United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Diatrim 200 mg/ml + 40 mg/ml Solution for Injection

Date Created: April 2018

PuAR correct as of 30/08/2018 when RMS was transferred to NL.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0613/001/DC
Name, strength and pharmaceutical form	Diatrim 200 mg/ml + 40 mg/ml Solution for Injection
Applicant	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel The Netherlands
Active substance(s)	Sulfadiazine, trimethoprim
ATC Vetcode	QJ01EW10
Target species	Cattle, pigs, dogs and cats
Indication for use	Treatment of infections caused by, or associated with, organisms sensitive to the trimethoprim-sulfadiazine combination.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

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 conclusion of the decentralised procedure	22nd November 2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Croatia, Denmark, France, Germany, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Slovenia, Spain

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, Diatrim 200 mg/ml + 40 mg/ml Solution for Injection, submitted in accordance with Article 13 1) of Directive 2001/82/EC, as amended. The reference product is Duphatrim IS Injectable Solution Trimethoprim 40 mg and Sulfadiazine 200 mg Solution for Injection, marketed in the UK since June 1992. The reference product was authorised via informed consent, based on Norodine 24 Solution for Injection, marketed in the UK since June 1988. The applicant claimed exemption from the requirement for bioequivalence studies 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 2).

The product is indicated for the treatment of infections caused by, or associated with, organisms sensitive to the trimethoprim-sufldiazine combination. The dose rate in cattle and pigs is 2.5 mg trimethoprim and 12.5 mg sulfadiazine per kilogram bodyweight, equivalent to 1 ml of product per 16 kg bodyweight. The product is delivered via intramuscular or slow intravenous injection. In dogs and cats, the recommended dose rate is 5 mg trimethoprim and 25 mg sulfadiazine per kilogram bodyweight, equivalent to 1 ml of product per 8 kg bodyweight. Given by subcutaneous injection only.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions

observed are indicated in the SPC.[1] The product is safe for the user, the consumer of foodstuffs from treated animals (cattle, pigs), and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 200 mg/ml sulfadiazine, 40 mg/ml trimethoprim and the excipients sodium hydroxide, disodium edetate, sodium formaldehyde sulfoxylate, N-methylperrolidone and water for injections.

The container/closure system consists of vials of uncoloured glass type II filled with 50 ml or 100 ml with a fluoropolymer coated chlorobutyl stopper type I secured with an aluminium cap. One vial is presented in a cardboard box. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative, (the product is self-preserving), are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the weighing of raw materials, mixing of the ingredients over several steps, adjustment of pH, filtration and packing into sterilised vials.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are trimethoprim and sulfadiazine, established active substances described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

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. Acceptable Certificates of Suitability were provided.

All excipients apart from sodium formaldehyde sulfoxylate, which is monographed in the United States National Formulary, are monographed in the Ph. Eur.

The Certificates of Suitability provide details of the packaging for the active substances and finished product. Clear, type II glass vials, comply with a Ph. Eur monograph. A specification was provided for the closures.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product include those for: identity and assay of the active substances, appearance, clarity, volume, pH, density and sterility.

II.F. Stability

Stability data on the active substances 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

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 28 days.

Do not store in a refrigerator after broaching

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the legal basis of the application, no toxicological or pharmacological data were submitted. A user risk assessment and environmental risk assessment were submitted.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The same safety warnings as those currently used for the reference product were included.

Warnings and precautions as listed on the product literature, (which includes information updated from that of the reference product), are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- The product may cause an allergic reaction in people sensitised to sulfonamides.
- People with known hypersensitivity to sulfonamides should avoid contact with the veterinary medicinal product.
- The excipient N-methylpyrrolidone (NMP) is a suspected human teratogen; therefore, women of child-bearing age must be very careful to avoid exposure via spillage onto the skin or accidental self-injection when administering the product. If you are pregnant, think you may be pregnant or are attempting to conceive, you should not administer the product.
- If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.
- This product may cause skin and eye irritation.
- Avoid contact with skin or eyes.
- In case of skin or eye contact, wash exposed area with plenty of clean water. If symptoms persist, seek medical advice.
- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP[3] guidelines.

Phase I:

A Phase I exposure assessment considering both active substances was submitted. In addition to the product being indicated for dogs and cats, it is also indicated for use in cattle and pigs. Therefore, consideration of contamination of the environment by pasture and intensively reared animals was considered.

The Phase I decision tree was followed to Question 17. The initial predicted environmental concentration (PEC) for the sum of trimethoprim and sulfadiazine, in soil, exceeded the trigger value of 100 µg/kg, as follows:

Intensively-reared species

Treatment	$PEC_{soil\ initial}$ (µg/kg)		
	Trimethoprim	Sulfadiazine	SUM
Calf	35.7	178.5	214.2
Dairy cow	20.1	100.3	120.4
Cattle (0 – 1 year)	31.5	157.4	188.9
Cattle (>2 years)	36.5	182.1	218.6
Weaner pig (to 25 kg)	54.3	271.5	325.8
Fattening pig (22 – 125 kg	36.8	184.2	221.0
Sow (with litter)	13.1	65.38	78.9

Pasture-reared species

Treatment	$PEC_{soil\ initial}$ (µg/kg)		
	Trimethoprim	Sulfadiazine	SUM
Dairy cow	17.5	87.5	105.0
Beef cattle	26.2	130.6	156.8

As a result, a Phase II assessment for the relevant scenarios for pigs and cattle was provided.

Phase II Tier A:

A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines, including studies on physicochemical properties, environmental fate and effects. In accordance with the Guideline on Pharmaceutical Fixed Combination

[3] Committee for Medicinal Products for Veterinary Use

Products (EMEA/CVMP/83804/ 2005), the Phase II assessment was based on the effects of the combination of both actives.

Physicochemical properties

trimethoprim

Study type	Result
Molecular weight	290.3
Water solubility (OECD 105)	400 mg/l
Dissociation constants in water pKa (OECD 112)	7.12
UV-Visible Absorption Spectrum (OECD 101)	Absorption maxima: Aqueous acid: 271 nm Aqueous alkali: 287 nm
Melting Point (OECD 102)	199 to 203°C
Vapour Pressure (OECD 104)	1.32 x 10^{-6} Pa at 25°C
n-Octanol/Water Partition Coefficient logP_{ow} (OECD 107)	0.91 logP_{ow} <4, indicates low bioaccumulative potential

sulfadiazine

Study type	Result
Molecular weight	250.3
Water solubility (OECD 105)	77 mg/l
Dissociation constants in water pKa (OECD 112)	6.36
UV-Visible Absorption Spectrum (OECD 101)	Absorption maxima: Aqueous acid: 242 nm Aqueous alkali: 240 nm
Melting Point (OECD 102)	255.5°C
Vapour Pressure (OECD 104)	5.74 x 10^{-6} Pa at 25°C
n-Octanol/Water Partition Coefficient logK_{ow}	0.09 logK_{ow} <4, indicates low bioaccumulative potential

Environmental fate and behaviour

trimethoprim

Study type	Result
Soil adsorption (OECD 106)	K_{OC} values range between 606 and 1650
Degradation in Soil (OECD 307)	DT_{50} 20°C values range between 11 and 85 days

The lowest K_{OC} value indicates trimethoprim to have slight mobility in soil. Trimethoprim is persistent in some soils.

sulfadiazine

Study type	**Result**
Soil adsorption (OECD 106)	K_{OC} values of between 59 and 1650 l/kg
Degradation in Soil (OECD 307)	Range of DT_{50} 20°C: 0.778 to 13 days

Results indicate that sulfadiazine has medium/high mobility in soil depending on the soil tested. Sulfadiazine is not persistent in soil.

Environmental effects - trimethoprim

Study type	**Result**
Blue/green algae (OECD 201)	EC_{50} (growth rate) 72 hour: >16.7 mg/l
Daphnia magna (OECD 202)	EC_{50} 24/48 hour: 112 mg/l NOEC 24/48 hour: 55.2 mg/l
Zebra fish (OECD 203)	LC_{50} 96 hour: >104 mg/l NOEC 96 hour: ≥ 104 mg/l
Soil nitrification (OECD 216)	% effect. No significant effects
Terrestrial Plants, Growth Test/*Species* (OECD 208)	NOEC Species / NOEC (Germination / Height / Dry weight): *Cucumis sativus*: ≥100 / ≥100 / ≥100 *Lactuca sativa*: 33.33 / 1.23 / ≥100 *Vigna radiata*: ≥100 / ≥100 / ≥100 *Lycopersicon esculentum*: ≥100 / ≥100 / ≥100 *Zea mays*: ≥100 / ≥100 / ≥100 *Allium cepa*: ≥100 / ≥100 / 11.11
Earthworm reproduction (OECD 222)	NOEC: >39.1 mg/kg_{dwt}

sulfadiazine

Study type	**Result**
Blue/green algae (OECD 201)	EC_{50} growth rate: >39.06 mg/l NOEC growth rate: 2.5 mg/l
Daphnia magna acute immobilisation test (OECD 202)	48 hour EC_{50}: >100 mg/l 24/48 hour NOEC: 6.25 mg/l
Zebra fish (OECD 203)	LC_{50} 96 hour: >75 mg/l
Soil nitrification (OECD 216)	At 28 days: a significant effect on nitrogen transformation (>25% difference with control) is demonstrated at sulfadiazine levels 11.6 and 116 x the highest PECsoil (271.5 µg/kg).

Study type	Result			
Terrestrial plants growth test (OECD 208)	Species	mg sulfadiazine/kg $soil_{dwt}$		
		Emergence	Weight	Survival
		EC_{50}		LC_{50}
	Brassica napus	26.3	28.6	>32.0
	Pisum sativum	66.9	84.0	>76.8
	Helianthus annuus	>442.4	77.6	186.0
	Beta vulgaris	141.2	55.3	404.0
	Cucumis sativus	156.2	120.0	>184.3
	Zea mays	225.4	90.9	165.1
	Allium cepa	92.9	>76.8	>76.8
	Avena sativa	257.6	>76.8	>76.8
Earthworm subacute/reproduction (OECD 220/222)	NOEC: >335.92 mg/kg			

An unacceptable risk for nitrogen transformation at >28 days is indicated at Tier A.

Exposure assessment (Predicted exposure concentration)
PEC value for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated for 'weaner pigs' which is considered to be the worst case scenario.

Active Ingredient	PEC			
	Soil (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)*	Surfacewater (µg/l)**
Sulfadiazine	272	29.7	9.91	65.31
Trimethoprim	54.3	1.26	0.42	13.06

* Based on PECgroundwater/3
** Based on direct excretion by cattle using default CVMP calculation 6.2.4.2.1 (Direct excretion of active substances into surface waters by pasture animals).

An unacceptable risk to groundwater (PEC>0.1 µg/l) is indicated at Tier A.
Further refinement based on FOCUS modelling was required at Tier B.

Risk Characterisation (Risk Quotient)
Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for each target animal as follows.

Aquatic organism	Active ingredient	*PNEC* (µg/l)	*PEC* (µg/l)	Individual RQ	Combined RQ
Cyanobacteria (growth/yield inhibition)	sulfadiazine	391	65.31	0.167	0.245
	trimethoprim	167	13.06	0.078	
Invertebrates (immobilisation)	sulfadiazine	100	65.31	0.653	0.770
	trimethoprim	112	13.06	0.117	
Freshwater fish (acute toxicity test)	sulfadiazine	75	65.31	0.871	0.997
	trimethoprim	104	13.06	0.126	

For aquatic organisms, all risk quotient values are <1 at Tier A.

Terrestrial organism	Active ingredient	PEC (µg/kg)	PNEC (µg/kg)	Individual RQ	Combined RQ
Nitrogen transformation	sulfadiazine	**At 28 days: >25% difference with control. Possible long term effect; the study should be continued up to a maximum duration of 100 days.**			Not applicable
	trimethoprim	At 28 days: <25% difference with control. No long term effects expected.			
Terrestrial plants	sulfadiazine	271.5	263	**1.03**	**1.08**
	trimethoprim	54.3	1000	0.054	
Earthworms	sulfadiazine	271.5	33 592	0.008	0.022
	trimethoprim	54.3	3910	0.014	

For terrestrial organisms, nitrogen transformation is affected for an unacceptable period and a risk to plants was identified and further refinement at Tier B was required.

Tier B refinement:

Nitrogen transformation (sulfadiazine)
At 42 days, no significant effect on nitrogen transformation (<25% difference with control) is demonstrated at sulfadiazine levels 11.6 and 116 x the highest PECsoil (271.5 µg/kg).

Risk to groundwater
As the initial PEC for groundwater exceeded the 0.1 µg/l drinking water standard that has been established in the EU, it was refined using the groundwater model FOCUS PEARL. Results demonstrated that the 80th percentile annual average concentration of amoxicillin in leachate was 0.000 µg/l for all soils; confirming that appropriate use of the product will not pose a risk to drinking water.

Risk to plants
Eight terrestrial plant species were tested with sulfadiazine, which is considered a sufficient number to be able to perform a species sensitivity distribution (SSD) for this substance. In accordance with the CVMP reflection paper on higher plant testing (EMA/CVMP/ERA/147844/2011), five dicotyledonous species and three monocotyledonous species were tested. Using the SSD method, the concentration at which 95% of the species theoretically are protected (HC5) can be estimated. It is acceptable for the ETX 2.1 program to have been used for

the HC5 calculations. The calculations passed all required statistical validation tests available in the ETX program at all significance levels. The lowest $LLHC_5$ of 0.378 mg/kg, demonstrated for seedling emergence, can be applied as PNEC. With this PNEC the RQs for plants are as presented below.

Compound	PEC (µg/kg)	PNEC	RQ
sulfadiazine	271.5	378 µg/kg	0.72
trimethoprim	54.3	1000 µg/kg	0.054

The SSD assessment confirmed that there is no risk for terrestrial plants following the use of the test product as recommended.

As a result, in conclusion the product is not expected to pose a risk for the environment when used as recommended.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted due to the nature of the application. After full consideration, these were not required.

MRLs

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Trimethoprim	Trimethoprim	All food producing species except *Equidae*	50 50 50 50 50	Muscle* Fat** Liver Kidney Milk	For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for fat, liver and kidney do not apply to fin fish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which eggs are produced for human consumption
		Equidae	100 100 100 100	Muscle* Fat** Liver Kidney	

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Sulfonamides (all substances belonging to the sulphonamide group)	Parent drug	All food producing species	100 100 100 100	Muscle Fat Liver Kidney	The combined total residues of all substances within the sulphonamide group should not exceed 100 µg/kg. For fin fish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for fat, liver and kidney do not apply to fin fish. Not for use in animals from which eggs are produced for human consumption.

Excipients

Disodium edetate dihydrate (cited under 'ethylenediaminetetraacetic acid and salts'), N-methylpyrrolidone, sodium formaldehydesulfoxylate and sodium hydroxide (E524) are all included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as no MRL required. Water purified is included in the most recent 'Out of Scope' list (EMA/CVMP/519714/2009–Rev.34, April 2016).

Withdrawal Periods

Based on the data provided, the following withdrawal periods are justified.

Cattle:

Meat and offal: 12 days

Milk: 48 hours

Pig:

Meat and offal: 20 days

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Due to the legal base of the application, no pharmacodynamic data were required.

Pharmacokinetics

No pharmacokinetic data were required, as the applicant claimed exemption from providing bioequivalence studies under Section 7.1.a) of the EMA guideline EMA/CVMP/016/00-Rev.2.

Tolerance in the Target Species

Tolerance studies were not required due to the legal base of the application

Resistance

No data were required to be submitted due to the legal base of the application, however, the applicant was asked to submit a review of recent literature regarding the use of antimicrobials, in the interest of supporting the responsible use of these. The SPC and product literature carries suitable warnings.

IV.II. Clinical Documentation

The test and reference products have the same pharmaceutical form, are quantitatively and qualitatively the same in terms of the active substances, and qualitatively similar in terms of excipients. The test and reference products have been determined to have similar physico-chemical properties. In accordance with the legal base, clinical studies have not been provided.

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 of the product is not favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)