect observed with use of midazolam, also including hypersensitivity, angioedema, anaphylactic shock, behavioural changes, and effects on cardiorespiratory function.

Appropriate warnings were included in section 3.5 of the proposed SPC regarding the potential for hypersensitivity reactions in humans, and the measures to be taken (urgent medical attention) in the event of such a reaction occurring.

Excipients

It was considered that the toxicity of the veterinary medicinal product would be determined primarily by its active substance, midazolam. However, the preservative may produce hypersensitivity reactions, including local irritation and skin reactions. Therefore, hypersensitivity reactions due to the presence of the preservative could not be fully excluded. This risk was adequately captured in the proposed SPC, with appropriate mitigation measures.

User safety

The quantitative user risk assessment presented by the applicant was not conducted in line with CVMP guidance (EMA/CVMP/543/03-Rev.1). Margins-of-exposure (MOEs) were not calculated for the active substance, midazolam, for the potential dermal and parenteral (self-injection) routes of exposure. While it could be accepted that the exposure scenarios considered by the applicant were indeed worst-case, it was noted that the applicant had not compared the estimated exposure to a toxicological reference value.

It was also noted that, contrary to the applicant's claim that no effect was anticipated following exposure to the excipients, the preservative in the formulation is known to cause hypersensitivity reactions in humans. However, as hypersensitivity reactions are not relative to exposure, the omission of a quantitative risk assessment for this particular excipient could be accepted. Additionally, the remaining excipients were all well-known and widely used in pharmaceutical formulations, and generally regarded as safe.

Prior to withdrawal of the application, the applicant had been requested to present an updated user safety assessment supported by adequate toxicity data that would allow characterisation of the risk to

users of the product. Based on the risks identified in the context of that assessment, appropriate measures to mitigate the risk to users were to be proposed. The applicant was reminded that, in assessing the dossier provided for the current MAA, claimed comparability to the marketing authorisation of another midazolam containing solution for injection authorised in the EU, and reference to the safety data underpinning that authorisation, was not considered appropriate, and that the user safety statements proposed for Equidormin should be based on a '*stand-alone*' user risk assessment supported by toxicity data generated by the applicant or sourced from the published domain.

Environmental risk assessment

An environmental risk assessment was provided in accordance with the CVMP 'Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38' (EMA/CVMP/ERA/418282/2005-Rev.1-Corr.1).

The Applicant followed the Phase I decision tree and concluded that the environmental risk assessment could stop in Phase I, as the candidate VMP was intended only for use in non-food animals, and further that it was only intended for use in individual animals.

No specific environmental warnings were considered necessary and the standard text relating to disposal of unused product was proposed for inclusion in the SPC of the candidate product and this was considered acceptable. It could be concluded that the candidate formulation would not present an unacceptable risk for the environment when handled, used, stored, and disposed of in accordance with the recommendations included in the proposed SPC.

Overall conclusions on the safety documentation: safety tests

This application was submitted in accordance with Article 23 of Regulation (EU) 2019/6 (limited markets). The application was made through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

Pharmacology

See Part 4A of this report.

Toxicology

The toxicity data submitted by the applicant relating to midazolam were derived from a single article from published literature (Schlappi, 1983). This paper presented a high-level summary of the findings of acute, subchronic, reproductive/developmental and mutagenicity studies. The source of the information included in the paper is unclear (the paper did not cite any other publications) but was assumed to be the Biological Pharmaceutical Research Department of F. Hoffmann-La Roche & Co Ltd, Basel, Switzerland (the address given for the author). Further, there is no information on the GLP status of the various studies, nor the extent to which they complied with relevant (current) guidance, etc.

Based on the limited published data provided, it was not possible to conclude on the toxicological profile of the active substance. The following points, in particular, were noted:

- Limited data on reproductive and developmental toxicity were presented by the applicant. Nonetheless, it was claimed that no embryotoxic or teratogenic effects were to be anticipated with the use of midazolam, and that treatment would not affect fertility or post-natal development. Accordingly, the following text was proposed for inclusion in the SPC of the candidate veterinary

medicinal product: "*Laboratory studies in mice, rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects*." However, the absence of foetotoxic effects was not universally accepted – according to classifications provided by marketing authorisation holders to ECHA, midazolam is sometimes classified as '*suspected of damaging fertility or the unborn child*' (ECHA Summary of Classification and Labelling – Midazolam).

- Regarding evaluation of mutagenic potential specifically, the author claimed no mutagenic effect based on Ames tests; however, such limited testing would not normally be accepted. In accordance with the requirements of Annex II to Regulation (EU) 2019/6, as amended, the expectation is that "*A standard battery of genotoxicity tests in accordance with standard tests based on established guidance (including VICH GL23 and OECD tests) shall usually be carried out on the active substance(s).*"
- Additionally, no final conclusion was drawn by the author of the cited article (Schlappi, 1983) in relation to carcinogenicity: it is simply stated that "*Cancerogenicity studies are in progress*."
- Appropriate documented toxicity endpoints (NOAEL/LOAEL) should be proposed (for the purposes of conducting a meaningful URA).
- The single publication provided was not considered to meet the very basic requirements for what would be considered appropriate bibliography in accordance with section IV.5 of Commission Delegated Regulation (EU) 2021/805. The CVMP considered it likely that further information on the toxicological properties of midazolam would have come to light since the Schlappi (1983) article was published. The applicant was therefore requested to provide updated toxicity data based on review of more recent scientific literature. The applicant was reminded that particular attention should be paid to information on reproductive/developmental effects (and the highlighted discrepancy between the proposed SPC text and the information publicly available from other sources) and the potential for genotoxicity or carcinogenicity.

User safety

The applicant had been requested to present an updated user safety assessment, supported by adequate toxicity data, to allow characterisation of the risk to users of the product. Based on the risks identified in the context of that assessment, appropriate measures to mitigate the risk to users were to be proposed. The applicant was reminded that the user safety statements proposed for Equidormin needed to be based on a '*stand-alone*' user risk assessment supported by toxicity data either generated by the applicant or sourced from the published domain.

Environmental safety

An environmental risk assessment was provided in accordance with the CVMP 'Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38' (EMA/CVMP/ERA/418282/2005-Rev.1-Corr.1).

The applicant followed the Phase I decision tree and concluded that the environmental risk assessment could stop in Phase I, as the candidate VMP is intended only for use in non-food animals, and further that it is only intended for use in individual animals.

No specific environmental warnings were considered necessary and the standard text relating to disposal of unused product was proposed for inclusion in the SPC of the candidate product and this was considered acceptable. It could be concluded that the candidate formulation would not present an unacceptable risk for the environment when handled, used, stored, and disposed of in accordance with the recommendations included in the proposed SPC.

Part 4 – Efficacy

This application was submitted in line with the requirements for submissions under Article 23 of Regulation (EU) 2019/6 – an application for limited markets and concerns the candidate product 'Equidormin 5 mg/ml solution for injection for horses', which contains the active substance midazolam intended for use in the target animal species horses (non-food producing).

At the time of submission, the applicant applied for the following indications:

Intravenous co-induction of anaesthesia (especially) with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia. Other combinations are possible, e.g. with thiopental and alfaxalone.

As part of partial intravenous anaesthesia (PIVA) and total intravenous anaesthesia (TIVA) for maintenance for medium duration processes.

Anti-convulsant, for treatment of seizures.

The applicant provided bibliographic references from the public domain in order to meet pre-clinical and clinical data requirements.

Consistent with the guidance as provided in the Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 (EMA/CVMP/52665/2020-Rev.1), the provision of published literature rather than proprietary studies could be accepted in principle.

As the applicant provided bibliographic references from the public domain in order to meet pre-clinical and clinical data requirements, the criteria that are taken into account when establishing 'well-established veterinary use' as detailed in IV.5.3.1 of Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 were therefore considered relevant to this assessment, and the data were assessed according to these criteria.

Concerning the legal basis of the ongoing MAA, the applicant had been requested to provide (updated) evidence that the conditions of Article 23 of Regulation (EU) 2019/6 were met by this application, as it was the current view of the CVMP that the conditions of an Article 23 were not met due to the existence of other authorised products for the following proposed indications:

- Intravenous co-induction of anaesthesia (especially) with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia. Other combinations are possible, e.g. with thiopental and alfaxalone.

- As part of partial intravenous anaesthesia (PIVA) and total intravenous anaesthesia (TIVA) for maintenance for medium duration processes.

In the event that eligibility for Article 23 of Regulation 2019/6 could not be supported, the applicant was requested to confirm acceptance of a change in legal basis of the application to Article 22 of Regulation (EU) 2019/6.

Pre-clinical studies

Pharmacology

Pharmacodynamics

The applicant cited two references for the purpose of describing the pharmacodynamics of the active substance midazolam. The first of these, a summary of product characteristics for a midazolam solution for injection authorised for use in humans contained a brief description of the chemical structure of midazolam and the mechanism of action of benzodiazepines, specifically noting that this group of pharmacotherapeutics enhance GABAergic transmission at inhibitory synapses. The applicant also included text from an entry in the veterinary pharmacology reference book 'Plumb's Veterinary Drug Handbook' that described in brief the pharmacodynamic effects of midazolam inclusive of anxiolytic, sedative, anticonvulsant effects, and skeletal muscle relaxation. This text was general and did not apply to a specific animal species.

The applicant did not provide information concerning the pharmacodynamics of midazolam in the target animal species horses, as is foreseen in the relevant CVMP guideline. Prior to withdrawal of the application the applicant had been requested to provide further information, as available, on the pharmacodynamics of the active substance midazolam in horses, with particular emphasis on the intended effects and the possibility of secondary pharmacological effects in this target animal species. Further updates to section 4.2 of the SPC could also have been required pending the provision of further information.

Pharmacokinetics

The applicant cited two references for the purpose of describing the pharmacokinetics of the active substance midazolam. Of these, the CVMP considered the publication by Hubbel et al. (2013)[2] to be of particular relevance noting that it describes a pharmacokinetic study of midazolam in horses.

With regard to the pharmacokinetics of midazolam, the distribution of midazolam in the horse following intravenous administration is rapid and relatively extensive, and the volume of distribution (Vd) at steady state was reported to be 2094 mL/kg (range 2076 – 2413 mL/kg) when midazolam was administered at 0.05 mg/kg bw. It is also reported that (in humans) midazolam is highly plasma protein bound, mainly to albumin. It is concluded that based on a rapid onset of clinical effect, midazolam crosses the blood brain barrier rapidly.

Regarding metabolism, (in humans) midazolam is biotransformed in the liver by glucuronide conjugation. Midazolam is converted to the primary active metabolite alpha-hydroxy-midazolam, and other inactive metabolites by cytochrome P450-3A4, and metabolites are excreted primarily in urine as glucuronide conjugates. Cimetidine and other inhibitors of this pathway could result in accumulation of midazolam.

Regarding elimination, Hubbel et al. (2013)[2] report an elimination half-life of 216 minutes following administration of a dose of 0.5 mg/kg bw by intravenous bolus. As noted above, the main route of elimination is renal with < 10 % eliminated in the faeces.

[2] Hubbell, J. A., Kelly, E. M., Aarnes, T. K., Bednarski, R. M., Lerche, P., Liu, Z., & Lakritz, J. (2013). Pharmacokinetics of midazolam after intravenous administration to horses. Equine veterinary journal, 45(6), 721–725. https://doi.org/10.1111/evj.12049

It is concluded by the authors of Hubbel et al. (2013)[2] that an intravenous bolus of midazolam in horses produced muscle relaxation (postural sway and ataxia) and some agitation, but no sedation.

The proposed SPC contained a precaution concerning the possibility of drug accumulation following repeated doses (in section 3.5 Special precautions for use), however the potential for drug accumulation was not addressed by the applicant in this section of the dossier. Noting that midazolam could also be used for induction of anaesthesia before a constant rate infusion (as part of a PIVA or TIVA protocol) is initiated, and considering the reported elimination half-life of 216 minutes, the potential for accumulation of midazolam in the horse is a relevant pharmacokinetic property, as it is one which could have implications for target animal tolerance. Prior to withdrawal of the application the applicant had therefore been requested to provide further information concerning accumulation of the active substance midazolam. In the context of major objections raised concerning the proposed indications for use as part of PIVA / TIVA protocols, the applicant was requested to discuss any implications of accumulation of midazolam for target animal tolerance, particularly in animals in which midazolam is used for induction of anaesthesia before initiation of a midazolam-containing TIVA/PIVA maintenance protocol.

In addition, the applicant was requested to provide information on the kinetics of midazolam in horses following co-administration with other active substances as cited in the SPC. Noting that these active substances can modify the cardiac output, it may be expected that clearance of midazolam and accumulation will be impacted in cases of co-administration with other active substances.

Information concerning use of midazolam in hypoalbuminaemic horses and information concerning possible interactions with other medicinal products, including drugs that are known to inhibit or enhance CYP450 metabolism was proposed for inclusion in the relevant sections of the SPC.

The applicant provided a summary of the pharmacokinetics of midazolam following administration of a single intravenous bolus based on published literature and considered information relevant to the target animal species. However, further information concerning the potential for accumulation of midazolam and effects on pharmacokinetics of co-administration with other active substances was outstanding. In respect of the information currently proposed for inclusion in section 4.3 Pharmacokinetics of the SPC, updates to the SPC resulting from the questions raised may have been required.

Dose determination and confirmation

Dose justification

The proposed SPC contained 4 indications for the candidate VMP, each of which is associated with a specific dose rate. These are:

1. Co-induction of anaesthesia – midazolam at a dose of 0.06 mg/kg bodyweight in combination with ketamine at a dose of 2.2 mg/kg bodyweight. Other combinations are possible, e.g., with thiopental and alfaxalone.
2. Part of partial intravenous anaesthesia (PIVA) – along with a suitable inhalant anaesthetic agent, a constant rate infusion (CRI) of midazolam at 0.018 mg/kg/hour in combination with ketamine and xylazine at 1.2 and 0.3 mg/kg/hour respectively.
3. Part of total intravenous anaesthesia (TIVA) – a constant rate infusion of midazolam at 0.12 mg/kg/hour in combination with ketamine and xylazine at 1.8 and 0.96 mg/kg/hour respectively; OR a midazolam-ketamine-romifidine infusion at about 0.1 – 3 – 0.1 mg/kg/hour respectively.

4. Anti-convulsant treatment of seizures – intravenous or intramuscular use.
   Foals – 0.04 to 0.1 mg/kg and repeated when necessary

   Adult horse – 25-50 mg/horse and repeated when necessary

The proposed doses as listed above were justified by the applicant based on bibliographic references. The justification of each proposed dose rate is further evaluated below.

In support of the dose rate proposed for indication numbered 1., that is, co-induction of anaesthesia, the applicant stated that the proposed dose is cited in approximately 20 scientific articles and is identical to the dose stated in the SPC of the 'essentially similar' to another authorised VMP.

The applicant's reference to the dose rate of an authorised VMP that they consider to be essentially similar to the candidate VMP was noted but not considered further in the context of this application. The scientific articles are referenced briefly in this section, and further assessment of these literature references is included in the Clinical trial(s) section, below. In summary however, it was accepted that the dose rate for co-induction of anaesthesia proposed by the applicant in section 3.9 of the SPC, that is 0.06 mg/kg bw in combination with ketamine at 2.2 mg/kg bodyweight was suitably supported by the literature references provided.

In support of the dose rates proposed for the indications numbered 2. and 3. above (i.e., as part of PIVA and TIVA protocols respectively), the applicant made general reference to published articles in this section, and further assessment of these literature references is included in the Clinical trial(s) section below. In summary however, it was accepted by the CVMP that the choice of dose rates for the candidate VMP in PIVA and TIVA protocols as proposed by the applicant in section 3.9 of the SPC represented the most commonly reported protocols for this use in the literature references provided. Notwithstanding this point, it was noted that major objections were raised in respect of the safety and efficacy of these proposed indications.

In support of the dose rate proposed for the indication numbered 4. above, that is treatment of seizures in foals and adult horses, the applicant cited a veterinary reference text 'Plumb's Veterinary Drug Handbook' in which the dose '2 – 5 mg (total dose) for a 50 kg foal given IV or IM, may be repeated to effect' is stated. This dose is also included in the reference ('Wilkins 2005'[3]) that was also cited by the applicant. Neither reference provided by the applicant provide clear evidence of how the dose rate 2 – 5 mg (total dose for a 50 kg foal) was selected, nor determined to be effective, and neither reference refers to use of midazolam as a treatment for seizures in adult horses. It was concluded that the literature references provided do not suitably support the proposed dose rate for midazolam for control of seizures in either foals or adult horses. A major objection was raised concerning this indication.

Tolerance in the target animal species

In order to characterise the target animal safety profile of the candidate product, the applicant provided bibliographic references, rather than proprietary target animal safety data generated using the candidate formulation.

The applicant noted that in the publication authored by Hubbel et al. (2013)[2], in which horses were administered midazolam as an intravenous bolus at either 0.05 or 0.1 mg / kg bw, most / all horses (for the 0.05 and 0.1 mg/kg doses respectively) were observed to be ataxic within 5 minutes of treatment and this effect was observed for 55 minutes and 90 minutes (for the 0.05 and 0.1 mg/kg doses respectively). These horses were not sedated following treatment and 4/5 and 4/5 horses (for

[3] Wilkins, P. (2005). How to use midazolam to control equine neonatal seizures. Proc Annu Meeting Am Assoc Equine Pract. 51. 279-280.

the 0.05 and 0.1 mg/kg doses respectively) were mildly agitated or agitated. Heart and respiratory rates were not altered from baseline following treatment.

The applicant made general reference to the published articles provided in support of efficacy as evidence of target animal tolerance (when midazolam is used as a co-induction agent with ketamine). The applicant also concluded that for the proposed use as part of PIVA or TIVA protocols, as the candidate product will be administered slowly, that the safety profile for use as a single IV bolus could be applied to these scenarios (posologies) also.

No reference was made by the applicant concerning target animal tolerance for the proposed indication 'anti-convulsant, for treatment of seizures' for which a specific dose was proposed for adults and for the sensitive target animal sub-species, foals.

Section 3.6 of proposed SPC for the candidate product in which the adverse event profile is detailed, was the same as that in the SPC of an authorised VMP containing midazolam. The applicant proposed that this approach could be taken 'for the sake of SPC harmonisation.' Extrapolation of proprietary safety data from the authorised VMP was not considered an acceptable approach in the context of this application. The safety profile of the candidate product should solely be derived from / supported by the bibliographic references provided by the applicant.

Notwithstanding this point, the CVMP considered that, based on the available bibliography, the adverse events as reported in section 3.6 of the SPC (namely ataxia / incoordination during recovery, and urination and respiratory depression during induction of anaesthesia) could be accepted as suitably accurate when considering use of the candidate VMP for co-induction of anaesthesia in conjunction with ketamine.

For the remaining proposed indications (i.e., for PIVA/TIVA and treatment of seizures), it was concluded by the CVMP that the safety profile of the candidate product had not been suitably characterised by the applicant. Specifically, it was noted that the applicant had not addressed the potential impact of accumulation of midazolam when used as part of a PIVA/TIVA protocol on target animal safety, and particularly on recovery of a horse from anaesthesia. Major objections were raised in respect of both safety and efficacy of these indications, and the applicant was requested to suitably describe and summarise the available bibliographic target animal tolerance data for these indications for use (and the associated posologies). Should these indications be retained in the SPC, the applicant was required to reflect relevant information concerning target animal tolerance in section 3.6 of the proposed SPC.

With regard to other sections of the SPC (besides 3.6) that contain information related to target animal safety, the applicant based the text in the proposed SPC on the SPC of an authorised VMP containing midazolam. As most of this information is general in nature, and not proprietary / specific to the VMP, this approach was considered acceptable in principle, however a number of points concerning this information remained outstanding.

In summary, prior to withdrawal of the application the CVMP concluded that the safety profile (adequate tolerance and recovery) of the candidate formulation in the target animal species when administered once as a co-induction agent with ketamine was suitably characterised and reported in section 3.6 of the SPC. With regard to the proposed indications for use as part of PIVA/TIVA protocols, and as an anti-convulsant, tolerance in the target animal species was not suitably characterised by the applicant. Major objections that concerned both safety and efficacy of the candidate product when used for these indications were raised. As such, no conclusions on safety of the candidate product in the target animal species horses when used as part of PIVA/TIVA protocols, or as an anti-convulsant, could be made. Further updates to sections 3.3, 3.5, 3.8 and 3.10 of the SPC had been requested of the applicant.

Clinical trial(s)

In support of efficacy of the candidate product for the proposed indications at the proposed posologies associated with these indications, the applicant referred to published literature from the public domain.

The applicant addressed the applicability of / bridging of bibliographic data to the candidate product noting that the cited data concerned aqueous solutions and were administered via the intravenous route. Considering that the candidate VMP is a single active substance presented in an aqueous solution intended for intravenous administration (for all the proposed indications), which is also the case for the presentations and use of midazolam in the presented bibliographic references, the conclusion of the applicant could be accepted. The cited data could be considered applicable to the candidate VMP (when administered intra-venously), and no further bridging data were required in order to extrapolate safety and efficacy data for this route of administration from the bibliographic studies presented. It was noted however that the intramuscular route of administration was also described for one of the proposed indications (anti-convulsant for the treatment of seizures). In order to extrapolate safety and efficacy data for this route of administration from the bibliographic data provided, the applicant had been required to further justify how the data generated using different formulation(s) in the cited published papers could be considered applicable to the candidate VMP formulation when administered via intra-muscular injection.

The applicant noted that midazolam is included in the Annex to Commission Regulation (EC) 1950/2006 (in the sub-category 'Sedation and premedication (and antagonism).' While inclusion of midazolam in the above list of substances essential for the treatment of *Equidae* was noted, it was also considered relevant that information concerning midazolam was included in the following recently-adopted document: Scientific advice under Article 115(5) of Regulation (EU) 2019/6 on veterinary medicinal products, regarding the list of substances which are essential for the treatment of equine species and for which the withdrawal period of equine species shall be six months (EMA/CVMP/159047/2023-Corr.[2]). Midazolam is one of the substances in Regulation (EU) 1950/2006 that was proposed to be removed in the afore-mentioned scientific advice.

The applicant proposed 4 indications, with associated posologies for the candidate VMP. The first of these indications was as follows:

Intravenous co-induction of anaesthesia (especially) with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia. Other combinations are possible, e.g. with thiopental and alfaxalone.

In support of the safety and efficacy of this indication, the applicant made reference to more than 40 peer-reviewed published journal articles, and a small number of conference proceedings, all of which describe the use of midazolam as part of an anaesthesia induction protocol, almost exclusively with the dissociative anaesthetic agent ketamine. Co-administration of a benzodiazepine with ketamine for the purpose of induction of general anaesthesia is commonly practiced in equine medicine, for the purpose of muscle relaxation resulting in a so-called 'smooth' induction. The applicant contends that based on the literature provided, the use of midazolam for the purpose of induction of anaesthesia when administered with ketamine could be considered a 'well-established use.'

The applicant presented a dossier based entirely on bibliographic data in support of the safety and efficacy of the candidate VMP. The criteria that are taken into account when establishing 'well-established veterinary use' as detailed in IV.5.3.1 of Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 were therefore considered relevant to this assessment. The point detailed in IV.5.3.2 of the above-mentioned Delegated Regulation was also noted:

the period of time required for establishing a well-established veterinary use of a constituent of a medicinal product shall not be less than 10 years from the first systematic and documented use of that substance as a veterinary medicinal product in the Union.

On this point, it was noted that the first presented published account of the use of midazolam as part of a protocol for induction of anaesthesia in the horses was 1992. Of the bibliographic references presented, a number of them (20) detail the exact posology and protocol as proposed by the applicant in section 3.9 of the SPC, that is 0.06 mg/kg midazolam in combination with 2.2 mg/kg ketamine administered intravenously. The earliest presented accounts of the exact posology and protocol concerned by this application were published in 2001 (Gangl *et al,* 2001[4] and Bouts *et al,* 2002[5]). The applicant concluded that in totality, the literature provided describes approximately 500 administrations of this protocol to horses for the purpose of induction of anaesthesia, a number which was accepted by CVMP as accurate. Multiple other publications reference use of similar protocols such as 0.05 mg/kg midazolam, and 2.5 mg/kg ketamine. Several of the publications presented detail use of the proposed midazolam-ketamine induction protocol in studies that were not designed to investigate the anaesthetic induction protocol *per se*, but rather are studies describing another area of research interest. This point was considered to lend further support to the contention that the induction protocol in question is indeed in 'well-established veterinary use' and is no longer considered experimental.

In respect of tolerance in the target animal species, based on the widely reported use of midazolam for the proposed indication of co-induction of anaesthesia with ketamine, and at the proposed posology, it was accepted by the CVMP that single use of midazolam in the context of this specific protocol could be considered safe. Based on the bibliographic references provided, the adverse events reported in section 3.6 of the SPC, specifically ataxia / incoordination during recovery (common), and urination and respiratory depression (uncommon) during induction of anaesthesia could be accepted as accurate when considering use of the candidate VMP for co-induction of anaesthesia in conjunction with ketamine.

In respect of efficacy, it was accepted that for the proposed indication co-induction of general anaesthesia with ketamine, efficacy was suitably supported by the bibliographic references provided and the use of midazolam for this purpose could be considered compatible with the accepted description of 'well-established veterinary use.' However, it was noted that the indication as currently worded in the proposed SPC also references use of midazolam in other combinations (besides ketamine), e.g. with thiopental and alfaxalone. The applicant did not provide relevant bibliographic references that support the use of midazolam with these active substances for the purpose of induction of anaesthesia and was requested to remove reference to use of midazolam in combination with active substances other than ketamine from section 3.2 of the SPC.

The following proposed indication was included in section 3.2 of the SPC:

As part of partial intravenous anaesthesia (PIVA) and total intravenous anaesthesia (TIVA) for maintenance for medium duration processes.

For the indication and associated posology for PIVA, the applicant presented 5 peer-reviewed journal articles that describe the use of midazolam in association with other VMPs administered intravenously by means of a continuous rate infusion (CRI) and an inhalant anaesthetic (usually isoflurane) to

[4] Gangl, M., Grulke, S., Detilleux, J., Caudron, I., & Serteyn, D. (2001). Comparison of thiopentone/guaifenesin, ketamine/guaifenesin and ketamine/midazolam for the induction of horses to be anaesthetised with isoflurane. The Veterinary record, 149(5), 147–151. https://doi.org/10.1136/vr.149.5.147

[5] Bouts, T., Gasthuys, F., Vlaminck L., & Van Branteghem, L. (2002). Comparison of romifidine-ketamine-midazolam and romifidine-tiletamine-zolazepam total intravenous anaesthesia (TIVA) for clinical anaesthesia in horses. (abstract in the Proceedings of the Association of Veterinary Anaesthetists Autumn Meeting, Dunblane, Scotland 5-7 September 2001), Veterinary Anaesthesia and Analgesia **29,** 90-96.

maintain anaesthesia. It was concluded by the applicant that the most reported PIVA protocol is midazolam 0.018 mg/kg/hr – ketamine 1.2 mg/kg/hr – xylazine 0.3 mg/kg/hr administered intravenously as a constant rate infusion, and this is the posology and protocol proposed by the applicant in section 3.9 of the SPC. Noting that this exact posology was used in the publications by Auer and Moens (2011)[6] and Ambrisko (2012)[7] only, the CVMP concluded that 28 horses in total were reported to have been administered the protocol as described above, in combination with isoflurane for maintenance of anaesthesia.

Although the earliest provided report of use of midazolam as part of a PIVA protocol is 2005, the CMVP did not consider that the volume and nature of the information in the literature provided by the applicant concerning midazolam as part of a PIVA protocol was consistent with 'well-established veterinary use.' Based on the bibliographic information provided, there does not appear to be an accepted consensus on a PIVA protocol that includes midazolam, and this approach does not appear to be in widespread use (beyond the field of anaesthesia research) as a veterinary anaesthesia technique. While there may be some evidence of clinical advantages to such a protocol in respect of a sparing effect on inhalant anaesthesia used (Kushiro et al., 2005[8]), and maintenance of a higher blood pressure (as compared to horses maintained on isoflurane alone) as reported by Mosing et al. (2007)[9], the CVMP did not consider that sufficient data was presented in order to reach the conclusion that use of midazolam at the proposed posology and as part of the proposed protocol was in well-established use and could therefore be accepted as safe and effective in the target animal species. It was noted, for example that in the protocol described by Mosing et al. (2007)[9], the midazolam component of the protocol was reversed using sarmazenil to improve anaesthetic recovery. Concern that use of midazolam over time (such as in a CRI as is proposed for this indication) will result in accumulation of midazolam and consequently, more pronounced ataxia and poorer recovery outcomes was expressed by authors of several of the publications presented by the applicant.

Based on the data provided, the CVMP could not conclude that the proposed indication and posology for use of midazolam as part of a partial intravenous anaesthesia protocol (PIVA) was in well-established use, and therefore could be considered safe and effective. As such, the applicant had been requested to provide further reassurance based on available literature that the proposed indication and protocol is suitably safe and effective. In the absence of suitable justification, the applicant was required to remove reference to this indication from the SPC (major objection).

Regarding the indication and protocol for total intravenous anaesthesia (TIVA), the applicant provided 13 references, of which 12 are peer-reviewed published journal articles that reference use of midazolam as part of a TIVA protocol that is administered intravenously for the purpose of maintenance of anaesthesia. The first of these was published in 2007 (i.e., more than 10 years have elapsed since use was first reported). It was concluded by the applicant that the most reported TIVA protocol is midazolam 0.12 mg/kg/hr – ketamine 1.8 mg/kg/hr – xylazine 0.96 mg/kg/hr administered intravenously as a constant rate infusion. This posology is used in the publications by Hubbel et al.

[6] Auer, U., & Moens, Y. (2011). Neuromuscular blockade with rocuronium bromide for ophthalmic surgery in horses. Veterinary ophthalmology, 14(4), 244–247. https://doi.org/10.1111/j.1463-5224.2010.00870.x
[7] Ambrisko, T. D., Coppens, P., Kabes, R., & Moens, Y. (2012). Lithium dilution, pulse power analysis, and continuous thermodilution cardiac output measurements compared with bolus thermodilution in anaesthetized ponies. British journal of anaesthesia, 109(6), 864–869. https://doi.org/10.1093/bja/aes269
[8] Kushiro, T., Yamashita, K., Umar, M. A., Maehara, S., Wakaiki, S., Abe, R., Seno, T., Tsuzuki, K., Izumisawa, Y., & Muir, W. W. (2005). Anesthetic and cardiovascular effects of balanced anesthesia using constant rate infusion of midazolam-ketamine-medetomidine with inhalation of oxygen-sevoflurane (MKM-OS anesthesia) in horses. The Journal of veterinary medical science, 67(4), 379–384. https://doi.org/10.1292/jvms.67.379
[9] Mosing, M., Rezabek, S., & Iff, I. (2007). Clinical evaluation of an anaesthesia protocol with ketamine, midazolam and one of three α-2 adrenoreceptor agonists (detomidine, medetomidine, xylazine) in combination with isoflurane for castration in the stallion. Equine Medicine 23(4), 388-397.

(2012)[10], Toholj et al. (2014)[11], Sage et al. (2018)[12] and Aarnes et al. (2018)[13], and is the protocol proposed by the applicant in section 3.9 of the SPC. Based on these studies, the CVMP noted that a total of 67 horses were administered this protocol as described above for maintenance of anaesthesia.

Although use of midazolam as part of a TIVA protocol is described in the published literature to a greater extent than it is for PIVA, it was not clear to the CVMP that this use meets the criteria to be considered a 'well-established veterinary use.' For example, there did not appear to be a clear consensus on a posology and protocol between available published reports. Of the 67 horses referenced above, 46 horses were the subjects of one study, Aarnes et al. 2018.

With regard to tolerance in the target animal species, the quality of recovery from anaesthesia in horses that receive midazolam over a period of time, and who may also have received midazolam as part of an induction protocol is a concern noted by a number of authors. In the protocol described by Hopster et al. (2014)[14], midazolam is antagonised with flumazenil at the cessation of anaesthesia. As discussed in the pre-clinical section above, the possibility that accumulation of midazolam (resulting in prolonged clinical effects, including ataxia) will have a negative impact on target animal safety is considered a substantial concern. It is also noted by a number of authors that use of a TIVA protocol in the field (during which horses are not typically provided with supplemental oxygen) can result in significant impairment of oxygenation, a finding which is reported in the studies authored by Steblaj et al. (2014)[15] and Sage et al. (2018)[12].

With regard to efficacy, in the majority of the references provided, it was noted that a number of animals being maintained under anaesthesia on a TIVA protocol required so-called 'top-up' doses (usually) with ketamine in order to maintain an adequate plane of anaesthesia. Of the 67 horses to which the proposed protocol was administered, it is reported by the authors of the respective publications that 23 horses (in total) required additional anaesthetic agents (supplementary to the TIVA protocol) in order to maintain an appropriate depth of anaesthetic. Cause to administer supplemental doses of ketamine was commonly described as 'spontaneous movement.' It was the opinion of the CVMP that the number of horses that are reported to have required supplemental ketamine during anaesthesia while being maintained on the proposed protocol calls the efficacy of the proposed protocol into question.

Based on the bibliographic data provided, the CVMP could not conclude that the proposed indication and posology for use of midazolam as part of a total intravenous anaesthesia protocol was in well-established use, and therefore could be considered safe and effective. As such, the applicant had been requested to provide further reassurance based on available literature that the proposed indication and protocol is suitably safe and effective. In the absence of suitable justification, the applicant was required to remove reference to this indication from the SPC (major objection).

[10] Hubbell, J. A., Aarnes, T. K., Lerche, P., & Bednarski, R. M. (2012). Evaluation of a midazolam-ketamine-xylazine infusion for total intravenous anesthesia in horses. American journal of veterinary research, 73(4), 470–475. https://doi.org/10.2460/ajvr.73.4.470

[11] Toholj, B., Velibor, D., Milenko, R., Jovan, M., Smolec, O. (2014). The Use of Ketamine, Xylazine and Midazolam Combination for Total Intravenous Anesthesia (Tiva) in Surgical Removal of Abdominal Testis at Stallion. Macedonian Veterinary Review. 37. 185-188. 10.14432/j.macvetrev.2014.09.024.

[12] Sage, A. M., Keating, S. C., Lascola, K. M., Schaeffer, D. J., & Clark-Price, S. C. (2018). Cardiopulmonary effects and recovery characteristics of horses anesthetized with xylazine-ketamine with midazolam or propofol. Veterinary anaesthesia and analgesia, 45(6), 772–781. https://doi.org/10.1016/j.vaa.2018.07.005

[13] Aarnes, T. K., Lerche, P., Bednarski, R. M., & Hubbell, J. A. E. (2018). Total intravenous anesthesia using a midazolam-ketamine-xylazine infusion in horses: 46 cases (2011-2014). The Canadian veterinary journal = La revue veterinaire canadienne, 59(5), 500–504.

[14] Hopster, K., Müller, C., Hopster-Iversen, C., Stahl, J., Rohn, K., & Kästner, S. (2014). Effects of dexmedetomidine and xylazine on cardiovascular function during total intravenous anaesthesia with midazolam and ketamine and recovery quality and duration in horses. Veterinary anaesthesia and analgesia, 41(1), 25–35. https://doi.org/10.1111/vaa.12095

[15] Steblaj, B., Schauvliege, S., Pavlidou, K., Gasthuys, F., Savvas, I., Duchateau, L., Kowalczyk, L., & Moens, Y. (2014). Comparison of respiratory function during TIVA (romifidine, ketamine, midazolam) and isoflurane anaesthesia in spontaneously breathing ponies Part I: blood gas analysis and cardiorespiratory variables. Veterinary anaesthesia and analgesia, 41(6), 583–591. https://doi.org/10.1111/vaa.12167

In respect of the proposed indication for use of the candidate VMP as an 'anti-convulsant, for treatment of seizures' the applicant provided one reference from a conference proceedings. The information contained in this reference is based on the author's own clinical experience and that of other, experienced equine neonatologists. This reference is not peer-reviewed. No further support for the proposed posology, or for use of midazolam for this indication was provided.

The limited data provided in support of this indication were empirical in nature and did not allow the CVMP to conclude on the safety and efficacy of the proposed indication for foals and adult horses, noting that no data were presented in support of use of midazolam for this purpose in the latter category of horses. As such, the applicant had been requested to further support, or alternatively, delete this indication and the associated information in section 3.9 of the SPC (major objection).

In summary, in support of safety in the target animal and efficacy of the candidate VMP for the proposed indications the applicant presented bibliographic data.

In respect of the specific proposed indications, it was concluded that the target animal safety and efficacy of the proposed indications for use of midazolam as a component of PIVA and TIVA protocols, and as an anti-convulsant in foals and adult horses were not fully supported by the literature provided. The applicant was requested to either provide suitable justification that the proposed indications are safe and effective, or to remove these indications from the proposed SPC (major objections).

Target animal safety and efficacy of the indication regarding use of midazolam as a co-induction agent in combination with active substances other than ketamine, e.g. with thiopental and alfaxalone were not sufficiently supported, and the applicant was required to remove reference to these substances from the SPC.

Target animal safety and efficacy of the proposed indication for use of midazolam as a co-induction agent with ketamine (only) were considered to have been supported by the bibliographic data provided.

Overall conclusions on efficacy

This application was submitted in line with the requirements for submissions under Article 23 of Regulation (EU) 2019/6 – an application for limited markets and concerns the candidate product 'Equidormin 5 mg/ml solution for injection for horses', which contains the active substance midazolam intended for use in the target animal species horses (non-food producing).

The applicant provided bibliographic references from the public domain in order to meet pre-clinical and clinical data requirements. The criteria that are taken into account when establishing 'well-established veterinary use' as detailed in IV.5.3.1 of Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 were therefore considered relevant to this assessment, and the data was assessed according to these criteria.

Concerning the legal basis of the ongoing MAA, the applicant was requested to provide (updated) evidence that the conditions of Article 23 of Regulation (EU) 2019/6 were met by this application, as it was the view of the CVMP prior to withdrawal of the application that the conditions of an Article 23 were not met for two of the proposed indications. In the event that eligibility for Article 23 of Regulation 2019/6 could not be supported, the applicant was requested to confirm acceptance of a change in legal basis of the application to Article 22 of Regulation 2019/6.

Pharmacology

Pharmacodynamics

A high-level summary of the pharmacodynamic properties of midazolam was provided. The applicant did not provide information concerning the pharmacodynamics of midazolam in the target animal species horses. The applicant was requested to provide further information, as available, on the pharmacodynamics of the active substance midazolam in horses, with particular emphasis on the intended effects and the possibility of secondary pharmacological effects in this target animal species.

Pharmacokinetics

A summary of the pharmacokinetics of midazolam following administration of a single intravenous bolus based on published literature and considering information relevant to the target animal species was provided. Further information concerning the potential for accumulation of midazolam and effects on pharmacokinetics of coadministration with other active substances was requested from the applicant.

Dose determination and confirmation

The proposed SPC contained 4 indications for the candidate VMP, each of which was associated with a specific dose rate. The proposed dose rates were justified by the applicant based on bibliographic references, and the approach of the applicant, that is the omission of proprietary dose justification and/or confirmation study data in the target animal species, could be accepted based on relevant guidance.

Concerning the dose rate proposed for co-induction of general anaesthesia with ketamine, it was accepted that the proposed dose rate was suitably supported by the literature references provided.

Concerning the dose rates proposed for the indications for use of midazolam as part of PIVA and TIVA protocols it was accepted that these represent the most reported protocols for this use in the literature references provided. Notwithstanding this point, major objections were raised in respect of the safety and efficacy of these proposed indications.

Concerning the dose rate proposed for treatment of seizures in foals and adult horses it was concluded that the literature references provided do not suitably support the proposed dose rate for midazolam for control of seizures in either foals or adult horses.

Tolerance in the target animal species

To characterise the target animal safety profile of the candidate product, the applicant provided bibliographic references, rather than proprietary target animal safety data generated using the candidate formulation.

Based on the available bibliographic data, the adverse events as reported in section 3.6 of the SPC (namely ataxia / incoordination during recovery, and urination and respiratory depression during induction of anaesthesia) were accepted as suitably accurate when considering single use of the candidate VMP for co-induction of anaesthesia in conjunction with ketamine.

For the remaining proposed indications (i.e., for PIVA/TIVA and treatment of seizures), it was concluded by the CVMP that the safety profile of the candidate product was not suitably characterised by the applicant. No conclusions on safety of the candidate product in the target animal species horses when used as part of PIVA/TIVA protocols, or as an anti-convulsant, could be made.

Clinical trials

In support of safety in the target animal and efficacy of the candidate VMP for the proposed indications the applicant presented bibliographic data only. The approach of the applicant was acceptable in principle.

However, in respect of the specific proposed indications, it was concluded that the target animal safety and efficacy of the proposed indications for use of midazolam as a component of PIVA and TIVA protocols were not fully supported by the literature provided.

The applicant was requested to either provide suitable justification that the proposed indications are safe and effective, or to remove these indications from the proposed SPC (major objections).

Target animal safety and efficacy of the proposed indication for use of midazolam as an anti-convulsant in foals and adult horses was not supported by the bibliographic information provided and the applicant was requested to provide further supportive data or remove reference to this indication from the SPC (major objection).

Target animal safety and efficacy of the claim regarding use of midazolam as a co-induction agent in combination with active substances other than ketamine, e.g. with thiopental and alfaxalone was also not sufficiently supported.

Target animal safety and efficacy of the proposed indication for use of midazolam as a co-induction agent with ketamine (only) were considered to have been supported by the data provided.

Part 5 – Benefit-risk assessment

Introduction

Equidormin was a solution for injection containing midazolam. The active substance is well known.

Midazolam is a derivative of the imidazobenzodiazepine group, which exhibits similar pharmacologic actions as other benzodiazepines. The subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS are depressed through an enhancement of the GABAergic neurotransmission at inhibitory synapses, thus producing anxiolytic, sedative, skeletal muscle relaxant, and anticonvulsant effects.

At the time of submission, the product was intended for use in horses (non food-producing) for the following indications:

Intravenous co-induction of anaesthesia (especially) with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia. Other combinations are possible, e.g. with thiopental and alfaxalone.

As part of partial intravenous anaesthesia (PIVA) and total intravenous anaesthesia (TIVA) for maintenance for medium duration processes.

Anti-convulsant, for treatment of seizures.

The proposed dose of 5 mg/ml of midazolam for the indication co-induction of general anaesthesia with ketamine was confirmed (0.06 mg/kg IV).

The application was submitted under Article 23 of Regulation (EU) 2019/6 - limited market application.

Benefit assessment

Direct benefit

The proposed benefit of 'Equidormin' was its efficacy for the proposed indications. Demonstration of efficacy was based solely on bibliographic data.

Efficacy of 'Equidormin' for the indication 'Intravenous co-induction of anaesthesia (especially) with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia' was considered to have been suitably supported by the bibliographic data provided.

However, concerns remained regarding efficacy for the remaining, proposed indications – namely, use of Equidormin as co-induction agent in combination with active substances other than ketamine, part of partial and total intravenous anaesthesia protocols and use as an anti-convulsant.

Additional benefits

Pending resolution of outstanding major objections, 'Equidormin' may have provided a new treatment possibility for a limited market.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product was generally presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion, that the product should have a satisfactory and uniform performance in clinical use. However, there remained a number of questions to be addressed before a final conclusion regarding the quality of the product could be reached, in particular in relation to shelf life and in-use shelf life.

Safety

Risks for the target animal

Administration of 'Equidormin' for the purpose of co-induction of anaesthesia with ketamine, in accordance with SPC recommendations was generally well tolerated.

The main reported adverse reactions include ataxia / incoordination during recovery (common), and urination and respiratory depression (uncommon) during induction of anaesthesia.

A major objection was raised regarding target animal safety for the PIVA/TIVA and treatment of seizures claims.

A major objection was raised for further documentation on reproductive/developmental effects and the potential for genotoxicity or carcinogenicity.

Risk for the user

A number of concerns were raised in relation to deficiencies in the toxicological data provided for the active substance midazolam. No final conclusion could be drawn on user safety as those issues had not been satisfactorily addressed.

Risk for the environment

Equidormin was not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal was included in the SPC.

Risk management or mitigation measures

User safety

The presented quantitative user risk assessment was not conducted in line with CVMP guidance (EMA/CVMP/543/03-Rev.1). An updated user safety assessment was requested to be supported by adequate toxicity data that would allow characterisation of the risk to users of the product. Based on the risks identified in the context of that assessment, appropriate measures to mitigate the risk to users were to be proposed.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product was intended to be subject to a veterinary prescription.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

Intravenous co-induction of anaesthesia (especially) with ketamine for smooth induction and intubation and profound muscle relaxation during anaesthesia. Other combinations are possible, e.g. with thiopental and alfaxalone.

As part of partial intravenous anaesthesia (PIVA) and total intravenous anaesthesia (TIVA) for maintenance for medium duration processes.

Anti-convulsant, for treatment of seizures.

In the presence of major objections, no conclusions could be taken on the benefit-risk balance of the application.

The product information was reviewed and changes considered necessary. Comments on the SPC and product literature were included in a separate document.

Conclusion

Based on the original data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) considered that the application for ‘Equidormin’ was not approvable since "major objections" and "other concerns" had been identified which precluded a recommendation for marketing authorisation. No conclusions could be taken on the benefit-risk balance of the application.