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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Hemosyvet (EMEA/V/C/006461/0000)

INN: Etamsylate

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

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Introduction

The applicant Axience submitted on 30 April 2024 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Hemosyvet, 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 7 December 2023 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

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

Prevention and treatment of surgical, post traumatic, obstetric and gynaecological haemorrhages.

The active substance of Hemosyvet is etamsylate, a haemostatic and angioprotective active substance, which stimulates platelet adhesiveness, shortening bleeding time, and rapidly and lastingly normalizes the altered vascular fragility and permeability. The target species are Cat, Cattle, Dog, Goat, Horse, Pig and Sheep.

Hemosyvet solution for injection contains 125mg/ml Etamsylate and is presented in packs containing 1 vial of 25 ml and 1 vial of 50 ml.

The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

The rapporteur appointed is Andrea Christina Golombiewski and the co-rapporteur is Katarina Straus.

The dossier has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application. The reference product is HEMO 125 mg/ml solución inyectable which has been authorised nationally in Spain since July 1992 and marketed by Ecuphar Veterinaria S.L.U.

On 17 July 2025, the CVMP adopted an opinion and CVMP assessment report.

On 24 October 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Hemosyvet.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils 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

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at Produlab Pharma B.V. The declaration was based on an onsite audit by a third party which has taken into consideration the GMP certificate available for the active substance site issued by a competent authority following inspection.

GMP certification, which confirms the date of the last inspection and shows that the site is authorised activities indicated above, has been provided.

Finished product

Batch release of the finished product take(s) place at Produlab Pharma B.V. located in 4941 SJ Noord-Brabant in the Netherlands. The site has a manufacturing authorisation issued on 6th February 2024 by the competent authority of the Netherlands. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for bath release has been provided.

Overall conclusions on administrative particulars

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

Part 2 - Quality

Composition

The finished product is presented as a multidose aqueous solution for injection containing 125 mg/mL etamsylate as active substance.

Other ingredients are:

- benzyl alcohol as preservative
- sodium metabisulfite and sodium sulfite as antioxidants
- disodium edetate as chelating agent/antioxidant synergist

- water for injections as solvent

Hemosyvet is filled in 30 ml (pack size 25 ml) and 50 ml (pack size 50 ml) amber type I glass vials. All presentations are closed with rubber stoppers and alu caps as described in section 6.5 of the SPC. The pack sizes are consistent with the dosage regimen and duration of use.

Containers and closure system

The primary packaging is amber type I glass vial closed with rubber stoppers and alu caps. The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The secondary packaging is a cardboard box. Each cardboard box contains one vial.

Hemosyvet is a multidose preparation. Therefore, data has been provided to demonstrate that the integrity of the closure is maintained even following a number of potential withdrawals per vial. The Ph. Eur. tests for fragmentation and self-sealing have been performed in accordance with Ph. Eur. 3.2.9 and a stipulation that the stopper should not be punctured more than 25 times has been stated in the product information texts.

The container closure system has been validated by stability data and is in general adequate for the intended use of the product.

The applicant has clearly outlined the specification of the glass vials, rubber stoppers and caps as used by the finished product manufacturer. Pre-sterilised vials, rubber stoppers and caps are used in the filling process.

Product development

The objective of pharmaceutical development was to develop a generic of HEMO 125 mg/ml solución inyectable which has been authorised nationally in Spain since July 1992 and marketed by Ecuphar Veterinaria S.L.U.

The generic should be developed to be as close as possible to the originator regarding qualitative and quantitative aspects. The applicant used publicly available information, such as the Summary of Product Characteristics (SPC), as well as laboratory trial batches in order to achieve this.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

The manufacturing, including sterilisation process, has been developed in-line with the guidelines.

A confirmation that this sterilisation process has been validated has been provided.

The use of amber coloured vials has been justified by a photo stability study.

A comparison study has been performed between the originator product and the candidate formulation. The results are considered comparable. In order to support the claimed biowaiver, additional data comparing the osmolarity of the reference product and Hemosyvet has been provided.

The applicant has included the same preservative, in the same quantity, as the reference product (as per reference product SPC) and therefore the inclusion of the preservative is considered acceptable. The preservative efficacy at the lower shelf-life specification limit has been proven and appropriate results of the preservative efficacy testing for two batches, including the 25 ml and 50 ml fill size, at the end of the in-use shelf life have been provided.

Description of the manufacturing method

The solution for injection is manufactured in a standard manufacturing process involving sequential addition and dissolution of the product constituents in water for injections. Preparation of the solution takes place under nitrogen atmosphere.

A flow chart and detailed written description of the manufacturing process has been provided and is satisfactory.

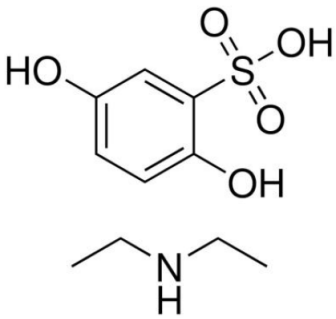
Several parameters throughout the manufacturing process have been tested in order to prove the process is robust and reproducible.

A process validation has been performed on two production batches. Filter validation and validation of holding times are part of the process validation report and is acceptable. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Control of starting materials

Active substance

The chemical IUPAC name of etamsylate is ethylethanamine 2,5-dihydroxybenzenesulfonate and has the following structure:



The etamsylate is a white or almost white, crystalline powder. Polymorphism has been observed for etamsylate.

There is a monograph of etamsylate in the Ph. Eur. (1204), and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for etamsylate, a copy of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

Additional specifications have been set for the microbiological quality of the API. The CEP indicates a re-test period of 48 months if stored packed in a double polyethylene bag (outer black) placed in a cardboard drum.

Batch analysis data (n=2) of the active substance have been provided. All tested parameters are within the specification and the results are consistent from batch to batch.

In the last step of the synthesis of the active substance purified water is used. Therefore, a test for the determination of endotoxins has been included in the active substance specification.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The list of excipients is included in section 2 of the SPC. Appropriate results of the microbiological contamination of the excipients have been provided.

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

The product does not contain any materials derived from human or animal origin.

Control tests on the finished product

The finished product specification includes tests for appearance, colour, extractable volume, density, clarity, pH, identification and assay of etamsylate, identification and assay of the preservative benzyl alcohol, identification and assay of the antioxidants sodium metabisulfite and sodium sulfite, degradation products and sterility.

The specifications proposed for release and at the end of shelf-life are in general considered appropriate to control the quality of the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for two production batches (each for the fill size of 25ml and 50ml) confirming in general the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the CVMP guidance on risk management requirements for elemental impurities in veterinary medicinal products. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

Stability

Stability data of batches of finished product (each for the fill size of 25 ml and 50 ml) stored under long term conditions for 18 months at 25 ºC/60% RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guideline were provided. The batches of Hemosyvet are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The applicant has confirmed that long term studies will be continued through the proposed shelf life and that a third commercial scale batch of maximum batch size will be placed on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The specifications proposed at the end of shelf-life are in general appropriate to control the quality of the finished product. The specification limits proposed at the end of shelf-life are the same as those proposed at release except that the lower acceptance limit for the pH, the assay of benzyl alcohol, the assay of sodium metabisulfite and sodium sulfite, the absolute density and determination of total impurities have been widened.

Based on the available stability data, the proposed shelf-life of 30 months is considered acceptable. The sterility has been shown for the last actual tested time point in the long-term and accelerated stability studies.

Based on the available in-use stability data, the proposed in-use shelf-life of 28 days is in general considered acceptable. However, no sterility has been investigated in the provided in-use stability studies. The applicant confirmed that the in-use shelf-life study will be performed post authorisation with a batch approaching the end of its shelf-life. This in-use stability study will also include a test for sterility and a further preservative efficacy test.

Considering that the API etamsylate is sensitive to light the storage conditions "Store in the original container in order to protect from light" has been incorporated in PI texts. Section 2.F.2.5 of the dossier includes a storage statement regarding the protection from light.

Overall conclusions on quality

The medicinal product is presented as a multidose solution for injection in two pack sizes (25ml, and 50ml).

Water for injections is used as solvent. Additionally, it contains sodium metabisulfite and sodium sulfite as antioxidants, benzyl alcohol as preservative and disodium edetate as chelating agent/antioxidant synergist. The product is a clear, colourless to slightly brownish solution.

Information on the composition and development of the finished product has been presented. Validation data for the filters used in the manufacturing process have been provided during development.

The maximum number of punctures that can be applied to the stoppers has been determined as part of the development and a respective advice has been stated in the SPC.

Considering the extensive experience of the finished product manufacturer, the simple manufacturing process and the terminal sterilisation by moist heat, the manufacturing process in general can be regarded as standard process.

A process validation has been performed on production batches.

Etamsylate is described in the Ph. Eur. (1204). One API manufacturer has been applied for that has a CEP for Etamsylate. The current CEP version has been provided and the API specification is considered acceptable. Since purified water is used in the last step of the synthesis a control of endotoxins has been included in the API specification.

Hemosyvet is packaged in amber type I glass vials and closed with ~~r~~ rubber stoppers and alu caps. The necessity of amber glass has been proven by a photo stability study during the development. Rubber stoppers have been treated with a coating, which renders them inert. The vials are further individually packed in outer cardboard boxes.

30ml vials are used for the 25ml fill size and 50ml vials are used for the 50ml fill size.

Pre-sterilised glass vials, rubber stoppers and caps are used in the manufacturing process. The applicant has clearly outlined the specification of the glass vials, rubber and stopper as used by the finished product manufacturer.

The excipients of the formula are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards.

The specifications and analytical methods proposed to control the finished product are considered sufficient.

The validation of the used analytical methods is in general considered acceptable and in line with VICH GL1 and 2.

The suitability of the test for sterility has been demonstrated and appropriate validation data for the method has also been provided.

A risk assessment on elemental impurities has been performed, leading to results below the control threshold and the outcome of the risk assessment is that no further controls are required.

Stability studies on the finished product are considered sufficient to justify the proposed shelf life of 30 months with the storage precaution" Store in the original container in order to protect from light". Appropriate results of a freeze-thaw stability study have been provided in order to justify the omission of the storage condition "Do not freeze.".

In-use stability studies on the finished product are considered sufficient to justify the proposed in-use shelf-life period of 28 days.

Part 3 – Safety documentation (Safety and residues tests)

This application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 (generic veterinary medicinal product) through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6. The application refers to 'HEMO 125 mg/ml solución inyectable' as the reference product. The active substance is etamsylate, a haemostatic and angioprotective drug.

The waivers from bioequivalence study requirements for immediate release formulations are described in section 7 of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4). Accordingly, the omission of bioequivalence studies is justified as Hemosyvet 125 mg/ml solution for injection is intended for the IV and IM administration and it contains the same active substance and identical excipients in similar amounts as the reference product. Therefore, the criteria for a biowaiver as described in section 7.1 a) and b) of the guideline are fulfilled and no bioequivalence studies are required. See Part 4 for further details.

No proprietary data are provided. However, the applicant refers to data from the reference product and to the toxicological data and conclusions described in the EMA summary report for etamsylate (EMEA/MRL/500/98-FINAL, September 1998).

Safety tests

In accordance with Article 18 of Regulation (EU) 2019/6, an application for a marketing authorisation for a generic veterinary medicinal product does not need to contain the documentation on safety and efficacy if the conditions for a generic VMP are met. The candidate and reference formulations are qualitatively and quantitatively the same in terms of active substance and bioequivalence is accepted (see Part 4). The toxicological aspects of the candidate product are considered equivalent to those of the reference product. In addition, it is noted that the active substance etamsylate was previously assessed by the CVMP in the context of the establishment of MRLs (EMEA/MRL/500/98-FINAL).

Other requirements

Observations in humans

In addition to the data already reported in the MRL summary report for etamsylate, the applicant provided information on the SmPC of a human oral capsule formulation of etamsylate (cyclonamine) for use in adults that describes adverse effects after oral use of cyclonamine, i.e. gastrointestinal, nervous system, skin and subcutaneous tissue and general disorders as well as rarely arthralgia, immune system and musculoskeletal and connective tissues disorders and very rarely vascular, blood and lymphatic system disorders and sensitiveness.

Excipients

Hemosyvet contains the same excipients as the reference product 'HEMO 125 mg/ml solución inyectable' and in similar amounts. All the excipients are well-known and commonly used in veterinary medicinal products. Any difference between candidate and reference products are not expected to present a safety concern. The risk profiles of Hemosyvet and the reference product are considered to be comparable.

User safety

The candidate and reference formulations are qualitatively and quantitatively similar and bioequivalence is accepted. A qualitative and quantitative user risk assessment was provided. The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline EMA/CVMP/543/03-Rev.1. The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection, dermal and eye exposure.

The worst-case scenario for quantitative user risk assessment is accidental self-injection with an estimated MOE of 50. However, the user safety warnings provided by the applicant are essentially similar to those of the reference product and are considered sufficient to mitigate the risk of the user.

Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

In accordance with the reflection paper on the interpretation of Article 18(7) of Regulation (EU) 2019/6 (EMA/CVMP/ERA/622045/2020) no environmental risk assessment is to be required when a similar veterinary medicinal product (same active substance, same pharmaceutical form, indicated for use in the same target species when administered at the same or a higher total dose) has been authorised in the European Union after 1 October 2005. Consequently, the submission of a phase II environmental risk assessment is not deemed necessary since there is a similar veterinary medicinal product 'HEMOSYLATE 125 mg/ml solución inyectable' that was authorised in 2020 which has the same MAH, Ecuphar Veterinaria S.L.U., to which reference can be made.

Additionally, a phase I decision tree according to VICH GL6 and the CVMP Guideline on the environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) was provided showing that the environmental risk assessment can stop in phase I, question 5, as the product is intended for individual treatments.

No unacceptable environmental risks are to be expected for Hemosyvet 125 mg/ml solution for injection for cattle, sheep, goats, pigs, horses, dogs and cats when used as recommended in the SPC.

Residue tests

MRLs status

The active substance in Hemosyvet is an allowed substance as described in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRL**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Etamsylate	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	No ENTRY

The excipients listed in section 2 of the SPC are allowed substances for which Table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Depletion of residues

Hemosyvet 125 mg/ml solution for injection has been developed as a generic veterinary medicinal product according to Article 18 of Regulation (EU) 2019/6.

An application for a generic veterinary medicinal product does not need to contain the documentation on safety if the conditions for a generic veterinary medicinal product are met. The waiver from bioequivalence study requirements for immediate release formulations are described in section 7 of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4).

The candidate and reference products are of the same pharmaceutical form and are intended for the same route of administration, dose rate, target species and indications. The candidate and reference product formulations are qualitatively and quantitatively similar regarding the active ingredient as well as excipients. Therefore, the depletion of residues is expected to be the same as for the reference product and no additional depletion studies for edible tissues and milk from the target species are required. Based on the similar composition of the candidate and reference products this expectation is also applicable for the behaviour of residues at the site of administration.

Withdrawal periods

Since the product intended to be authorised is qualitatively and quantitatively essentially similar in terms of active substance, excipients and pharmaceutical form to the reference products and both present the same target animals, dosage and route of administration, the withdrawal periods of the reference product can be also applied to the generic.

Meat and offal:

Cattle, sheep, goats, horses, pigs:

Intravenous administration: Zero days.

Intramuscular administration: 1 day.

Milk:

Cattle, sheep, goats, horses:

Intravenous and intramuscular administration: Zero hours.

Overall conclusions on the safety documentation: safety and residues tests

This application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 (generic veterinary medicinal product) through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6. In accordance with Article 18 of Regulation (EU) 2019/6, an application for a marketing authorisation for a generic veterinary medicinal product does not need to contain the documentation on safety and efficacy if the conditions for a generic VMP are met. The candidate and reference formulations are qualitatively and quantitatively the same in terms of active substance and bioequivalence is accepted (see Part 4).

Hemosyvet contains the same excipients as the reference product 'HEMO 125 mg/ml solución inyectable' in comparable amounts. All excipients are well-known and commonly used in veterinary medicinal products. Any difference between candidate and reference products are not expected to present a safety concern.

User safety:

A user risk assessment in line with the relevant guidance document has been presented. Based on that assessment, the potential health risk of the product to users is considered acceptable when used in accordance with the SPC. The appropriate warnings for the user have been included in the product literature. The CVMP concluded that Hemosyvet is not expected to pose a risk to the user when used in accordance with the SPC.

Environmental risk assessment:

In accordance with the reflection paper on the interpretation of Article 18(7) of Regulation (EU) 2019/6 (EMA/CVMP/ERA/622045/2020) no environmental risk assessment is required since there is a similar veterinary medicinal product, HEMOSYLATE 125 mg/ml solución inyectable, that was authorised in 2020 (i.e. after 1 October) by the same MAH, Ecuphar Veterinaria S.L.U., to which reference can be made.

Additionally, a phase I decision tree according to VICH GL6 and the CVMP Guideline on the environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) was provided showing that the environmental risk assessment can stop in phase I, question 5, as the product is intended for individual treatments.

Hence, no unacceptable environmental risks are to be expected for Hemosyvet 125 mg/ml solution for injection for cattle, sheep, goats, pigs, horses, dogs and cats when used as recommended in the SPC.

Residue tests:

This application fulfils the requirements of Article 18 of Regulation (EU) 2019/6 for a generic veterinary medicine. Moreover, the criteria for a biowaiver as described in section 7.1 a) and b) of the Guideline

on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4) are fulfilled and the same dose and route of administration are intended for the candidate and reference product. Therefore, the depletion of residues is expected to be the same as for the reference product and no additional depletion studies for edible tissues and milk from the target species are required. Based on the similar composition of the candidate and reference products this expectation is also applicable for the behaviour of local residues.

The applicant's proposal on applying the same withdrawal period as approved for the reference products can be accepted.

Part 4 – Efficacy

Pre-clinical studies

Hemosyvet is a solution for injection with the active substance Etamsylate, a hemostatic and angioprotective substance. Hemosyvet is intended for use in cattle, sheep, goats, pigs, horses, dogs and cats and is indicated for the prevention and treatment of different types of haemorrhages. The proposed dose is 5 to 12.5 mg Etamsylate per kg bodyweight administered by intravenous or intramuscular injection.

This application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 (generic veterinary medicinal product). The application refers to 'HEMO 125 mg/ml solución inyectable' as the reference product.

The candidate and reference products are of the same pharmaceutical form and are intended for the same route of administration, dose rate, target species and indications. The candidate and reference product formulations are qualitatively and quantitatively the same in respect of the active substance, etamsylate, and have comparable excipients. Bioequivalence is claimed based on biowaivers according to section 7.1.a and 7.1.b of the "Guideline on the conduct of bioequivalence studies for veterinary medicinal products" (EMA/CVMP/016/2000-Rev.4) for the intravenous and intramuscular route of administration, respectively. No proprietary data were provided.

Pharmacology

Pharmacodynamics

Etamsylate is a haemostatic and angioprotective substance that stimulates platelet adhesiveness resulting in shortening of bleeding time and normalizing vascular permeability by inhibiting the prostacyclin (PGI2) synthesis and activating P-selectine. While PGI2 causes platelet disaggregation, vasodilation and increase capillary permeability, P-selectine facilitates the interaction between platelets, leucocytes and endothelium. Due to this mode of action etamsylate only affects the primary haemostasis without affecting prothrombin time, fibrinolysis or platelet count.

As this is a generic application according to Article 18 of Regulation (EU) 2019/6 and bioequivalence with the reference product is acceptable, no proprietary data on pharmacodynamics were presented. The pharmacodynamic properties of etamsylate have already been adequately characterised for the

reference product 'HEMO 125 mg/ml solución inyectable' and cross-reference to the dossier of the reference products is appropriate.

Pharmacodynamic properties described in section 4.2 of the SPC reflect the information that is included in the Spanish product literature of the reference product 'HEMO 125 mg/ml solución inyectable'. Some minor editorial amendments were proposed and agreed.

Pharmacokinetics

As this is an application according to Article 18 of Regulation (EU) 2019/6 and bioequivalence with the reference product is acceptable, no proprietary data on pharmacodynamics were presented. The pharmacodynamic particulars of etamsylate have already been adequately characterised for the reference product 'HEMO 125 mg/ml solución inyectable' and cross-reference to the dossier of reference products is appropriate.

Pharmacokinetic properties described in section 4.3 of the SPC reflect the information that is included in the Spanish product literature of the reference product 'HEMO 125 mg/ml solución inyectable'. Some minor editorial amendments were proposed and agreed.

Bioequivalence studies

The candidate product Hemosyvet 125 mg/ml solution for injection and the reference product 'HEMO 125 mg/ml solución inyectable' are aqueous solutions for injection (intravenous and intramuscular administration), contain the same active substance (etamsylate) in the same concentration and the same excipients in comparable amounts. The physicochemical properties (i.e., pH and density) of both products are very similar and it can be accepted that both formulations are bioequivalent.

The omission of *in vivo* bioequivalence studies as justified by biowaivers according to section 7.1.a for the intravenous route of administration and in accordance with section 7.1.b for the intramuscular route of administration (EMA/CVMP/016/00-Rev.4) can be accepted.

Dose determination and confirmation

As this is a generic application according to Article 18 of Regulation (EU) 2019/6 and bioequivalence with the reference product is acceptable, no proprietary data on dose determination or confirmation were presented. The dosage regimen has already been adequately demonstrated for the reference product 'HEMO 125 mg/ml solución inyectable' and cross-reference to the dossier of the reference product is appropriate.

Tolerance in the target animal species

As this is a generic application according to Article 18 of Regulation (EU) 2019/6 and bioequivalence with the reference product is acceptable, no proprietary data on tolerance in the target animal species were presented. The safety of the product has been adequately proven for the reference product 'HEMO 125 mg/ml solución inyectable' and cross-reference to the dossier of the reference product is appropriate.

The information regarding the safe and efficient use in the target species as stated in the Spanish product literature of the reference product 'HEMO 125 mg/ml solución inyectable' are adequately reflected in the SPC of the candidate product Hemosyvet 125 mg/ml solution for injection. Some minor amendments were proposed and agreed.

Clinical trial(s)

As this is a generic application according to Article 18 of Regulation (EU) 2019/6 and the applicant justified bioequivalence with the reference product, no clinical data were presented and cross reference to the dossier of the reference product 'HEMO 125 mg/ml solución inyectable' is appropriate.

Overall conclusions on efficacy

As this is a generic application according to Article 18 of Regulation (EU) 2019/6 and bioequivalence with the reference product 'HEMO 125 mg/ml solución inyectable' is claimed, the applicant did not submit any data on pharmacology, target animal safety or clinical field trials.

Based on the quantitative and qualitative composition and physicochemical properties of reference and candidate formulations provided by the applicant, an exemption from bioequivalence studies according to the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/EWP/16/2000-Rev.4*), sections 7.1.a and 7.1.b for the intravenous and intramuscular route of administration, respectively, can be accepted.

Efficacy and target animal safety are considered to be the same for the candidate and reference product.

The SPC of the candidate product Hemosyvet 125 mg/ml solution for injection adequately reflects the information of the Spanish product literature of the reference product 'HEMO 125 mg/ml solución inyectable'.

Part 5 – Benefit-risk assessment

Introduction

Hemosyvet 125 mg/ml solution for injection contains the active substance etamsylate and is intended for use in cattle, sheep, goats, pigs, horses, dogs and cats. The indication applied for is for the prevention and treatment of surgical, post traumatic, obstetric and gynaecological haemorrhages. The proposed withdrawal period for meat and offal from cattle, sheep, goats, horses and pigs after intramuscular administration is 1 day.

Etamsylate is a haemostatic and angioprotective drug that stimulates the platelet adhesiveness and thus shortens the bleeding time and normalizes the altered vascular permeability.

The application is submitted under Article 18 of Regulation (EU) 2019/6 – a generic application.

Benefit assessment

Direct benefit

The therapeutic benefit of Hemosyvet 125 mg/ml solution for injection is its efficacy in the prevention and treatment of surgical, post traumatic, obstetric and gynaecological haemorrhages. This direct therapeutic benefit is considered established as the candidate product is administered at the same

dose, route of administration and dosing interval as recommended in product information of the reference product.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been 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.

Safety

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal

The administration of Hemosyvet in accordance with SPC recommendations is not expected to pose an increased risk for the target animals. The only adverse event mentioned in the SPC of the reference product HEMO 125 mg/ml solución inyectable is anaphylaxis, which is caused by the presence of sulphites in the formulation and was observed in humans. The frequency of those adverse events in the target species, however, is unknown.

Risks for the user

User risks have been identified, mainly associated with accidental self-injection and dermal or eye exposure. These risks are mitigated by specific user safety warnings included in the product literature.

Risks for the environment

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

Risk for the consumer

Hemosyvet is not expected to pose a risk to the consumer of meat and milk derived from treated animals when used according to the proposed SPC recommendations. The withdrawal periods established to ensure depletion of residues below the MRLs are as follows:

Meat and offal:

Cattle, sheep, goats, horses, pigs:

Intravenous administration: Zero days.

Intramuscular administration: 1 day.

Milk:

Cattle, sheep, goats, horses:

Intravenous and intramuscular administration: Zero hours.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

Consumer safety

The withdrawal periods of the reference product are considered as also suitable for the generic to ensure safety for the consumer.

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 is subject to a veterinary prescription.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: Prevention and treatment of surgical, post traumatic, obstetric and gynaecological haemorrhages.

As bioequivalence to the reference product 'HEMO 125 mg/ml solución inyectable', which is authorized in Spain can be accepted, the benefit-risk balance is identical to the reference product and thus in principle is considered positive.

The product information has been reviewed and is considered to be acceptable.

Conclusion

Based on the original data presented on quality. safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Hemosyvet is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.