IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Tolfine

PRODUCT SUMMARY

EU Procedure number	IE/V/0661/001/DC
Name, strength and pharmaceutical form	Tolfine 80 mg/ml solution for injection
Active substance(s)	Tolfenamic acid
Applicant	Vetoquinol Ireland Limited, 12 Northbrook Road, Ranelagh, Dublin 6, Ireland
Legal basis of application	Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of Authorisation	25/05/2022
Target species	Cattle
Indication for use	Adjunct treatment for the reduction of acute inflammation associated with respiratory diseases. Adjunct treatment of acute mastitis.
ATC vet code	QM01AG02
Concerned Member States	AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, IT, LT, LU, LV, NL, PL, PT, SI, SK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars
The product contains the active susbtance 80 mg/ml tolfenamic acid and the excipients diethylene glycol monoethyl ether, ethanolamine and water for injections.
The container/closure system is composed of amber type I glass vials closed with chlorobutyl rubber stoppers and oversealed with an aluminium seal with a polypropylene flip-off cap.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is tolfenamic acid, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification has been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on Intermediate Products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a hybrid application according to paragraph 3 of Article 13 of Directive 2001/82/EC, as amended, and bioequivalence with the reference product has been accepted, the results of safety tests are not required. The reference product cited by the applicant is Tolfine (40 mg/ml solution for injection - VPA10983/031/001 - Vetoquinol Ireland Limited) which was first authorised in the Reference Member State on 04/02/2000 in accordance with a full application dossier and for which the marketing authorisation remains valid. The reference product has been authorised for in excess of ten years and can therefore be accepted as a valid reference product in this generic application.
The safety aspects of this product are considered to be the same as the reference product.
Warnings and precautions as listed on the product literature are similar to those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

With regards the intramuscular route of administration, the Applicant presented the results of a well-designed GLP-compliant *in vivo* bioequivalence study, which compared the pharmacokinetics of tolfenamic acid in cattle. Plasma concentrations of tolfenamic acid were measured following single intramuscular administration of the candidate and reference formulations with blood samples collected at appropriate time points.
Following administration of tolfenamic acid at 2 mg/kg bodyweight (test article), mean maximum plasma concentrations (C_{max}) of 1.77 ± 0.45µg/ml were achieved at approximately 2.4 hours(0.25-8 hours), with a mean terminal eliminationhalf-life ($T_{½\lambda z}$)of 9.41 ± 2.72 hours. Based upon the results of the bioequivalence study conducted and the subsequent statistical analysis, it is accepted that for the intramuscular route of administration, the candidate product formulation can be considered bioequivalent to the reference product formulation.
With regards the intravenous route of administration, an exemption from the requirement for conducting bioequivalence studies was justified in accordance with section 7.1(a) of the Guideline on the conduct of bioequivalence studies for veterinary

medicinal products (EMA/CVMP/016/00-Rev.3). Given that the criteria of waiver 7.1(a) of the bioequivalence guideline can be considered satisfied, the omission of the results of bioequivalence studies for the intravenous route of administration for the candidate formulation has been accepted.
Based on the information provided, bioequivalence with the reference formulation has been accepted. Consequently, the results of pharmacological tests are not required.

Toxicological Studies
This application was submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC, as amended (a hybrid application). Based upon the results of an *in-vivo* bioequivalence study and additional data provided, the toxicological aspects of this product are considered to be the same as for the reference product. Accordingly, the results of toxicological studies are not required.

Other Studies
The Applicant has presented the results of additional studies which show that the test article is non-corrosive and is not a skin sensitiser, however, it is considered to be an ocular and skin irritant.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product does not present any greater risk to the user than that presented by the reference product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

The veterinary medicinal product is irritant to eyes.
In case of accidental eye exposure, flush the eyes immediately with clean water and seek medical advice immediately.
The veterinary medicinal product is irritant to skin. In case of accidental spillage onto skin, wash the skin immediately with soap and water.
Seek medical attention if irritation persists.
Wash hands after use.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or label to the physician.
People with known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) should avoid contact with the veterinary medicinal product.
In view of the risk of accidental self-injection and the known adverse class-effects of NSAIDs on pregnancy and/or embryofoetal development, pregnant women or women attempting to conceive should administer this veterinary medicinal product with care.

Environmental Risk Assessment
Phase I
The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the Phase I assessment showed that the PEC_{soil} was less that the trigger value of 100 µg/kg for all types of cattle.
Conclusion
Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation
Residue Studies
For the intramuscular route of administration
Two studies were conducted in cattle to characterise depletion of residues from meat and milk following administration of the final formulation. Both studies were conducted in accordance with GLP and relevant guidance.

For the intravenous route of administration
No tissue residue depletion study was conducted in cattle for the intravenous route of administration because bioequivalence of the candidate product with the reference product has been accepted in accordance with waiver 7.1(a) of the bioequivalence guideline and given that injection site residues following intravenous administration of the candidate product are not expected, the results of residue studies are considered unnecessary for the derivation of withdrawal periods as these may be extrapolated from the reference product.
One study was conducted in cattle to characterise depletion of residues from milk following intravenous administration of the final formulation. This study was conducted in accordance with GLP and relevant guidance.

MRLs
Tolfenamic acid is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active Substance	Marker residue	Animal Species	MRL	Target Tissues
Tolfenamic acid	Tolfenamic acid	Bovine Porcine	50 µg/kg 400 µg/kg 100 µg/kg	Muscle Liver Kidney
		Bovine	50 µg/kg	Milk

Withdrawal Periods

Based on the residue data provided, the following withdrawal periods are justified for cattle:

Following intramuscular administration:
Meat and offal: 20 days
Milk: 0 hours

Following intravenous administration:
Meat and offal: 4 days
Milk: 12 hours

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals
The applicant conducted three GLP compliant studies evaluating target animal safety.
In one negatively controlled study, cattle were administered the test article intravenously at up to 2 times the recommended daily dose on up to 6 occasions at 24 or 48 hour intervals. Tolerance was evaluated by clinical examination, injection site evaluation, blood testing for biochemical and haematological parameters, milk production and bodyweight. The only clinically relevant abnormalities observed during the study period were injection site reactions with inflammation and swelling observed persisting for up to 38 days.
Another two GLP-compliant studies evaluated local tolerance following intramuscular administration of the test article; in both of these studies injection site reactions were observed with inflammation and swelling persisting for up to 14 days.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies
As this is a hybrid application according to paragraph 3 of Article 13 of Directive 2001/82/EC, as amended, and bioequivalence with the reference product has been accepted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.