



MINISTERIO  
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medicamentos y  
productos sanitarios

DEPARTAMENTO DE  
MEDICAMENTOS  
VETERINARIOS

# Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8  
28022 – Madrid  
España  
(Reference Member State)

DECENTRALISED PROCEDURE

## PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

**ESPACOX 50 mg/ml oral suspension for pigs**

CORREO ELECTRÓNICO

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13594.docx

F-DMV-25-01

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## MODULE 1

### PRODUCT SUMMARY

|  |   |
|--|---|
| EU Procedure number                    | ES/V/0206/001/DC                          |
| Name, strength and pharmaceutical form | Espacox 50 mg/ml oral suspension for pigs |
| Applicant                              | Industrial Veterinaria, S.A.              |
| Active substance(s)                    | Toltrazuril                               |
| ATC Vet code                           | QP51AJ01                                  |
| Target species                         | Pigs                                      |
| Indication for use                     | See SPC                                   |



## **MODULE 2**

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (<http://www.hma.eu>).



## MODULE 3

### PUBLIC ASSESSMENT REPORT

|  |   |
|--|---|
| Legal basis of original application                                    | Decentralised application in accordance with Directive 2001/82/EC as amended by Directive 2004/28/EC): hybrid application |
| Date of completion of the original decentralised procedure             | 23/04/2014  |
| Date product first authorised in the Reference Member State (MRP only) |   |
| Concerned Member States for original procedure                         | AT, BE, BG, CY, CZ, DE, DK, EL, HU, IE, IT, FR, NL, PL, PT, RO, SK, UK  |

#### 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 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. *Composition*

The product contains toltrazuril (50 mg) and excipients (sodium docusate, simethicone emulsion, sodium propionate, sodium benzoate, bentonite, citric acid anhydrous, xanthan gum, propylene glycol and purified water).

The container/closure system are 250 ml and 1000 ml HDPE bottles with a HDPE screw cap. The particulars of the containers and controls performed are provided and conform to the regulation.

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 is toltrazuril, an established active substance. 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.

An ASMF is included.

### 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.

### 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 shelf life when stored under the approved conditions.

The claim of an in use stability of 6 months is based on the demonstration of stability for two batches.

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

Not applicable.

#### **J. Other Information**

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

This is a hybrid application according to Article 13(3) of Directive 2001/82/EC and amendments.

Since bioequivalence between the reference product and the test product cannot be demonstrated through bioavailability studies, the results of the appropriate safety and residue test are provided.

#### **III.A Safety Testing**

##### **Pharmacological Studies**

The applicant has provided bibliographical data which show toltrazuril is a triazinon derivative that acts against coccidian of the genus *Isospora*. It is acting against all intracellular development stages of coccidian of the merogony and gamogony. All stages are destroyed, thus the mode of action is coccidiocidal.

The applicant has also provided bibliographical data which show relevant pharmacokinetic properties.

##### **Toxicological Studies**

The applicant has provided bibliographical data which show a low acute toxicity of toltrazuril. It was not mutagenic and carcinogenic.

- Single Dose Toxicity  
LD<sub>50</sub> close to 2000 mg/kg bw (rats)  
LD<sub>50</sub> > 5000 mg/kg bw (mice)
- Repeated Dose Toxicity  
NOEL= 1.5 mg/kg bw/day (3-months oral toxicity study conducted in dogs)
- Reproductive Toxicity, including Teratogenicity:  
NOEL<sub>maternotoxicity</sub>= 3 mg/kg bw/day (rats)  
NOEL<sub>embriotoxicity</sub>= 10 mg/kg bw/day (rats)  
NOEL= 0.5 mg/kg bw/day (rabbits)

##### **User Safety**

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product does not pose an unacceptable risk for user.

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

##### **Ecotoxicity**



The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product does not pose an unacceptable risk for environment.

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**

#### **Residue Studies**

The applicant has conducted a residue depletion study in piglets using the final formulation.

Samples of kidney, liver, fat plus skin and muscle were taken from animals at several time points. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period.

An alternative approach of the results was used to set the withdrawal period.

The analytical method was HPLC-MS/MS. The method was fully validated.

#### **MRLs**

The active substance, Toltrazuril, is included in Table 1 of the Annex of Commission Regulation (EU) No. 37/2010 in accordance with the following table:

| <b>Active substance</b> | <b>Marker residue</b> | <b>Animal species</b> | <b>MRL</b>                                       | <b>Target tissues</b>                 |
|-------------------------|-----------------------|-----------------------|--|---------------------------------------|
| Toltrazuril             | Toltrazuril sulfone   | Porcine               | 100 µg/kg<br>150 µg/kg<br>500 µg/kg<br>250 µg/kg | Muscle<br>Skin+fat<br>Liver<br>Kidney |

#### **Withdrawal Periods**

Based on the data provided above, a withdrawal period of 73 days for meat is justified.

## **IV. CLINICAL ASSESSMENT (EFFICACY)**

As this is a hybrid application according to Article 13.(3). of Council Directive 2001/82/EC, as amended, and equivalence with a reference product has been demonstrated, the efficacy claims for this product are equivalent to those of the reference product.

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

#### **Pharmacology**

Both the Pharmacodynamic properties and the Pharmacokinetic characteristics are adequately described in the SPC, sections 5.1. and 5.2.





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

See also “IV.B: Clinical studies”.

### ***Resistance***

Adequate warnings and precautions appear on the product literature.

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

The applicant has conducted an equivalence trial, which demonstrated that the product is equivalent to the reference product. An adequate tolerance by the target species was also shown.



## 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 veterinary Heads of Agencies website ([www.hma.eu](http://www.hma.eu)).

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