5 December 2024
EMA/8800/2025
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Tolfenamic acid VMD (EMEA/V/C/006234/0000)

INN: Tolfenamic acid

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

Introduction

The applicant VMD N.V. submitted on 25 April 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Tolfenamic acid VMD, 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 10 November 2022 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 indications:

- Cattle: as an adjunct in the treatment of pneumonia by improving general conditions and nasal discharge and as an adjunct in the treatment of acute mastitis,
- Pigs: as an adjunct in the treatment of metritis mastitis agalactia syndrome,
- Dogs: symptomatic treatment of inflammatory and painful conditions of the osteoarticular and musculoskeletal systems; reduction of post-surgical pain,
- Cats: treatment of febrile syndromes.

The active substance of Tolfenamic acid VMD is tolfenamic acid, a non-steroidal anti-inflammatory drug (NSAID) belonging to the fenamate group, which inhibits cyclo-oxygenase leading to a reduction of the synthesis of prostaglandins and thromboxanes, which are important inflammatory mediators. The target species are cattle, pigs, dogs and cats.

Tolfenamic acid VMD solution for injection contains 40 mg/ml tolfenamic acid and is presented in packs containing 1 vial of 25, 50, 100 or 250 ml.

The rapporteur appointed is Leona Nepejchalová and the co-rapporteur is Cristina Muñoz Madero.

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 products are Tolfine for cattle and pigs (MAH Vetoquinol Ireland Limited, Ireland) and Tolfedine 4% solution injectable for dogs and cats (MAH Vetoquinol, France).

On 5 December 2024, the CVMP adopted an opinion and CVMP assessment report.

On 3 February 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Tolfenamic acid VMD.

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

Manufacture of the active substance takes place within the EEA. The GMP certificates and a valid QP declaration are provided. The QP declaration states that the active substance is manufactured in compliance with EU GMP. The declaration is based on on-site audits which were performed in 2023 by a third party.

Manufacturing, primary and secondary packaging and quality control of the finished product takes place in the EEA. A valid GMP certificate is available. GMP certification for these sites has been provided, which confirms the date of the last inspection and shows that the sites are authorised for the activities indicated above.

Batch release takes place at V.M.D. Hoge Mauw 900, BE-2370 Arendonk, Belgium or LABORATOIRES BIOVE 3 rue de Lorraine, 625 10 ARQUES, France. The sites have EU GMP certification, which confirms the date of the last inspection and shows that the sites are authorised for the batch release of such veterinary dosage forms.

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 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 clear, colourless to slightly yellow aqueous solution for injection containing 40 mg/ml of tolfenamic acid as active substance.

Other ingredients are: benzyl alcohol, ethanolamine, diethylene glycol monoethyl ether and water for injections. The inclusion of benzyl alcohol as a preservative is justified with reference to the publicly available information on the composition of both reference products.

The product is available in 25 ml, 50 ml, 100 ml and 250 ml brown type II glass vials closed with a chlorobutyl rubber stopper with aluminium cap, each vial is packed in a cardboard box as described in section 5.4 of the SPC.

Containers and closure system

The primary packaging is brown type II glass vials with chlorobutyl rubber stoppers. The material complies with the relevant European Pharmacopoeia requirements (Ph. Eur. 3.2.1 for glass vials type II and 3.2.9 for stoppers type I). The glass vials are packaged in outer cardboard boxes containing one vial per box.

Certificates of analysis for the primary packaging have been supplied demonstrating compliance with the proposed specifications.

Product development

Tolfenamic acid VMD 40 mg/ml solution for injection has been submitted as a generic application. The applicant has applied for a waiver from in vivo bioequivalence study requirements citing section 7.1.a and 7.1.b of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4).

Formulation development for the generic product is based on the formulation of the reference products Tolfine (MAH Vetoquinol Ireland Limited, Ireland) and Tolfedine 4% solution injectable (MAH Vetoquinol, France), particularly on the publicly available information relating to the reference products SPC and on analysis carried out by the applicant on reference product batches. Information in the SPCs of the reference products allowed the applicant to determine the quantitative composition with respect to the active substance 4% (m/V), i.e. 40 mg/ml tolfenamic acid, the preservative benzyl alcohol 10.4 mg/ml and the full qualitative composition with respect to excipients. The composition of the reference products was determined by analysis on two batches of the reference product Tolfine and on one batch of the reference product Tolfedine 4% solution injectable and a comparison was made with the candidate product Tolfenamic acid VMD. The same concentration of active substance and the same concentration of benzyl alcohol was found as in the reference products. The concentrations of diethylene glycol monoethyl ether and ethanolamine (to adjust the pH) were very similar in the generic and reference products. The pH and the relative density of the generic and the reference products were found very similar. The impurities were found below detection limit in the reference products and in the candidate product. In summary, Tolfenamic acid VMD contains the same concentration of active substance tolfenamic acid as the reference products. The excipients are qualitatively identical and quantitatively very similar and any minor difference in concentration is not expected to influence the absorption of tolfenamic acid. The physicochemical results from the batch analyses of generic Tolfenamic acid VMD and reference products Tolfine and Tolfedine 4% solution injectable are comparable.

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.

In order to demonstrate that the formulation is self-preserving, the efficacy of the antimicrobial preservative was tested in accordance with Ph. Eur. 5.1.3 and criteria A for parenteral preparations were met. The method used was appropriately validated.

The chosen manufacturing process is based on the laboratory scale process development.

The product is manufactured with a standard manufacturing process.

In regard to primary packaging the brown glass vials closed with a chlorobutyl rubber stoppers have been chosen with reference to the packaging of the reference products "Tolfine" and "Tolfedine". The brown vials are justified by the fact that the tolfenamic acid should be stored protected from light as indicated in the Ph. Eur. monograph for this substance. The suitability of glass vials of hydrolytic class II for the proposed product has been demonstrated based on the stability data. With respect to the proposed pack sizes of 25 ml, 50 ml, 100 ml and 250 ml, all are within the range of the packaging available for the reference products.

Fragmentation and self-sealing tests were performed on chlorobutyl rubber stoppers according to the current edition of the Ph. Eur. 3.2.9. Based on the results it can be concluded that the stopper of the 25, 50 and 100 ml vials may be punctured up to 20 times, the stopper of the 250 ml vials may be punctured up to 25 times. The information about maximum punctures of stoppers is stated in the SPC and package leaflet.

Description of the manufacturing method

The manufacturing process consists of the following main steps: preparation of bulk by mixing all components, pre-filtration and filtration of the solution, filling and terminal sterilisation of the product filled in the container. The process is considered to be a standard manufacturing process.

A batch size range is proposed. The manufacturing formulas are provided for both the minimum and maximum batch. The quantity of tolfenamic acid to be weighed is adjusted according to the assay of the batch of active substance used. Formula for calculation of factorisation is stated. No overage is applied during the manufacturing of the product.

A step-wise narrative description of the manufacturing process is provided including a flow chart and in-process controls. Overall, the manufacturing process is deemed sufficiently described. The in-process controls are considered appropriate for the manufacture of a sterile solution. The bioburden limit is in line with the guideline on sterilisation (EMA/CHMP/CVMP/QWP/850374/2015)

The manufacturing process has been validated on three pilot scale bulk batches filled in 25 ml, 100 ml and 250 ml vials. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of pharmaceutical form.

The absence of process validation data on production scale batches in the dossier can be accepted based on the standard nature of the manufacturing process. Acceptable process validation protocols for future commercial scale batches are provided. It is accepted that process validation on full scale batches will be performed on three batches at both ends of the range proposed, post-authorisation. The process validation data on the first 3 commercial scale batches should be available at the manufacturing site for inspection.

Control of starting materials

Active substance

Applicant's dossier

One manufacturer is proposed by the applicant that is supported by an ASMF. The active substance tolfenamic acid is controlled as per Ph. Eur. monograph no. 2039 with additional tests on residual solvent and an elemental impurity. The limits are compliant with the relevant (V)ICH guidelines. As the active substance is to be incorporated into a sterile dosage form, the active substance specification appropriately includes a test for microbiological quality with limits in line with the Ph. Eur. 5.1.4 acceptance criteria for microbiological quality of non-sterile substances for pharmaceutical use. The control methods are those of the current Ph. Eur. monographs except for the additional control methods that are sufficiently described. The method for control of the residual solvent is the same as that described and validated in the ASMF. For control of an elemental impurity the applicant uses his own method which is sufficiently described and validated.

Batch analysis data of three batches of the active substance have been provided including certificates of analysis from the same batches tested by the applicant confirming compliance with the applicant's own active substance specification.

ASMF

The information on the active substance Tolfenamic acid is provided according to the Active Substance Master File (ASMF) procedure.

Tolfenamic acid is synthesised in one step synthesis followed by purification and isolation from commercially available materials which are considered acceptable as starting materials. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF. The information in the Restricted part is satisfactory.

Discussion on impurities is acceptable. Organic impurities, mutagenic impurities, residual solvents and catalysts are sufficiently covered.

The specifications of tolfenamic acid comply with the Ph. Eur. monograph with additional controls on residual solvent, catalyst and microbiological quality. The specification is acceptable.

Control methods are those of the Ph. Eur. monographs. For the residual solvent and the catalyst, in-house methods are used for which descriptions and validations are provided. The information is acceptable.

Batch data are provided demonstrating compliance with the specifications. The batch data are satisfactory.

The container-closure is adequately described and controlled.

Long-term and accelerated stability studies of Tolfenamic acid are performed under VICH conditions (general case). No significant degradation trends are observed in any of these studies. Satisfactory long-term data are provided up to 24 months. The company claims retest period 36 months referring to standard VICH extrapolation and it is accepted. The substance should be protected from light. No temperature storage precautions are needed.

The applicant proposed at first a second supplier of active substance but this second manufacturer was withdrawn during the procedure. The same 3 pilot batches of finished product have been used for batch and stability testing, and manufacturing process validation. One of those batches was manufactured with active substance from the withdrawn supplier. CVMP considered that the data provided including that obtained with product using active substance from the withdrawn manufacturer acceptable.

Excipients

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.

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.

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 specifications proposed at release are appropriate to control the quality of the finished product.

The finished product specification includes tests for appearance: colour, clarity and visible particles, active substance identification, active substance assay, specified, unspecified and total impurities, identification and assay of the preservative benzyl alcohol, pH, relative density, filling volume and sterility. The finished product specifications are generally acceptable and include relevant test parameters for the dosage form.

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. The risk assessment for elemental impurities follows the CVMP reflection paper EMA/CVMP/QWP/153641/2018 and principles in ICH Q3D. The company follows the component approach and provides evaluation of those elements relevant for parenteral use (class 1, 2A and Li, Sb and Cu from class 3). The results of the analysis show that all the elemental impurities concentrations are below control threshold (i.e. <30% of PDE). Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The analytical methods used are adequately described and have been appropriately validated in accordance with VICH GL2.

Batch analysis results are provided for three pilot-scale bulk batches that were filled in 25 ml, 100 ml and 250 ml vials confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data is provided for three pilot scale batches of finished product filled in the primary packaging proposed for marketing i.e. 25 ml, 100 ml and 250 ml vials and stored under long term (25 °C/60% RH), intermediate (30 °C/65% RH) and accelerated (40 °C /75% RH) conditions according to the Guideline on stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022). These batches are the same as those used in process validation. The composition of batches is identical to those proposed for marketing. The 50 ml vials were not used in stability studies following the VICH GL45 bracketing approach which is justified by the fact that the 50 ml vials and stoppers are made of the identical materials as the 25 ml and 100 ml vials. Results of long-term and intermediate stability studies are presented up to 24 months, the studies are ongoing and will be finalized after 36 months. The accelerated stability study is finalized, results are presented up to 6 months. All submitted stability results are well within the proposed limits of the shelf-life specification, no significant changes have been observed. The proposed shelf-life of 36 months without storage conditions that is stated in SPC can be accepted based on the stability data provided.

The in-use stability study was performed on three recently manufactured pilot scale batches (3 months old) stored for 3 months at 25 °C/60% RH and at 30 °C/65% RH according to the guideline on in-use stability testing EMEA/CVMP/424/01 - FINAL. The study was done by using the 25 ml, 100 ml and 250 ml commercial vials. It was not performed on the 50 ml vials following a bracketing approach which is accepted. Multiple vial broachings were performed on vials across the 28-day duration of study to simulate the use of the proposed product in clinical practice. All the results of the in-use stability study at both 25 °C/60% RH and at 30 °C/65% RH comply with the specifications during the tested period, no significant change can be observed. The presented stability data support the proposed in-use shelf life of 28 days. The applicant has committed to perform the in-use stability study on one batch approaching the end of its shelf-life in accordance with the requirements of the guideline on in-use stability testing EMEA/CVMP/424/01-final.

The specifications proposed at the end of shelf-life are in general deemed appropriate to control the quality of the finished product. The specifications proposed at the end of shelf-life are the same as those proposed at release except for the parameters: filling volume which is only performed at release which is acceptable and the test for efficacy of antimicrobial preservation is only performed at the end of stability studies which is accepted.

Overall conclusions on quality

The finished product is a clear, colourless to slightly yellow aqueous solution for injection containing 40 mg/ml of tolfenamic acid as active substance. Other ingredients are: benzyl alcohol, ethanolamine, diethylene glycol monoethyl ether and water for injections. The inclusion of benzyl alcohol as a preservative is justified.

The product is available in 25 ml, 50 ml, 100 ml and 250 ml brown type II glass vials closed with a chlorobutyl rubber stopper with aluminium cap, each vial is packed in a cardboard box. The proposed pack sizes are within the range of the packaging available for the reference products.

Tolfenamic acid VMD 40 mg/ml solution for injection has been submitted as a generic application. The applicant has applied for a waiver from in vivo bioequivalence study requirements citing section 7.1.a and 7.1.b of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4).

Formulation development for the generic product is based on the formulation of the reference products Tolfine (MAH Vetoquinol Ireland Limited, Ireland) and Tolfedine 4% solution injectable (MAH Vetoquinol, France), particularly on the publicly available information relating to the reference products SPC and on analysis carried out by the applicant on reference product batches. In summary, Tolfenamic acid VMD contains the same concentration of active substance tolfenamic acid as the reference products. The excipients are qualitatively identical and quantitatively very similar and any minor difference in concentration is not expected to influence the absorption of tolfenamic acid. The physicochemical results from the batch analyses of generic Tolfenamic acid VMD and reference products Tolfine and Tolfedine 4% solution injectable are comparable.

The active substance tolfenamic acid is controlled as per Ph. Eur. monograph no. 2039. One manufacturer is proposed by the applicant that is supported by ASMF. Additional tests to the Ph. Eur. monograph are controls of residual solvent and an elemental impurity. As the active substance is to be incorporated into a sterile dosage form, the active substance specification appropriately includes a test for microbiological quality. The control methods are those of the current Ph. Eur. monographs except for the additional control methods that are sufficiently described. For control of an elemental impurity the applicant uses his own method which is sufficiently described and validated. Therefore, the specification is acceptable.

The information in the ASMF Restricted part is satisfactory.

Batch analysis data of three batches have been provided including certificates of analysis from the same batches tested by the applicant confirming compliance with the applicant's own active substance specification.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards.

In regard to primary packaging the brown glass vials closed with a chlorobutyl rubber stoppers have been chosen with reference to the packaging of the reference products "Tolfine" and "Tolfedine". The brown vials are justified by the fact that the tolfenamic acid should be stored protected from

light. The suitability of glass vials of hydrolytic class II for the proposed product has been demonstrated based on the stability data.

Based on the results of fragmentation and self-sealing tests performed on chlorobutyl rubber stoppers it can be concluded that the stopper of the 25, 50 and 100 ml vials may be punctured up to 20 times, the stopper of the 250 ml vials may be punctured up to 25 times. The information about maximum punctures of stoppers is stated in the SPC and package leaflet.

The manufacturing process consists of the following main steps: preparation of bulk by mixing all components, pre-filtration and filtration of the solution, filling and terminal sterilisation of the product filled in the container by moist heat according to standard Ph. Eur. conditions. It is considered to be a standard manufacturing process. The manufacturing process is sufficiently described.

The manufacturing process has been validated on three pilot scale bulk batches filled in 25 ml, 100 ml and 250 ml vials. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The absence of process validation data on production scale batches in the dossier can be accepted based on the standard nature of the manufacturing process. Acceptable process validation protocols for future commercial scale batches are provided. The process validation on full scale batches will be performed on three batches at each extreme of the proposed range post authorisation.

The specifications proposed at release are appropriate to control the quality of the finished product.

The analytical methods used are adequately described and have been appropriately validated in accordance with VICH GL2.

Batch analysis results are provided for three pilot-scale bulk batches filled in all vial sizes confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Long term, intermediate and accelerated stability data is provided for three pilot scale batches of finished product filled in the primary packaging proposed for marketing. Results of long-term and intermediate stability studies are presented up to 24 months, the studies are ongoing and will be finalized after 36 months. The accelerated stability study is finalized, results are presented up to 6 months. All submitted stability results are well within the proposed limits of the shelf-life specification. The proposed shelf-life of 36 months without storage conditions can be accepted.

The in-use stability study was performed on three pilot scale batches All results of the in-use stability study comply with the specifications and support the proposed in-use shelf life of 28 days. The applicant has committed to perform the in-use stability study on one batch approaching the end of its shelf-life in accordance with the requirements of the guideline on in-use stability testing EMEA/CVMP/424/01-final.

The specifications proposed at the end of shelf-life are appropriate to control the quality of the finished product.

The applicant proposed at first a second supplier of active substance. This second manufacturer was withdrawn during the procedure. The same 3 pilot batches of finished product have been used for batch and stability testing, and manufacturing process validation. One of those batches was manufactured with active substance from the withdrawn supplier. CVMP considered that the data provided including that obtained with product using active substance from the withdrawn manufacturer acceptable.

In summary, the information on the development, manufacture and control of the active substance and the finished product and stability 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.

Part 3 – Safety documentation (Safety and residues tests)

This application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 (a generic veterinary medicinal product).

The active substance of Tolfenamic acid VMD is tolfenamic acid, a compound that acts as non-steroidal anti-inflammatory drug (NSAID). Tolfenamic acid VMD contains 40 mg of tolfenamic acid per ml of solution. The target species are cattle, pigs, dogs and cats.

The reference products are Tolfine for cattle and pigs, from Vetoquinol Ireland Limited, MA number VPA10983/031/001, and Tolfedine 4% solution injectable for dogs and cats, from Vetoquinol France, MA number FR/V/7241352 0/1986.

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 veterinary medicinal product are met. The applicant has submitted a user safety risk assessment with reference to the two reference products and the CVMP Summary Reports on tolfenamic acid (EMEA/MRL/183/97-FINAL), benzyl alcohol (EMEA, 1997), and diethylene glycol monoethyl ether (EMEA/MRL/488/98-FINAL).

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

No new data was presented. The active substance tolfenamic acid was previously assessed by the CVMP in the context of the establishment of MRLs (EMEA/MRL/183/97-FINAL). Toxicological reference values established in the EPMAR are used in the user safety assessment.

Excipients

The excipients used in this veterinary medicinal product are commonly used at similar quantities in injectable formulations for the same target species. Benzyl alcohol, diethylene glycol monoethyl ether, ethanolamine and water for injections are not considered to represent a safety concern in the

candidate formulation and no effect is anticipated. Therefore, the toxicity of the finished product for the user can be assessed based on the toxicity of the active substance.

User safety

The applicant has submitted a user risk assessment (URA) relating to the reference products. 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 that could be considered as the worst-case scenario, and dermal contact with the product. Considering the legal basis of the application, the applicant has aligned the product literature with that of the reference product.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the assessment can stop at question no. 3 of the decision tree for dogs and cats as non food-producing species, and for cattle and pigs at question no. 5 of the decision tree as the veterinary medicinal product will be used to treat a small number of animals in a flock or herd.

As is the case for the reference products, no specific environmental warnings are considered necessary and the standard text relating to disposal of unused product is proposed for inclusion in the SPC of Tolfenamic acid VMD.

It can be concluded that Tolfenamic acid VMD will 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.

Residue tests

MRLs status

The MRL status of the constituents of Tolfenamic acid VMD is as follows:

The active substance in Tolfenamic acid VMD 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**
Tolfenamic acid	Tolfenamic acid	Bovine, porcine	50 µg/kg 400 µg/kg 100 µg/kg	Muscle Liver Kidney	NO ENTRY	Anti-inflammatory agents / Nonsteroidal anti/inflammatory agents
		Bovine	50 µg/kg	Milk		

The excipients listed in section 2 of the SPC are either 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

This application for Tolfenamic acid VMD solution for injection for cattle, pigs, dogs and cats has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 (generic veterinary medicinal product).

Based on the legal basis of this application, the omission of residue studies is considered acceptable and cross-references may be made to the dossier of the reference product. According to the Annex II to Regulation (EU) 2019/6 Section IV (IV1.5.) the following additional data shall be provided for generic product intended to be administered by intramuscular, subcutaneous or transdermal routes: ”a) evidence to demonstrate equivalent or differing depletion of residues from the administration site, which may be substantiated by appropriate residue depletion studies;...”.

According to the “Guideline on the conduct of bioequivalence studies for VMP (EMA/CVMP/016/2000-Rev.4)”, the omission of bioequivalence studies is justified for the candidate product by the fulfilment of condition 7.1 a), b). Tolfenamic acid VMD is essentially similar to the reference products in terms of the active substance, excipients, physicochemical parameters of pharmaceutical form which is intended to be administered by the same routes and at the same dose, and to the same target species as those of the two reference products. Therefore, on the basis of essential similarity of the products the depletion of residues in the injection site for the generic product is expected to be the same as that of the reference products.

No further residue study has been performed in any target species which is considered acceptable.

Residue analytical method

Since this is a generic application submitted in accordance with Article 18 of Regulation (EU) 2019/6 and the omission of bioequivalence studies has been justified no further information on the analytical method is required.

Withdrawal periods

The product Tolfenamic acid VMD is essentially similar to the reference products in terms of the active substance, excipients, physicochemical parameters of pharmaceutical form which is intended to be administered by the same routes and dose and to the same target species as those of the two reference products, therefore the same withdrawal periods and restrictions of use as for the reference product Tolfine (intended for cattle and pigs) have been applied to Tolfenamic acid VMD. The differences in the amount of excipients in the product, if any, are not expected to affect the rate of residue depletion.

The withdrawal periods are as follows:

Cattle:

- Intramuscular injection:

  Meat and offal: 12 days.

  Milk: Zero hours.

- Intravenous injection:

  Meat and offal: 4 days.

  Milk: 24 hours.

Pigs:

Meat and offal: 16 days.

Overall conclusions on the safety documentation: safety and residues tests

Pharmacology:

See part 4.

Toxicology:

In this generic application no additional toxicological data are provided with the exception of the CVMP Summary Reports referenced by the applicant. The excipients used in this product are commonly used at similar quantities in injectable formulations in the same target species and do not represent a safety concern.

User safety:

A user safety assessment and an expert report, including the tabular form, have been submitted. Based on the similarities between the candidate and the reference products, no difference in exposure to the candidate formulation compared to the reference products is anticipated. The risk posed to the user by Tolfenamic acid VMD is not expected to differ to that posed by the reference products. Therefore, and considering the legal basis of the application, the applicant has aligned the product literature with that of the reference product.

Environmental risk assessment:

An appropriate environmental risk assessment was provided. The product Tolfenamic acid VMD is not expected to pose a risk for the environment when used according to the SPC.

Residue tests:

The depletion of residues is expected to be the same as that of the reference product and no additional depletion studies for cattle and pigs are required. The withdrawal periods of the reference product can be applied to the generic.

Part 4 – Efficacy

Pre-clinical studies

Tolfenamic acid VMD 40 mg/ml solution for injection for cattle, pigs, dogs and cats contains tolfenamic acid, a non-steroidal anti-inflammatory drug (NSAID) belonging to the fenamate group. The product is intended for use in cattle as an adjunct in the treatment of pneumonia by improving general conditions and nasal discharge and as an adjunct in the treatment of acute mastitis, in pigs as an adjunct in the treatment of metritis mastitis agalactia syndrome, in dogs for symptomatic

treatment of inflammatory and painful conditions of the osteoarticular and musculoskeletal systems and for reduction of post-surgical pain, and in cats for the treatment of febrile syndromes.

The proposed dosage regimen is:

Cattle:

- For inflammation associated with respiratory disease: 2 mg of tolfenamic acid/kg body weight by intramuscular injection. The treatment may be repeated once after 48 hours.
- For use in mastitis: 4 mg of tolfenamic acid/kg body weight as a single intravenous injection.

Pigs:

- For use in metritis mastitis agalactia syndrome: 2 mg of tolfenamic acid/kg body weight as a single intramuscular injection.

Dogs:

- For symptomatic treatment of inflammatory and painful conditions of the osteoarticular and musculoskeletal systems: 4 mg of tolfenamic acid/kg body weight subcutaneously or intramuscularly, which can be repeated 48 hours later or treatment may be continued orally.
- For reduction of post-surgical pain: 4 mg of tolfenamic acid/kg body weight by intramuscular route, preferably 1 hour before induction of anaesthesia.

Cats:

- For treatment of febrile syndromes: 4 mg of tolfenamic acid/kg body weight subcutaneously, which can be repeated 48 hours later or treatment may be continued orally.

Pharmacology

Pharmacodynamics

Tolfenamic acid is a NSAID acting by an inhibition of cyclo-oxygenase and thus reducing the synthesis of prostaglandins and thromboxane, thereby exerting anti-inflammatory, analgesic and antipyretic effects.

This is a generic application and the applicant has claimed exemption from conducting in vivo bioequivalence studies in accordance with the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4), sections 7.1 a) and b).

Tolfenamic acid VMD is essentially similar to the reference products in terms of the active substance, excipients and physico-chemical parameters of the pharmaceutical form, and is intended to be administered by the same routes, at the same dosage and to the same target species as those of the two reference products. Therefore, the conditions set out in sections 7.1 a) and b) of the aforementioned CVMP bioequivalence guideline are considered fulfilled and thus bioequivalence between the candidate and reference products can be accepted.

It can be accepted that the pharmacodynamic properties of tolfenamic acid have already been adequately characterised for the reference products and that cross-reference to the dossier of reference products is appropriate. The applicant proposes to include in SPC section 4.2 the same information on pharmacodynamic properties of the active substance as included in the SPC of the reference products. Given that bioequivalence between the candidate and reference products can be accepted, this is considered appropriate.

Pharmacokinetics

Based on the data provided by the applicant in terms of quantitative and qualitative composition and physico-chemical properties of reference and candidate formulations, it is considered that the pharmacokinetic profile of the active substance is not affected and the biowaiver according to the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4), sections 7.1 a) and b) can be accepted.

It can also be accepted that the pharmacokinetic particulars of tolfenamic acid have already been adequately characterised for the reference products and that cross-reference to the dossier of reference products is appropriate. The applicant proposes to include in SPC section 4.3 the same information on pharmacokinetic properties of the active substance as included in the SPC of the reference products. Given that bioequivalence between the candidate and reference products can be accepted, this is considered appropriate.

Dose determination and confirmation

No data on dose determination and dose confirmation has been provided.

Given the legal basis of the application (generic veterinary medicinal product) and the fact that the candidate product is considered bioequivalent with the reference products, the omission of dose determination and dose confirmation data can be accepted.

Tolerance in the target animal species

No data on target animal tolerance has been provided.

In accordance with the legal basis of the application and taking into account that the proposed generic product is considered bioequivalent with the reference products, the omission of target animal tolerance data can be accepted.

Clinical trials

No clinical trial data has been provided.

In accordance with the legal basis of the application and given the bioequivalence of the candidate product with the reference products, the omission of clinical trial data can be accepted.

Overall conclusions on efficacy

In accordance with the legal basis of the application, the applicant has not submitted any data on pharmacodynamics, pharmacokinetics, dose determination/confirmation, target animal tolerance or clinical trials. This is considered acceptable.

Based on the data in terms of quantitative and qualitative composition and physico-chemical properties of reference and candidate formulations provided by the applicant, an exemption from conducting in vivo bioequivalence studies according to the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4), sections 7.1 a) and b) can be accepted.

Consequently, the characteristics of the candidate product in terms of efficacy and target animal tolerance are considered to be the same as for the two reference products.

The SPC of the generic product includes the same information as that of the reference products Tolfine and Tolfedine 4% solution injectable. As there are two reference products, the corresponding SPC sections have been merged by the applicant.

Part 5 – Benefit-risk assessment

Introduction

Tolfenamic acid VMD is a solution for injection containing tolfenamic acid, an active substance which is well-known.

The active substance, tolfenamic acid, is a non-steroidal anti-inflammatory drug (NSAID) belonging to the fenamate group, which inhibits cyclo-oxygenase leading to a reduction of the synthesis of prostaglandins and thromboxanes, which are important inflammatory mediators. The product is intended for use in cattle, pigs, dogs, and cats for the following indications:

- Cattle: as an adjunct in the treatment of pneumonia by improving general conditions and nasal discharge and as an adjunct in the treatment of acute mastitis,
- Pigs: as an adjunct in the treatment of metritis mastitis agalactia syndrome,
- Dogs: symptomatic treatment of inflammatory and painful conditions of the osteoarticular and musculoskeletal systems; reduction of post-surgical pain,
- Cats: treatment of febrile syndromes.

The application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 – a generic application.

Benefit assessment

Direct benefit

The evidence for the direct therapeutic benefit is considered established when the candidate product is administered at the same dose, route of administration and dosing interval as recommended in the marketing authorisation for the reference products.

The proposed benefit of Tolfenamic acid VMD is its efficacy as an adjunct in the treatment of pneumonia by improving general conditions and nasal discharge and as an adjunct in the treatment of acute mastitis in cattle, as an adjunct in the treatment of metritis mastitis agalactia syndrome in pigs, for symptomatic treatment of inflammatory and painful conditions of the osteoarticular and musculoskeletal systems and for reduction of post-surgical pain in dogs and for the treatment of febrile syndromes in cats.

Risk assessment

Quality

Information on the development, manufacture and control of the active substance and the 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

Risk for the target animal

Tolfenamic acid VMD is not expected to pose a risk for the target animals when used according to the SPC recommendations. It is not expected that the formulation proposed presents a higher risk for the target species than the reference products. The main reported adverse reactions stated in the SPC include diarrhoea and vomiting in dogs and cats (rare) and adverse events whose frequency cannot be estimated from available data: collapse after rapid intravenous administration in cattle and increase in thirst and/or diuresis, anorexia and presence of blood in faeces in dogs and cats. The safety of the veterinary medicinal product during pregnancy was not established in the target species dogs and cats, thus the use of the product is not recommended during pregnancy in these species.

Risk for the user

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Considering the legal basis of the application, the applicant has aligned the product information with that of the reference product.

Risk for the environment

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

Risk for the consumer

Tolfenamic acid VMD is not expected to pose a risk to the consumer of meat, offal and milk derived from treated animals when Tolfenamic acid VMD is used according to the proposed SPC recommendations.

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. It is considered appropriate that the warnings and risk mitigation measures proposed for inclusion in the candidate product SPC reflect those approved for the reference products.

Regarding consumer safety the withdrawal periods are the same as those for the reference product:

- Cattle (intramuscular injection): 12 days for meat and offal and zero hours for milk.
- Cattle (intravenous injection): 4 days for meat and offal and 24 hours for milk.
- Pigs: 16 days for meat and offal.

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:

- Cattle: as an adjunct in the treatment of pneumonia by improving general conditions and nasal discharge and as an adjunct in the treatment of acute mastitis,

- Pigs: as an adjunct in the treatment of metritis mastitis agalactia syndrome,
- Dogs: symptomatic treatment of inflammatory and painful conditions of the osteoarticular and musculoskeletal systems; reduction of post-surgical pain,
- Cats: treatment of febrile syndromes.

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

Based on the data presented to date, the overall benefit-risk balance is considered positive.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including withdrawal period, have been included in the SPC and other product information.

The product information has been reviewed and is considered to be satisfactory and in line with the assessment.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Tolfenamic acid VMD 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.