



Veterinary  
Medicines  
Directorate

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Veterinary Medicines Directorate  
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**DECENTRALISED PROCEDURE**

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

**Shotaflor 300 mg/ml Solution for Injection for Cattle  
Florfenicol**

**PuAR correct as of 17/04/2018 when RMS was transferred  
to DE. Please contact the RMS for future update**

## MODULE 1

### PRODUCT SUMMARY

EU Procedure number	UK/V/0315/002/DC
Name, strength and pharmaceutical form	Shotaflor 300 mg/ml Solution for Injection for Cattle Florfenicol
Applicant	Virbac S.A. 1ère avenue 2065 m L.I.D. 06516 Carros Cedex France
Active substance(s)	Florfenicol
ATC Vetcode	QJ01BA90
Target species	Cattle
Indication for use	Diseases caused by florfenicol susceptible bacteria. Preventive and therapeutic treatment of respiratory tract infections in cattle due to <i>Mannheimia haemolytica</i> , <i>Pasteurella multocida</i> and <i>Histophilus somni</i> . The presence of the disease in the herd should be established before preventive treatment

## **MODULE 2**

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website ([www.hma.eu](http://www.hma.eu)).

## **MODULE 3**

### **PUBLIC ASSESSMENT REPORT**

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	30 June 2010
Concerned Member States for original procedure	Austria Belgium Denmark France Germany Greece Ireland Italy Netherlands Portugal Spain

## I. SCIENTIFIC OVERVIEW

Shotaflor 300 mg/ml solution for injection for cattle (florfenicol) contains the active substance florfenicol. The product is authorised to be used in cattle for the treatment of diseases caused by florfenicol susceptible bacteria. In particular, preventive and therapeutic treatment of respiratory of respiratory tract infections in cattle due to *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. The presence of the disease in the herd should be established before preventive treatment.

This is an application for an extension to the Marketing Authorisation for Shotaflor 300 mg/ml Solution for Injection for Cattle (florfenicol) to add a new route of administration (subcutaneous), submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. Consequent to the additional subcutaneous route of administration, there is an additional indication: Preventive and therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. The presence of the disease in the herd should be established before preventive treatment.

Bioequivalence is claimed with the reference product Nuflor Injectable Solution.

The product which consists of a light yellow to yellow clear viscous liquid is delivered intramuscularly or subcutaneously for treatment and subcutaneously for prevention.

For treatment, the dosage rate is 20 mg/kg bodyweight (1 ml/15 kg), administered twice, at an interval of forty eight hours intramuscularly or 40 mg/kg (2 ml/15 kg) administered once subcutaneously. For prevention, the dosage rate is 40 mg/kg bodyweight (2 ml/15 kg) administered once subcutaneously. The product should only be given in the neck of the animal and bodyweight should be assessed as accurately as possible in order to avoid under-dosing.

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<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 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.

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<sup>1</sup> Summary of Product Characteristics

## II. QUALITY ASPECTS

Quality data were originally supplied for Shotaflor 300 mg/ml Solution for Injection for Cattle (florfenicol), and these data are included in this section. No further information for this extension application was required.

### **A. Composition**

The product contains florfenicol as an active substance and excipients dimethyl sulfoxide, propylene glycol and macrogol 400.

The container/closure system consists of amber glass (Type I) bottles of nominal capacity 50, 100 or 250 ml, closed with bromobutyl rubber stopper and aluminium seal.

The choice of the formulation is justified.

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 from a licensed manufacturing site.

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

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

The active substance florfenicol is an established active substance and supporting data have been provided in the form of a European Drug Master File (EDMF). It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

### **D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies**

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

### **E. Control on intermediate products**

There are no intermediate products.

### **F. 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.

### **G. 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 2 year shelf life.

In-use stability testing has been carried out on fresh and aged samples. This is adequate to justify a 28 day in-use shelf life.

### **H. Genetically Modified Organisms**

Not applicable

### **J. Other Information**

#### **Special precautions for storage:**

No special warnings for storage

#### **Shelf life**

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years

Shelf-life after first opening the immediate container: 28 days

### **III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)**

As this application is an extension to the Marketing Authorisation for Shotaflor 300 mg/ml Solution for Injection for Cattle (florfenicol) to add a new route of administration, submitted in accordance with Article 13 (1) of directive 2001/82/EC, and bioequivalence with the reference product has been demonstrated, results of toxicological and toxicological tests and clinical trials are not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and consumers. An appropriate environmental risk assessment was submitted.

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

As this is a generic application according to Article 13.1, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

The pharmacological aspects of this product are identical to the reference product.

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

#### ***Toxicological Studies***

As this is a generic application according to Article 13.1, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

The toxicological aspects of this product are identical to the reference product.

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

#### ***User Safety***

As bioequivalence has been demonstrated with the reference product and the two products are of the same pharmaceutical form and the active ingredients are of the same qualitative and quantitative composition, there is no requirement to submit any additional safety data.

The following operator warnings are included in the SPC and product literature:-

- Care should be taken to avoid accidental self-injection.
- In the case of accidental self injection, seek medical advice and show the label to the doctor.
- Do not use the product in known cases of sensitivity to florfenicol, propylene glycol and/or polyethylene glycols.



- In case of accidental contact with eyes, rinse immediately with plenty of water.

### **Ecotoxicity**

The applicant provided a Phase I & II environmental risk assessment in compliance with the relevant guidelines. The predicted no effect concentration (PNEC) values derived from several studies were acceptable and in accordance with VICH guidelines. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

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

Bioequivalence with the reference product was demonstrated. However, differences at the injection site could occur and thus two residue depletion studies were conducted in cattle. In the first study, Shotaflor 300 mg/ml solution for Injection for Cattle (florfenicol) was administered intramuscularly at 20 mg/kg bodyweight, twice, forty-eight hours apart, to an appropriate number of cattle. Post-mortem examination took place at various time points for a variety of tissues, including material derived from the injection site. All tissue samples had residues below the LOQ<sup>2</sup> at all time points. In the second study, Shotaflor 300 mg/ml Solution for Injection for Cattle (florfenicol) was administered subcutaneously at 40 mg/kg on a single occasion to an appropriate number of cattle. All tissue samples had residues below the LOQ and these results were acceptable.

### **MRLs**

Florfenicol is listed in Annex I of Council Regulation 2377/90. The marker substance is florfenicol-amine.

MRLs are listed below:

Muscle	200 µg/kg
Liver	3000 µg/kg
Kidney	300 µg/kg

### **Withdrawal Periods**

The withdrawal periods for meat and offal by IM<sup>3</sup> and SC<sup>4</sup> routes are thirty days and forty-four days respectively.

The product is not to be used in lactating animals producing milk for human consumption.

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<sup>2</sup> Limit of Quantification

<sup>3</sup> Intramuscular

<sup>4</sup> Subcutaneous

## IV CLINICAL ASSESSMENT (EFFICACY)

As this application is for an extension to the Marketing Authorisation for Shotaflor 300 mg/ml Solution for Injection for Cattle to add a new route of administration, submitted in accordance with Article 13 (1) of Directive 2001/82/EC, the applicant has not submitted any new pharmacodynamic, systemic tolerance, resistance or clinical efficacy data.

### **Pharmacology**

#### Pharmacodynamic:

Florfenicol is a synthetic broad spectrum antibiotic effective against most Gram-positive and Gram-negative bacteria isolated from domestic animals. Florfenicol acts by inhibiting protein synthesis at the ribosomal level and is bacteriostatic. Laboratory tests have shown that florfenicol is active against the most commonly isolated bacterial pathogens involved in bovine respiratory disease which include *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. Florfenicol is considered to be a bacteriostatic agent, but *in vitro* studies of florfenicol demonstrated bactericidal activity against *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

Acquired resistance to florfenicol is mediated by efflux pump resistance associated with a *floR* gene. Such resistance has not yet been identified in the target pathogens except for *Pasteurella multocida*. Cross resistance with chloramphenicol can occur. Resistance to florfenicol and other antimicrobials has been identified in the food-borne pathogen *Salmonella typhimurium*.

#### Pharmacokinetic:

A study was conducted to demonstrate the bioequivalence of Shotaflor 300 mg/ml Solution for Injection for Cattle (florfenicol) to the reference product, Nuflor Injectable solution 300 mg/ml. A single subcutaneous injection at a dose rate of 40 mg florfenicol/kg bodyweight was administered to an appropriate number of cattle. Blood samples were taken before administration of the products, and at a variety of time points subsequently. AUC<sup>5</sup> was used to demonstrate bioequivalence in accordance with the bioequivalence guidelines. Confidence intervals calculated from Cmax<sup>6</sup> and AUC were within the stipulated range of 80 – 125%, bioequivalence was therefore established.

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<sup>5</sup> Area under the curve

<sup>6</sup> Maximum concentration

### ***Tolerance in the Target Species of Animals***

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC, no systemic tolerance data was submitted. The applicant submitted tolerance data in cattle as part of the residue depletion study.

The first study was conducted in cows injected intramuscularly with the product as described in the SPC (administered twice 48 hours apart). The rectal temperature was measured and the injection sites were examined for signs of changes in behaviour or locomotion or appearance of the site (erythema, oedema, scaling, pigmentation). The study concluded that there were no alterations of general health with the exception of a sporadic occurrence of non-serious diarrhoea during the post treatment observation period. Diarrhoea as a prolonged adverse effect was recorded in 12.5% of animals treated with the test product. Diarrhoea due to administration lasted 1-2 days. No visible lesions or changes of tissue of the injection sites were found during gross pathology. Inflammatory infiltration, proliferation of fibroblasts and skeletal muscle necrosis were found at the site of second administration of only 2 animals. No statistical differences were found between treated groups and / or the effects of the test or reference products for the physical examination of the injection site. The effect of the administered products was evaluated as negligible irritation.

The second study was conducted in cattle injected subcutaneously with the product at 40 mg/kg bodyweight. The local reaction was measured and the injection sites were examined for signs of changes in behaviour or locomotion or appearance of the site (erythema, oedema, scaling, pigmentation). The study concluded that there were no alterations of general health with the exception of a sporadic occurrence of non-serious diarrhoea during the post treatment observation period. Diarrhoea as a prolonged adverse effect was recorded in 25% of animals treated with the test product. Diarrhoea cleared up within 3 days. No macroscopic damage to the injection site tissue was seen during necropsy. An inflammatory response was seen in all animals sacrificed after 22 days, one animal sacrificed after 35 days and in another 2 animals sacrificed 42 days after the last administration. No statistical differences were found between treated groups and / or the effects of the test or reference products for the physical examination of the injection site.

### ***IV.B Clinical Studies***

As this is an extension application and bioequivalence has been demonstrated with the reference product, there is no requirement to provide results of toxicological or pharmacological tests and clinical trials.

## **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.

## **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.

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