



**Veterinary  
Medicines  
Directorate**

**United Kingdom  
Veterinary Medicines Directorate  
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**NATIONAL PROCEDURE**

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY  
MEDICINAL PRODUCT**

**Censutrim 200 mg/ml + 40 mg/ml Solution for Injection for Cattle, Pigs,  
Horses, Dogs and Cats**

**Date Created: March 2025**

## **MODULE 1**

### **PRODUCT SUMMARY**

Name, strength and pharmaceutical form	Censutrim 200 mg/ml + 40 mg/ml Solution for Injection for Cattle, Pigs, Horses, Dogs and Cats, Solution for injection
Applicant	DUGV (UK) Limited, Union House, 111 Union Street, Coventry, CV1 2NT
Active substances	Sulfadiazine Trimethoprim
ATC Vet code	QJ01EW10
Target species	Cats Cattle Dogs Horses Pigs
Indication for use	The product is indicated in the treatment of systemic 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](http://www.gov.uk/check-animal-medicine-licensed)

## MODULE 3

### PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 10) as amended.
Date of conclusion of the procedure	4/03/2025 (Northern Ireland) 10/04/2025 (Great Britain)

#### I. SCIENTIFIC OVERVIEW

These are generic applications for Northern Ireland (NI) and Great Britain (GB) with the reference product being Norodine 24% Solution for Injection. This reference product has been marketed in the UK since 1/10/1988. The applicant claimed exemption from the requirement for bioequivalence studies in accordance with exemption 7.1.a) and 7.1.b) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/2000-Rev.4) which was acceptable.

Censutrim 200 mg/ml + 40 mg/ml Solution for Injection for Cattle, Pigs, Horses, Dogs and Cats contains 200 mg sulfadiazine and 40 mg trimethoprim per ml of product. The product is indicated in the treatment of systemic infections caused by or associated with organisms sensitive to the trimethoprim: sulfadiazine combination.

The dose for cattle and pigs is 12.5 mg sulfadiazine and 2.5 mg trimethoprim per kg body weight (equivalent to 1 ml of product per 16 kg body weight), administered by intramuscular or slow intravenous injection, once daily until 2 days after symptoms resolve up to a maximum of 5 days. The dose rate in horses is 12.5 mg sulfadiazine and 2.5 mg trimethoprim per kg body weight, administered via slow intravenous injection only, once daily until 2 days after symptoms resolve up to a maximum of 5 days. The dose in dogs and cats is 25 mg sulfadiazine and 5 mg trimethoprim per kg bodyweight (equivalent to 1 ml of product per 8 kg bodyweight), administered by subcutaneous injection only, once daily until 2 days after symptoms resolve up to a maximum of 5 days.

The distribution category in GB and NI is POM-V, the same as the reference product.

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, any reactions

observed are indicated in the SPC<sup>1</sup>. 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<sup>2</sup> 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 sulfadiazine and trimethoprim, and the excipients disodium edetate, chlorocresol, sodium formaldehyde sulfoxylate sodium hydroxide, N-methyl pyrrolidone and water for injections.

The container/closure system consists of 100 ml and 250 ml amber glass vials, with bromobutyl stoppers and aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are justified.

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant regulatory 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 raw material weighing, production, filtration, packaging and steam sterilisation.

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

### ***II.C. Control of Starting Materials***

The active substances are sulfadiazine and trimethoprim, both established active substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice and are in accordance with a current CEP.

The active substances specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

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<sup>1</sup> SPC – Summary of product Characteristics.

<sup>2</sup> Efficacy – The production of a desired or intended result.

The excipients disodium edetate, chlorocresol, sodium hydroxide, N-methyl pyrrolidone and water for injections fulfil the requirements established in the current edition of the European Pharmacopoeia. Sodium formaldehyde sulfoxylate fulfils the requirements established in the current edition of the United States National Formulary (USNF).

The packaging material, 100 ml and 250 ml amber glass vials, with bromobutyl stoppers and aluminium caps, is appropriate for product preservation.

#### ***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 production site have been provided demonstrating compliance with the specification. Control tests on the finished product are those appropriate for this pharmacological form.

#### ***II.F. Stability***

Stability data on the active substances have been provided in accordance with applicable regulatory guidelines, demonstrating the stability of the active substances when stored under the approved conditions.

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

The claim of a 28-day stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at  $25 \pm 2^\circ\text{C}$ .

#### ***G. Other Information***

The shelf life of the veterinary medicinal product as packaged for sale is 2 years. The shelf life after first opening the immediate packaging is 28 days. The product should not be frozen and crystallisation of the product, which can occur at low temperatures, can be reversed by gentle warming.

### **III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACOTOXICOLOGICAL)**

Due to the legal basis of the applications, no new pharmacological or toxicological studies have been submitted. Evidence is based on data regarding the reference product. A user risk assessment and environmental risk assessment were submitted. No bioequivalence studies were performed to the reference product as the applicant claimed exemption from the requirement for these studies in accordance with exemption 7.1.a) and 7.1.b) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/2000-Rev.4).

Warnings and precautions as listed on the product literature are comparable to those of the reference product. However, as the reference product was granted a marketing authorisation in 1992, the applicant updated the user safety warnings in line with other similar, more recently authorised products. The warnings and precautions are adequate to ensure safety of the product to users/the environment/consumers.

#### ***III.A Safety Documentation***

##### ***Pharmacological Studies***

Due to the legal basis of the application no new pharmacological data were submitted.

Bibliographical data shows that sulfadiazine inhibits the incorporation of para-aminobenzoic acid into folic acid and trimethoprim inhibits the enzyme dihydrofolate reductase (DHFR) which converts dihydrofolic acid into tetrahydrofolic acid. Sulfadiazine and trimethoprim act together synergistically with a double-blockade mode of action and the combination is bactericidal. The combination has a broad bactericidal action against many Gram-positive and Gram-negative aerobic bacteria and a large proportion of anaerobic bacteria.

Bibliographical data shows that both active substances are rapidly absorbed after parenteral administration and distributed throughout the body.

Sulfadiazine is protein bound only to a limited extent and is well distributed. Metabolism occurs in the liver and the major products are excreted by the kidneys. The plasma half lives in cattle, pigs and dogs are 2 - 3 and 4 hours respectively. The half-life when given to horses in combination with trimethoprim is 3 hours.

Trimethoprim is a weak base with low water solubility. Trimethoprim is about 65% protein bound but, being lipid soluble, readily penetrates cellular barriers to become widely distributed. It is partly oxidised and conjugated in the liver and the metabolites, plus unchanged trimethoprim are excreted in the urine. The degree of metabolism varies: 80% in the dog and almost 100% in the cow. The

half-life is also variable: 4 hours in the horse, 2 hours in the pig and 1 hour in the cow.

The combination of 1:5 trimethoprim:sulfadiazine is well documented for veterinary use.

### ***Toxicological Studies***

Not required due to the legal basis of the application.

### ***User Safety***

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- This product may cause an allergic reaction in people sensitised to sulfonamides and/or chlorocresol. Hypersensitivity to sulfonamides may lead to cross reactions with other antibiotics. Allergic reactions to these substances may occasionally be serious. People with known hypersensitivity to sulfonamides or chlorocresol should avoid contact with the product.
- Administer the product with caution to avoid accidental self-injection and skin contact. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- This product may cause eye and skin irritation. Avoid the contact with skin and eyes. In case of contact with skin or eyes, rinse immediately with plenty of water. If irritation persists, seek medical attention.
- If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.
- Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of foetotoxic effects. Women of childbearing age, pregnant women or women suspected of being pregnant should use the veterinary medicinal product with serious caution to avoid accidental self-injection.
- Wash hands after use.

### ***Environmental Safety***

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

#### **Phase I:**

The initial predicted environmental concentration (PEC) in soil for trimethoprim was below the trigger value for a phase II assessment. For sulfadiazine, the initial predicted environmental concentration (PEC) in soil is greater than

100 µg/kg for all intensively reared categories, except sow with litter and also above the trigger value in beef cattle raised on pasture. Therefore, a Phase II ERA was required for sulfadiazine.

### 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 physico-chemical properties, environmental fate and effects. Studies were carried out using the active substances trimethoprim and sulfadiazine, unless indicated otherwise.

#### **Physico-chemical properties**

Study type	Guideline	Result- Trimethoprim	Results- Sulfadiazine
Water solubility	OECD 105	400 mg/l	77 mg/l
Dissociation constants in water pKa	OECD 112	6.76 (m)	6.57 (m)
UV-Visible Absorption Spectrum	OECD 101	Methanolic sols.: 288 nm (max) Aqueous acid: 271 nm (max) Aqueous alkali: 288 nm (max)	Methanolic sols.: 268 nm (max) Aqueous acid: 240 – 305 nm Aqueous alkali: 240 – 254 nm
Melting Point/Melting Range	OECD 102	199 – 203°C	252 – 256°C
Vapour Pressure	OECD 104	7.52E-09 mm Hg (c)	5.26E-09 mm Hg (c)
n-Octanol/Water Partition Coefficient logP <sub>ow</sub>	OECD 107	Log K <sub>ow</sub> = 0.952 ± 0.0033 (m)	Log K <sub>ow</sub> = 0.027 ± 0.0098 (m)

#### **Environmental fate**

Study type	Guideline	Result- Trimethoprim	Result - Sulfadiazine
Soil Adsorption/Desorption	OECD 106	Range of K <sub>f</sub> Adsorption: 26.06 – 232.2 l/kg Desorption: 44.53 – 393.49 l/kg	Range of K <sub>OC</sub> Adsorption: 18.9 – 837.9 l/kg Desorption: 226.4 – 3117.2 l/kg Geometric mean K <sub>OC</sub> : 208.46 l/kg
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT <sub>50</sub> : 53.35 – 60.73 days Geometric mean: 52.9 days	DT <sub>50</sub> results varied from 1.03 to 6.19 days. Geometric mean DT <sub>50</sub> : 2.15 days

**Environmental effects**

Study type	Guideline	Endpoint	Result- Trimethoprim	Result - Sulfadiazine
Algae, Growth Inhibition Test/ <i>Species</i>	OECD 201	EC50	EC <sub>50</sub> (growth rate) 72 h: 69.49 mg/l	EC <sub>50</sub> (growth rate) 72 h: 16.60 mg/l
<i>Daphnia</i> sp. immobilisation	OECD 202	EC50	48 h EC <sub>50</sub> : 22.30 mg/l	48 h NOEC: 24.60 mg/l
Fish, acute toxicity/ <i>Brachydanio rerio</i>	OECD 203	LC50	96 h NOEC: 50 mg/l	96 h NOEC: 24.74 mg/l
Soil Microorganisms: Nitrogen Transformation Test (28 days)	OECD 216	% effect	>±25%	>±25%
Terrestrial Plants, Growth Test/ <i>Species</i>	OECD 208	EC50	Combination of trimethoprim and sulfadiazine (1:5 ratio) EC <sub>50</sub> 13.5 mg/kg EC <sub>10</sub> = 6.0 mg/kg	
Earthworm/ <i>Eisenia foetida</i> subacute/reproduction	OECD 220/222	NOEC	NOEC (reproduction) = 8.6 mg/kg soil dwt EC <sub>50</sub> (reproduction) = 40.5 mg/kg soil dwt NOEC (mortality) = 27.8 mg/kg soil dwt NOEC (biomass) ≥50.0 mg/kg soil dwt	NOEC (reproduction) = 15.5 mg/kg dry soil EC <sub>50</sub> (reproduction) ≥50.0 mg/kg dry soil NOEC (mortality) ≥50.0 mg/kg dry soil NOEC (biomass) ≥50.0 mg/kg dry soil
Dung fly larvae	OECD 228	EC50		
Dung beetle larvae	OECD draft	EC50		

**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.

Trimethoprim

Target animal	PEC
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Target animal	PEC		
	Soil (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)
Intensively reared - Weaner pig	54.3 µg/kg	0.32 µg/l	0.106 µg/l
Pasture reared - Beef cattle	26.13 µg/kg	-	13.06 µg/l

#### Sulfadiazine

Target animal	PEC		
	Soil (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)
Intensively reared - Weaner pig	271.5 µg/kg	17.88 µg/l	5.96 µg/l
Pasture reared - Beef cattle	130.63 µg/kg	-	65.31 µg/l

#### Sum of trimethoprim and sulfadiazine

Target animal	PEC		
	Soil (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)
Intensively reared - Weaner pig	325.98 µg/kg	18.2 µg/l	6.066 µg/l
Pasture reared - Beef cattle	156.76 µg/kg	-	78.37 µg/l

#### **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.

Intensively Reared Animals					
Organism	Compound	PEC	PNEC	RQ	RQ SUM
Algae	Sulfadiazine	5.96 µg/l	166 µg/l	0.036	*0.0361
	Trimethoprim	0.106 µg/l	695 µg/l	0.00015	
<i>Daphnia</i>	Sulfadiazine	5.96 µg/l	246 µg/l	0.024	*0.0287
	Trimethoprim	0.106 µg/l	22.3 µg/l	0.0047	
Fish	Sulfadiazine	5.96 µg/l	247 µg/l	0.24	*0.0242
	Trimethoprim	0.106 µg/l	500 µg/l	0.00021	
Soil nitrification	Sulfadiazine	271.5 µg/kg	N/A	Acceptable risk	Acceptable risk
	Trimethoprim	54.3 µg/kg	N/A	Acceptable risk	Acceptable risk
Terrestrial plants	Sulfadiazine and Trimethoprim	325 µg/kg	135 µg/kg	<b>2.40</b>	<b>2.40</b>
Earthworms	Sulfadiazine	271.5 µg/kg	1550 µg/kg	0.175	0.237
	Trimethoprim	54.3 µg/kg	860 µg/kg*	0.062	

Pasture Reared Animals					
Organism	Compound	PEC	PNEC	RQ	SUM
Algae	Sulfadiazine	65.31 µg/l	166 µg/l	0.393	0.4117
	Trimethoprim	13.06 µg/l	695 µg/l	0.0187	
<i>Daphnia</i>	Sulfadiazine	65.31 µg/l	246 µg/l	0.265	0.2901
	Trimethoprim	13.06 µg/l	22.3 µg/l	0.585	
Fish	Sulfadiazine	65.31 µg/l	247 µg/l	0.264	0.2901
	Trimethoprim	13.06 µg/l	500 µg/l	0.0261	
Soil nitrification	Sulfadiazine	130.63 µg/kg	N/A	Acceptable risk	Acceptable risk
	Trimethoprim	26.13 µg/kg	N/A	Acceptable risk	Acceptable risk
Terrestrial plants	Sulfadiazine and Trimethoprim	156.76	135 µg/kg	1.16	<b>1.16</b>
Earthworms	Sulfadiazine	130.63	1550 µg/kg	0.1055	0.1355
	Trimethoprim	26.13	860 µg/kg*	0.030	

As the RQ value for terrestrial plants was >1 further assessment of the environmental risk was required.

## **Tier B**

PNEC were derived by the most sensitive endpoint with the addition of an assessment factor. This was further compared to the initial Tier A PEC values which resulted in a RQ of <1. The Tier B risk characterisation indicates an acceptable level of risk for terrestrial plants.

### ***III.B.2 Residues documentation***

#### ***Residue Studies***

No residue depletion studies were conducted due to the legal basis of the application.

#### ***Withdrawal Periods***

Based on the data provided, a withdrawal period of 12 days for meat and offal in cattle, 20 days for meat and offal in pigs, 28 days for meat and offal in horses and 48 hours for milk from cattle are justified. The product is not authorised for use in horses producing milk for human consumption.

## **IV. CLINICAL DOCUMENTATION**

### ***IV.I. Pre-Clinical Studies***

As this application is for a generic product, and bioequivalence with the reference product is accepted, no new pharmacological or tolerance studies are required.

Published data suggests that bacterial resistance to trimethoprim and to sulphonamides may appear. It is mediated by the following five main mechanisms:

1. The permeability barrier and/or efflux pumps
2. Naturally insensitive target enzymes
3. Regulation changes in the target enzymes
4. Mutational or recombinational changes in the target enzymes
5. Acquired resistance by drug-resistant target enzymes

Adequate warnings and precautions appear on the product literature.

### ***IV.II. Clinical Documentation***

As this application is for a generic product and bioequivalence with the reference product is accepted, no new clinical data is 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 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](http://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](http://www.gov.uk/check-animal-medicine-licensed))