IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Selectan 300 mg/ml Solution for Injection for Cattle and Swine

PRODUCT SUMMARY

EU Procedure number	IE/V/0189/001/DC
Name, strength and pharmaceutical form	SELECTAN 300 mg/ml solution for injection for cattle and swine.
Active substance(s)	Florfenicol
Applicant	LABORATORIOS HIPRA, S.A. Avda. la Selva, 135 17170 Amer (Girona) Spain
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	26th September 2007
Target species	Cattle and pigs
Indication for use	Cattle: Therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni.* Swine: Treatment of acute outbreaks of respiratory disease caused by strains of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.
ATCvet code	QJ01BA90
Concerned Member States	AT, BE, CZ, DK, FR, GR, HU, IT, LI, NL, PO, PT, SK, ES, SE,UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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; potential adverse effects are detailed 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains:

Active substance
Florfenicol 300 mg/ml

Excipients
N-methylpyrrolidone
Glycerol formal

The solution for injection is presented in 100 ml type II colourless glass bottle and 250 ml polypropylene bottle with type I polymeric elastomer stopper and aluminium overseal.
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 at 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 florfenicol which is not described in the European or British Veterinary Pharmacopoeia. 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.

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.

D. Control on intermediate products

Not applicable.

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 site have been provided demonstrating compliance with the specification.

F. 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.

G. Other Information

Not applicable

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (generic application) on the basis of essential similarity and therefore data on pharmacodynamics are not required.

It should be noted that the information in section 5.1 of the proposed SPC for Selectan is similar to that agreed for the mutually agreed SPCs for the reference products, Nuflor Injectable Solution and Nuflor Swine Injectable.

Pharmacokinetics

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (generic application), on the basis of essential similarity.
In support of this application, the Applicant conducted a single in vivo study in each of the proposed target species for the purposes of demonstrating that the test product (Selectan) and the pioneer products (Nuflor Injectable Solution and Nuflor Swine Injection) are bioequivalent. The bioequivalence studies are reviewed and commented on in Part IV of this report.
It should be noted that the information in section 5.2 of the proposed SPC for Selectan is similar to that agreed for the mutually agreed SPCs for the reference products, Nuflor Injectable Solution and Nuflor Swine Injectable.

Toxicological Studies

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (generic application), on the basis of essential similarity and therefore specific toxicological data relating to the active substance are not required.
As additional support for the present application, the Applicant has included a number of publications that relate to the toxicological properties of florfenicol. The principal source of this information was the EMEA/CVMP Maximum Residue Limit (MRL) Summary Reports for florfenicol. These data can be summarised as follows:

- Florfenicol, when administered orally was not acutely toxic to mice and rats (LD_{50} >2000 mg/kg bodyweight). After intraperitoneal administration, the LD_{50} was close to 2000 mg/kg bodyweight.

- Repeat dose studies were conducted in rats, mice and the dog. Toxic effects reported for rats included changes in haematologic parameters and atrophy of the testes. For dogs, an increase in liver weight was observed.

- Studies in laboratory animals have not provided any evidence of teratogenic or foetotoxic effects.

- Florfenicol is not considered to be genotoxic.

With respect to use during pregnancy, lactation and in breeding animals, it should be noted that the proposed SPC for Selectan includes the following safety statements:
‘Do not use in adult bulls or boars intended for breeding purposes.

Studies in laboratory animals have not produced any evidence of teratogenic or foetotoxic effects. Safety during

pregnancy and lactation has not been investigated in the target species. Use only according to the benefit/risk assessment of the responsible veterinarian.'

Other Studies

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (generic application), on the basis of essential similarity and therefore data on additional toxicological tests are not required.
To support the safety of the other substances used in this formulation, the Applicant states that all excipients are well known and are commonly used in both human and veterinary medicinal products. All excipients are included in Annex II of Council Regulation 2377/90, and as such are regarded as being safe.
The justification for the use of the excipients is satisfactory and their inclusion is acceptable.

User Safety

5.1. Inherent toxicity
The Applicant has provided details on florfenicol toxicity using information gathered from the published literature. In brief, it is noted that:

- Florfenicol, when administered orally was not acutely toxic to mice and rats (LD_{50} >2000 mg/kg bodyweight). After intraperitoneal administration, the LD_{50} was close to 2000 mg/kg bodyweight.

- Repeat dose studies were conducted in rats, mice and the dog. Toxic effects reported for rats included changes in haematologic parameters and atrophy of the testes. For dogs, an increase in liver weight was observed.

- Studies in laboratory animals have not provided any evidence of teratogenic or foetotoxic effects.

- Florfenicol is not considered to be genotoxic.

- The potential for florfenicol to cause blood dyscrasias, such as aplastic anaemia, was considered by CVMP. It was concluded that it was highly unlikely that residues resulting from veterinary use of florfenicol would cause serious blood dyscrasias in consumers.

- It has been demonstrated that florfenicol is non-irritating to rabbit skin and ocular exposure was considered essentially non-irritating.

In relation to the excipients, the Applicant states that they are well known and are commonly used in both human and veterinary medicinal products. All excipients are included in Annex II of Council Regulation 2377/90, and as such are regarded as being safe. It is noted that N-Methylpyrrolidone is classed as mildly/moderately irritating to rabbit skin and rabbit eye.

5.2. Exposure of the user
The Applicant states that because of the pharmaceutical form (ready to use solution for injection), product presentation (sealed vial) and route of administration (parenteral), there is limited potential for the user to come in contact with the product. The most likely routes of exposure for this injectable product are through skin contact or eye contact (associated with accidental spillage during administration) or accidental self-injection.
It is noted that this product will be subject to prescription control and as such the end user will typically be a veterinary surgeon or a farmer experienced in the administration of parenteral injections.
Given that this is a product for injection, it will be used for the treatment of individual animals and, consequently, the number of opportunities for a non-professional user to be exposed to the product will be limited.

5.3. Conclusion including the risk management proposals
The following user safety statements have been agreed and will appear on the SPC/Labelling:
Care should be taken to avoid accidental self-injection.
Avoid contact with eyes and skin.

If eye exposure occurs, flush eyes immediately with clean water.
If skin exposure occurs, wash the affected area with clean water.
Wash hands after use.
People with known hypersensitivity to florfenicol, propylene glycol or polyethylene glycol should avoid contact with the veterinary medicinal product.

Ecotoxicity

The Applicant provided an environmental risk assessment and concluded that the product when used in accordance with label recommendations will not pose a risk to the environment.
The wording of Section 6.6 of the SPC is the same as that agreed for the reference product and is considered appropriate. It reads: "Any unused product or waste material should be disposed of in accordance with national requirements."

III.B Residues documentation

Residue Studies

In accordance with the 'Note for Guidance: Approach towards harmonisation of withdrawal periods' (EMEA/CVMP/036/95) residue depletion studies would not normally be required for a generic product where bioequivalence has been satisfactorily demonstrated based on plasma pharmacokinetic profile. However, it is acknowledged that in the case of products administered subcutaneously or intramuscularly, differences in composition and/or manufacturing process may have significant effects on injection site depletion. Therefore, for such formulations, in addition to bioequivalence data, equivalent or faster depletion of residue from the injection site should be demonstrated. The Applicant conducted a confirmatory residue depletion study (conducted to Good Laboratory Practice (GLP)) in both target species.
The analytical method to determine florfenicol amine (FFA) in tissues uses acid hydrolysis to convert Florfenicol and its known metabolites to FFA, followed by sample clean up with ethyl acetate extraction, basification, solid-phase extraction and quantification by HPLC with mass spectrometry detection (HPLC-MS-MS).
Based on the validation data provided, it is accepted that the method is sufficiently accurate and precise for the determination of FFA in porcine and bovine tissues.

MRLs

Florfenicol is listed in Annex I of Council Regulation 2377/90.
All excipients in the product are included in Annex II of Council Regulation 2377/90.

Withdrawal Periods

Based on residue studies conducted with the final formulation, the following withdrawal periods can be accepted:
Cattle meat and offal – 30 days
Pigs meat and offal – 18 days.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

See above.

Pharmacokinetics

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (generic application), on the basis of essential similarity.
In support of this application, the Applicant conducted a single in vivo study in each of the proposed target species for the purposes of demonstrating that the test product (Selectan) and the pioneer products (Nuflor Injectable Solution and Nuflor Swine Injection) are bioequivalent. Both studies were GLP and were conducted with the final formulation. For each species, the test and reference products were administered at the recommended treatment dose (15 mg florfenicol/kg for pigs and 20 mg/kg for cattle) on a single occasion. The numbers of animals included in each study were determined based on the outcome of pilot studies. The test animals were considered representative of the target population.
Based on the data provided, it is evident that the test and reference products have a similar pharmacokinetic profile in plasma when administered by the intramuscular route to pigs and calves at the recommended treatment dose on a single occasion: the 90% confidence intervals for AUC_{0-84} fall within the limits 80-125% and the confidence interval for Cmax falls within the wider limits of 70-143%. It is argued that for Cmax the wider limits can be accepted as this parameter may exhibit a greater variation and is strongly dependant on the sampling scheme. In addition, the applicant provided data to confirm that the observed differences in pharmacokinetic profile, in particular Cmax, between products is of limited clinical relevance.
It should be noted that the information in section 5.2 of the proposed SPC for Selectan is similar to that agreed for the mutually agreed SPCs for the reference products, Nuflor Injectable Solution and Nuflor Swine Injectable. It is noted that the values for various pharmacokinetic parameters following intramuscular injection included in this section are Selectan specific values.

Tolerance in the Target Species of Animals

The Applicant provided tolerance data in both cattle and pigs. The principal effects observed following administration of the test product at the recommended treatment dose were diarrhoea in pigs and local injection site reaction in cattle. The warning/safety statements agreed for inclusion in sections 4.6 and 4.10 of the Selectan SPC reflect the text agreed for the authorised reference products.

Resistance

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (generic application) on the basis of essential similarity. Consequently, the Applicant suggests that information relating to resistance emerge can be extrapolated from the reference product.

IV.B Clinical Studies

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended on the basis of essential similarity and therefore data on clinical studies are not required. However, in support of this application, the Applicant has included a number of publications relating to use of florfenicol in field studies.
It should be noted that the proposed indications for use and posology for Selectan are identical to those detailed on the mutually recognised authorisation for the pioneer product, Nuflor Injectable Solution and Nuflor Swine Injectable.

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.

VI 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 HPRA website.

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.

Changes:
None.