LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Flunipaste Vet.
flunixin meglumin

Asp no: 2015-1460

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MODULE 1

PRODUCT SUMMARY

Asp no	2015-1460
Name, strength and pharmaceutical form	Flunipaste Vet., 50 mg/g, oral gel
Applicant	Biovet aps Kongevejen 66, 3480 Fredensborg, Denmark
Active substance(s)	flunixin meglumin
ATC Vetcode	QM01AG90
Target species	Horse
Indication for use	Aseptiska inflammationer i rörelseapparat hos häst.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Medical Products Agency's website (http://www.lakemedelsverket.se/english/).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original national procedure	2016-12-12

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 slight 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

B. Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests are not required.

The pharmacological and toxicological aspects of this product are identical to 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 / the environment / consumers.

III.A Safety Testing

Pharmacological Studies

A bioequivalence study comparing Flunipaste Vet. 50 mg/g oral gel to Finadyne Paste, 50 mg/g paste as reference product was conducted in horses. Bioequivalence between test and reference has been sufficiently demonstrated. For AUC_{0-t} the 90% confidence interval for the ratio of the test and reference products (0.973-1.117) fell within the conventional acceptance range of 80.00-125.00% whereas for C_{max} the 90% confidence interval for the ratio of the test and reference products (0.982-1.276) fell outside the conventional acceptance range of 80.00-125.00% but was within the widened acceptance range of 70-143%.

User Safety

No user risk assessment was provided by the applicant. As Flunipaste Vet. oral gel is similar to the reference product Finadyne Paste with respect to active compound as well as excipients, its use is not expected to result in a different risk for the user. The SPC section 4.5 for Flunipaste Vet. includes the same precautionary measures as for Finadyne Paste, with a slight revision in accordance with other products with comparable exposure scenarios, and is adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I because the product will be used to treat a small number of animals.

Conclusion

The ERA can stop at Phase I, i.e. Flunipaste Vet. is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because bioequivalence between test and reference has been sufficiently demonstrated.

MRLs

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

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Flunixin	Flunixin	Equidae	10 µg/kg	Muscle		
			20 µg/kg	Fat		
			100 µg/kg	Liver		
			200 µg/kg	Kidney		

Withdrawal Periods

A slightly higher upper limit of the 90% confidence interval for the C_{max} ratio than recommended for extrapolation of withdrawal periods (1.28 versus 1.25) was noted in the bioequivalence study. With a mean plasma elimination half-life of 4 hours no accumulation in plasma following repeated administration is expected. Based on the rapid absorption (median t_{max} was 1 hour) and the short plasma elimination half-life a slightly higher C_{max} on the last treatment day (day 5) for Flunipaste Vet. oral gel is not expected to result in flunixin levels in edible tissues that would increase the risk for consumers 15 days after the treatment. Extrapolation of the 15-day withdrawal period for Finadyne Vet. oral paste to Flunipaste Vet. oral gel can thus be accepted.

For clarification and to comply with other comparable products information that treatment of animals producing milk intended for human consumption is not allowed have been included in SPC section 4.11.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

Flunipaste Vet. 50 mg/g oral gel is applied as a generic product according to article 13(1) using Finadyne Paste, 50 mg/g, paste as reference product. A bioequivalence study comparing Flunipaste Vet. to Finadyne Paste was conducted in horses and is summarised below.

Study 20-12-0184-04 was a randomised two-period, two-treatment single-dose crossover study in the fasted state with a 5-7 day wash-out period conducted in 12 clinically healthy horses of various riding horse breeds (weight range 490-690 kg) comparing Flunidol Paste 50 mg/g oral gel (Flunipaste Vet. 50 mg/g oral gel) to Finadyne Paste. 50 mg/g, paste. The study was conducted by Harlan Biowervice for Science GmbH, Südkampen 31, 29664 Walsrode Germany (study location: Serumwerk Memsen, Memsen 13, 27318 Hoyerhagen, Germany) between 2nd February and16th February 2005. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. One animal rejected some of the reference drug and therefore administration was repeated in this animal in a separate period. It is not clearly stated in the protocol amendment that the data from the repeated administration should be used, which would have been preferable, but since the decision to repeat the administration was taken before plasma concentration values were available and since the rejection of some of the dose was noticed already at administration, no concern is raised. Plasma concentrations of flunixin were determined with a validated

LC/MS/MS method. For AUC_{0-t} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. For C_{max} the 90% confidence interval for the ratio of the test and reference products fell outside the conventional acceptance range of 80.00-125.00% but was within the suggested widened acceptance range of 70-143%.

The widening of acceptance limits for C_{max} was prospectively defined but not justified in the protocol. A justification was requested during the application procedure. The main concern was the possible risks associated with a higher C_{max} than the reference product. Based on comparisons with concentrations following intravenous injection of flunixin, which is approved at a dose of 1.1 mg/kg in horse, it was agreed that a slightly higher C_{max} is not critical from a safety perspective. The widening of the acceptance criteria for C_{max} was considered sufficiently justified.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for flunixin, n=12.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**20097.45±5217.29**	**3837.47±1004.58**	**1.00 (0.50-3.00)**
Reference	**19192.13±4598.46**	**3405.82±895.39**	**1.00 (0.50-4.00)**
***Ratio (90% CI)**	**1.042 (0.973-1.117)**	**1.119 (0.982-1.276)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Bioequivalence between test and reference has been sufficiently demonstrated.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

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 Medical Products Agency's website (http://www.lakemedelsverket.se/english/).

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.

None

Quality changes

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change (Type; application number)	**Section updated in Module 3**	**Approval date**
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	