IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Finadyne Transdermal 50 mg/ml pour-on solution for cattle.

PRODUCT SUMMARY

EU Procedure number	IE/V/0323/001/DC
Name, strength and pharmaceutical form	Finadyne Transdermal 50 mg/ml pour-on solution for cattle
Active substance(s)	Flunixin meglumine
Marketing Authorisation Holder	Intervet International B.V., Wim de Korverstraat 35, 5831 AN Boxmeer, The Netherlands.
Legal basis of application	Full application in accordance with Article 12.3 of Directive 2001/82/EC, as amended.
Date of completion of procedure	26th February 2014.
Target species	Cattle
Indication for use	For the reduction of pyrexia associated with bovine respiratory disease. For the reduction of pyrexia associated with acute mastitis.
ATCvet code	QM01AG90
Concerned Member States	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IS, IT, LT, LU, LV, NL, PL, PT, SE, SK, UK

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; the 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 50 mg/ml flunixin (as flunixin meglumine) and the excipients pyrrolidone, propylene glycol dicaprylocaprate, glycerol monocaprylate, levomenthol and allura red.
The container/closure system consists of high density polyethylene (HDPE) bottles with polypropylene (PP) closures which have a peelable foil laminate induction inner seal and a liner.
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.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C.Control of Starting Materials

The active substance is flunixin (as flunixin meglumine), 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 have been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

A declaration of TSE compliance of Finadyne Transdermal with the Annex to Commission Directive 1999/104/EC and the latest version of the guideline EMEA/410/01 is provided.

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 have been provided.
Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F.Stability

Stability data on the active substance have 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 have 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)

III.ASafety Testing

Pharmacological Studies

The applicant provided bibliographical data which show that Flunixin is a well-known NSAID with well-established analgesic, anti-pyretic and anti-inflammatory activities. It is a potent inhibitor of both COX-1 and COX-2 enzymes.

Toxicological Studies

The applicant referred to the toxicity data on the active substance which was previously reviewed by the CVMP in the context of an application to establish an MRL (maximum residue limit) for flunixin.

Based on the No-Observed Effect Level value of 0.6 mg flunixin free acid/kg bodyweight per day from a 90-day repeated dose study in dogs and applying a safety factor of 100, a toxicological Acceptable Daily Intake value of 0.006 mg/kg bw (i.e. 360 µg/person) was established.

There is no evidence that flunixin is a teratogen or has mutagenic or carcinogenic potential.

It can be accepted that the inherent toxicity of flunixin meglumine has been adequately characterised.

Other Studies

The applicant conducted studies investigating dermal toxicity, skin irritation, skin sensitisation and ocular irritation of the final formulation. Based upon the results from these studies, it was concluded that the product is an ocular irritant which may result in irreversible ocular damage. The formulation was not shown to be a skin sensitiser or skin irritant but the formulation may be harmful following accidental oral or dermal exposure.

Suitable warnings/advice has been included in the SPC in order to mitigate against the above risks.

Observations in Humans

Flunixin meglumine is not used in human medicine.

User Safety

A user safety assessment was provided. It was shown that a potential risk for the user may arise following accidental oral, dermal or ocular exposure to the formulation. The SPC includes a number of user safety warnings in order to mitigate against such risks.

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

Ecotoxicity

Phase I
The product is a non-steroidal anti-inflammatory drug intended for single application (pour-on) to individual animals. Consequently, the environmental risk assessment can stop in Phase I.

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.BResidue documentation

Residue Studies

The applicant conducted a number of residue depletion studies using the final formulation. Samples of tissues and milk were taken from animals at several time points.
Results show that after application of the product as recommended in the SPC, residues depleted to below the MRL in all tissues by 5 days and to below the MRL in milk by 24 hours.
Statistical analysis of the results was used to set the withdrawal periods.

The analytical method was based on liquid chromatography with MS/MS detection (LC - MS/MS) and was suitably described and validated.

A number of studies indicate that untreated in-contact animals may become exposed to the product following oral ingestion of the product through grooming of treated animals. As a result, the possibility for occurrence of residues in such animals exists. Consequently, the SPC includes a number of precautionary measures to avoid the occurrence of residues in untreated animals.

MRLs

Flunixin is listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissue	Other provisions
Flunixin	Flunixin	Bovine	20 µg/kg	Muscle	-
			30 µg/kg	Fat	
			300 µg/kg	Liver	
			100 µg/kg	Kidney	
5-Hydroxy flunixin		Bovine	40 µg/kg	Milk	-

Withdrawal Periods

Based upon the data provided, withdrawal periods of 7 days for meat and offal and 36 hours for milk are justified.

IV. CLINICAL ASSESSMENT

IV.APre-Clinical Studies

Pharmacology

The applicant conducted a number of studies in order to characterise the pharmacokinetics of flunixin in cattle, following topical application along the midline of the back of the animal.
Based on the data presented, it is evident that flunixin rapidly reaches the blood stream after topical application, with peak concentrations observed at 2 or 6 hours post-dosing in warm and cold ambient conditions respectively. Plasma elimination half-life was calculated to be 7.8 hours [range, 4.5-20.3 h] and bioavailability was shown to be approximately 44%.
The studies also showed that ambient temperature has an impact on PK profile. Rate of absorption of flunixin is slower when applied under colder ambient conditions.
A number of studies indicate that auto- or allo-grooming may have an impact on flunixin exposure. The possibility exists for exposure of untreated in-contact animals to the product, following oral ingestion of the product via grooming of treated animals.

Consequently, the SPC includes a number of precautions in order to limit the possible exposure of untreated animals to the product.

Tolerance in the Target Species of Animals

The applicant conducted a number of controlled target animal tolerance studies using multiples of the recommended dose rate on repeated occasions, in the target species. The product was administered on the midline of the back as recommended in the SPC.
The product was in general well tolerated.
A limited number of animals exhibited irritation, agitation or discomfort following topical application of the product. Some animals also displayed evidence of transient swelling and erythema of the application site.
Local application site changes (mainly of a cosmetic nature) were observed in most studies and included broken/brittle hair, hair thinning, alopecia, flaking, dandruff or thickened skin.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.
When the product was administered at higher than the recommended dose rate, localised inflammatory reactions of the skin, erosive and ulcerative abomasal lesions or faecal blood were reported.

Resistance

Given the nature of the active substance (a NSAID), data on resistance development are not required.

IV.B Clinical Studies

Laboratory Trials
The applicant conducted a number of dose determination/confirmation studies which support the choice of dose rate of 3.33 mg/kg on a single occasion. Based upon the data presented, the applicant chose the 6 hour time point (post-application) to demonstrate anti-pyretic effect of the product in clinical trials.

Field Trials
The applicant conducted a number of controlled, mulit-centre field studies in differing geographical locations and under different ambient temperatures. Results from these studies show that the product has an anti-pyretic affect when measured at 6 hours post-application, in cattle with naturally occurring bovine respiratory disease.
An anti-pyretic effect was demonstrated from 4 hours after application of the product.
A post-authorisation controlled field study was conducted in support of a new indication for the reduction of pyrexia in cows with acute mastitis.
Finadyne Transdermal was investigated in 64 cows with mastitis and efficacy for reducing rectal temperature was compared to placebo, which was used in 66 cows. At six hours post-treatment 95.3% of cows treated with Finadyne Transdermal showed a decrease in rectal temperature of more than 1.1°C, compared with 34.9% in the placebo group. After 6 hours, when antibiotic treatment had been added, there were no differences in rectal temperature between the groups.
A post-authorisation field study was conducted in support of a new indication for the reduction of pain and lameness associated with interdigital phlegmon, interdigital dermatitis and digital dermatitis. Results of this study show that the product reduced pain in cattle when measured at 6 hours post-treatment application.

A further post-authorisation study submitted in support of the same indication evaluated efficacy of the product in reducing experimentally-induced lameness by means of lameness scoring and biometric gait assessment. Results of this study demonstrated a clinically relevant improvement in lameness 6 hours post-treatment application.

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.

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.

Safety/Efficacy Changes

Summary of change **(Application number)**	**Approval date**
Addition of a new indication: For the reduction of pyrexia associated with acute mastitis. IE/V/0323/001/II/001	21st August 2015
Addition of a new indication: For the reduction of pain and lameness associated with interdigital phlegmon, interdigital dermatitis and digital dermatitis. IE/V/0323/001/II/005	18th November 2016