IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

TOLFEDOL, 40 mg/ml, solution for injection for cattle, pigs, cats and dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0344/001/DC
Name, strength and pharmaceutical form	TOLFEDOL, 40 mg/ml, solution for injection for cattle, pigs, cats and dogs
Active substance(s)	Tolfenamic Acid
Applicant	SP Veterinaria, S.A. Ctra Reus Vinyols km 4.1 Riudoms (43330) Spain
Legal basis of application	Article 13(1) – Generic Application of Directive 2001/82/EC as amended.
Date of completion of procedure	20th May 2015
Target species	Bovine Porcine Feline Canine
Indication 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 the treatment of inflammation associated with musculo-skeletal disorders and for the reduction of post-operative pain. **In cats** : as an adjunct in the treatment of upper respiratory disease in association with antimicrobial therapy, if appropriate.
ATCvet code	QM01AG02
Concerned Member States	DE, ES, FR, PT, RO, SK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the 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; possible adverse reactions that may be 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 40 mg/ml tolfenamic acid and the excipients benzyl alcohol, diethylene glycol monoethyl ether, sodium formaldehyde sulfoxylate, ethanolamine and water for injections.

The container/closure system is 20 ml, 50 ml, 100 ml and 250 ml amber polypropylene vials with grey (20 ml, 50 ml and 100 ml vials) or pink (250 ml vials) butyl rubber stoppers and aluminium caps with green flip-off seals.

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 substance described in the European. 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

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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)

This is a generic application, submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended. The active substance is tolfenamic acid, a non-steroidal anti-inflammatory drug (NSAID).

The reference product cited by the applicant was Tolfedine 4% w/v solution for injection for dogs and cats (Vetoquinol Ireland). Bioequivalence with a reference product and an additional product (Tolfine (Vetoquinol Ireland) with the same formulation but which is authorised for use in cattle and pigs) can be accepted. The omission of *in-vivo* bioequivalence studies can be accepted in accordance with section 7.1.b of the CVMP ‘Guideline on the conduct of bioequivalence studies for veterinary medicinal products’.

Consequently, the safety aspects of this product are considered to be similar to the reference product.

Warnings and precautions as listed on the product literature are in line with those of the reference product (and the additional product Tolfine) and other similar products containing NSAIDs recently authorised within the EU and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Testing

Pharmacological Studies

Toxicological Studies

This is a generic application submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended. Bioequivalence with a reference product (and the additional product (Tolfine) with the same formulation) has been demonstrated and the omission of *in-vivo* bioequivalence studies was accepted in accordance with section 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products'. Consequently, results of pharmacological and toxicological studies were not required.

User Safety

The applicant has provided a user safety assessment. It can be accepted that there will be no difference in risk for the user between the candidate and reference product formulations.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

An environmental risk assessment was provided.

Phase I

The environmental risk assessment could end in Phase I for cats and dogs as they are non-food animal species.

For cattle and pigs, it was accepted that the product will only be administered to a small number of animals. Consequently, the environmental impact assessment could end in Phase I.

A Phase II ERA was not required.

Conclusion

Based on the data provided, the ERA could end in Phase I. The product is not expected to pose an unacceptable risk for the environment when stored, handled, administered and disposed of in accordance with the recommendations included in the proposed SPC.

III.B Residues Documentation

Residue Studies

While evidence to demonstrate equivalent or differing depletion of residues from the administration site is normally required for injectable products, given that the formulation of the candidate formulation has been shown to be qualitatively and quantitatively identical to that of the reference product, it was accepted that the rate and extent of depletion of residues from the injection site is not expected to differ between candidate and reference product formulations. Consequently, injection site residue depletion studies were not required for this product and the withdrawal periods approved for the reference product formulation can be applied to this product.

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	Muscle
			400 µg/kg	Liver

			100 µg/kg	Kidney
		Bovine	50 µg/kg	Milk

Withdrawal Periods

The following withdrawal periods were accepted:

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.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

This is a generic application, submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended and bioequivalence with a reference product (and additional product (Tolfine) with the same formulation) has been demonstrated. The omission of *in-vivo* bioequivalence studies was accepted in accordance with section 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products'. Consequently, the results of pre-clinical trials were not required.

Tolerance in the Target Species of Animals

The product has been demonstrated as having the same formulation as that of the reference product. The proposed target species, dose rates and routes of administration are the same as those approved for the reference product (and additional product (Tolfine) with the same formulation). On that basis, no difference between candidate and reference product formulations in terms of local or systemic tolerance is to be expected and the omission of tolerance study data was accepted.

The SPC includes similar information concerning possible adverse events as included in the SPC of the reference product (and the product Tolfine) and other similar products recently authorised within the EU.

The product literature accurately reflects the type and incidence of adverse reactions which might be expected.

IV.B Clinical Studies

Laboratory Trials
Field Trials

This is a generic application, submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended and bioequivalence with a reference product (and additional product (Tolfine) with the same formulation) has been

demonstrated. The omission of *in-vivo* bioequivalence studies was accepted in accordance with section 7.1.b of the CVMP 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products'. Consequently, the results of clinical trials were not required.

V OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrates 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.

VI POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Changes:
None.