ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE VETERINARY MEDICINAL PRODUCT, ANIMAL SPECIES, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDER/APPLICANT IN THE MEMBER STATES

Member State	Applicant/Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration
Austria	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
Belgium	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
Germany	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
France	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
Ireland	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
Italy	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart

Poland	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
Portugal	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
Spain	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
The Netherlands	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart
United Kingdom	Gosmore Ltd 9 Pitch and Pay Lane Sneyd Park, Bristol United Kingdom	Fenflor 300 mg/ml solution for injection for cattle	Solution for injection	300 mg/ml	Cattle	Intramuscular injection 20 mg/kg bodyweight (1 ml/15 kg) to be administered twice 48 hours apart

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

OVERALL SUMMARY OF THE SCIENTIFIC CONCLUSIONS

1. Introduction

Fenflor contains florfenicol, which is a broad-spectrum primarily bacteriostatic antibiotic with a range of activity, including many Gram-negative and Gram-positive organisms. The product is presented as a solution for injection containing 300 mg of florfenicol per ml solution for injection and it is intended for the therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*.

During the mutual recognition procedure concerns were raised that Fenflor 300 mg/ml solution for injection for cattle may present a potential serious risk to the environment. In particular, concerns were raised over the adequacy of the data provided by the Marketing Authorisation Holder on the incidence of bovine respiratory disease (BRD) within an infected herd and as a consequence objections were raised over the proposal to deviate from the default value of 50% specified in CVMP Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in Support of the VICH Guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) as the value for the proportion of infected animals for use in calculation of the Predicted Environmental Concentration in soil (PEC_{soil}). The value of the resulting PEC_{soil} determines whether or not a Phase II environmental risk assessment is required.

2. Discussion

The environmental risk assessment is carried out as a two Phase process. In the first phase the extent of environmental exposure is determined based on the intended use of the veterinary medicinal product. It is assumed that veterinary medicinal products with limited use and limited environmental exposure will have a limited impact on the environment. Phase I identifies veterinary medicinal products that require a more extensive environmental risk assessment. If appropriate, the assessment proceeds to the second phase where the fate and effects of the product are determined and a risk assessment for the relevant environmental compartment is carried out. This overall process is described in VICH Phase I and Phase II guidelines (VICH Topic GL6 (Ecotoxicity Phase I; Guideline on environmental impact assessment (EIAS) for veterinary medicinal products — Phase I (CVMP/VICH/592/98-FINAL) and VICH GL 38 (Environmental impact assessment for veterinary medicinal products - Phase II (CVMP/VICH/790/03-FINAL)).

In Phase I the calculation of the initial PEC in soil is performed when more than a “small number of animals” are treated. The proportion of animals in the herd which are treated may be available from information in the dossier such as field trial data or from the scientific literature. When such specific information is not available then the default values given in Table 2 of the CVMP guideline in support of VICH guidelines (Guideline on Environmental Impact Aassessment for Veterinary Medicinal Products in Support of the VICH Guidelines GL6 and GL38 - EMEA/CVMP/ERA/418282/2005-Rev.1 - also known as the Technical Guidance Document - TGD) should be used.

The Marketing Authorisation Holder provided data with the aim of demonstrating that the percentage of herd animals that will be treated for Bovine Respiratory Disease (BRD) is less than the default value of 50% given in the CVMP guideline mentioned above (EMEA/CVMP/ERA/418282/2005-Rev.1).

To support the argument that the environmental risk assessment could be completed at Phase I, the Marketing Authorisation Holder also provided a manure degradation study, which was performed in accordance with the criteria laid out in the above mentioned CVMP guideline.

2.1 Incidence of BRD (Bovine Respiratory Disease)

The CVMP reviewed bibliographical information on the incidence of BRD in several EU countries and on the percentage of animals that have been treated therapeutically and preventatively.

The CVMP Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in Support of the VICH Guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) indicates that the proportion of animals in the herd which is treated may be available from information in the dossier such as field trial data or from the scientific literature. When such specific information is not available the default values given in the guideline are applied.

In this instance a number of publications were provided to substantiate the proportion of animals treated for BRD within a herd. The data available on BRD incidence within herds in the EU can be summarized as follows:

- Veal calves: The Netherlands - 19.8%, Belgium - 13.3% (Catry et al, 2009[1]).
- Commercial veal unit: UK - 75% (Miller et al, 1980[2]).
- Beef calves: Spain - 31.5%, UK - 13-15% (Martin et al, 2007[3]).
- Dairy calves: Sweden - 2.2-53.3% (Svensson et al 2006[4]).
- Commercial farms (several breeds and age): France - 15.7%, Germany - 20.3%, Italy - 15.2%, Spain - 17.1% (Godinho et al, 2005[5]).
- Dairy farm calves: Italy - 28.9% (Makoshey et al, 2008[6]).

In relation to the proportion of a herd to be treated, it was noted that disease incidence and subsequent therapy are difficult to dissociate. The incidence takes into account the number of ill animals at the start of the study and all additional animals becoming ill during the observation period.

From the above data it can be concluded that incidence of BRD within herds in the EU is generally below 50%. The incidence rate observed by Martin et al, 2007 was refined to include the animals presenting clinical signs of BRD before the study, with the result that the incidence was increased to 37.7%. Considering the totality of the data the CVMP considered that this figure represents a conservative estimate of the overall BRD incidence rate within herds in the EU.

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[1] Catry .B, Duchateau L, Van de Ven J, Laevens H, Opsomer, G., Haesebrouck F, DE Kruif, A. Efficacy of metaphylactic florfenicol therapy during natural outbreaks of bovine respiratory disease. Journal-of-Veterinary-Pharmacology-and-Therapeutics. 2009; 31(5): 479-487.

[2] Miller WM, Harkness JW, Richards MS, Pritchard DG. Epidemiological studies of calf respiratory disease in a large commercial veal unit. Res Vet Sci. 1980 May;28(3):267-74.

[3] Martin G., Partida E., Villalobos P., López C., López-Guerrero C. and Blanco A. (2007) Evaluation of Mass and Selective Metaphylaxis Medication with Florfenicol at Feedlot entry as a tool against Bovine Respiratory Disease Under Commercial Conditions in Spain. Cattle Practice. 15:309-311.

[4] Svensson C., Hultgren J. and Oltenacu P. (2006) Morbidity in 3-7 month old dairy calves in south-western Sweden, and risk factors for diarrhoea and respiratory disease. Preventative Veterinary Medicine. **74**:162-179

[5] Godinho K., Wolf R., Sherington J., Rowan T., Sunderland S. and Evans N. (2005) Efficacy of tulathromycin in the treatment and prevention of natural outbreaks of bovine respiratory disease in European cattle. Veterinary Therapeutics. **6**:122-135.

[6] Makoschey B., Munoz Bielsa J., Oliviero L., Roy O., Pillet F., Dufe D., Valla G. and Cavirani S. (2008) Field Efficacy of Combination Vaccines Against Bovine Respiratory Pathogens in Calves. Acta Veterinaria Hungarica. 56:485-493.

Because Fenflor 300 mg/ml solution for injection for cattle is indicated for treatment only (i.e. it is indicated only for use in clinically ill animals not for preventative use) it was considered that, in this case, it was appropriate to use the disease incidence within the herd as the proportion of animals treated.

The CVMP concluded that adequate evidence had been provided to demonstrate that the proportion of treated animals in a herd would not be higher than 38% for therapeutic treatment of respiratory tract infections in cattle due to Mannheimia haemolytica, Pasteurella multocida and Histophilus somni and that the data justified the use of this figure of 38% as the value for the proportion of treated animals in a herd, for use in calculating the PEC_{soil}.

2.2 PEC_{soil} CALCULATION

The PEC_{soil} for each cattle type (calves, dairy cows, cattle 0-1 year, cattle over 2 years) has been calculated using 38% as the proportion of the herd treated, according to the following formula (from the CVMP Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in Support of the VICH Guidelines GL6 and GL38 - EMEA/CVMP/ERA/418282/2005-Rev.1).

$$PEC_{soil\ initial} = \left(\frac{D \times Ad \times BW \times P \times 170 \times Fh}{1500 \times 10000 \times 0.05 \times Ny \times H} \right) \times 1000$$

$PEC_{soil\ initial}$	=	Predicted Environmental Concentration in soil [$\mu g.kg^{-1}$]
D	=	Daily dose of the active ingredient [$mg.kg_{bw}^{-1}.d^{-1}$]
Ad	=	Number of days of treatment [d]
BW	=	Animal body weight [kg_{bw}] (see Table 3 of the guideline.)
P	=	Animal turnover rate per place per year [$place^{-1}.y^{-1}$] (see Table 3 of the guideline)
170	=	EU nitrogen spreading limit [$kg\ N.ha^{-1}$]
Fh	=	Fraction of herd treated [value between 0 and 1] (see Table 2 of the guideline)
1500	=	Bulk density of dry soil [$kg.m^{-3}$]
10000	=	Area of 1 hectare [$m^2\ .ha^{-1}$]
0.05	=	Depth of penetration into soil [m]
Ny	=	Nitrogen produced in one year per place [$kg.N.\ place^{-1}.y^{-1}$] (see Table 3 of the guideline)
H	=	Housing factor either 1 for animals housed throughout the year or 0.5 for animals housed for only 6 months (see Table 3 of the guideline)
1000	=	Conversion factor [1000 $\mu g.mg^{-1}$]

Calf	PEC_{soil} =	$\frac{40 \times 1 \times 140 \times 1.8 \times 170 \times 0.38}{1500 \times 10000 \times 0.05 \times 10 \times 1} \times 1000$ =	86.8 µg/kg
Cattle (0 – 1 year)	PEC_{soil} =	$\frac{40 \times 1 \times 200 \times 1 \times 170 \times 0.38}{1500 \times 10000 \times 0.05 \times 18 \times 0.5} \times 1000$ =	76.6 µg/kg
Cattle (> 2 years)	PEC_{soil} =	$\frac{40 \times 1 \times 450 \times 1 \times 170 \times 0.38}{1500 \times 10000 \times 0.05 \times 35 \times 0.5} \times 1000$=	88.6 µg/kg
Dairy cow	PEC_{soil} =	$\frac{40 \times 1 \times 425 \times 1 \times 170 \times 0.38}{1500 \times 10000 \times 0.05 \times 60 \times 0.5} \times 1000$=	48.8 µg/kg

All PEC_{soil} values calculated are below the Phase II trigger value of 100 µg/kg, with the highest PEC_{soil} (88.6 µg/kg) calculated for cattle of over 2 years of age.

2.3 Degradation of residues in manure

According to the CVMP Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in Support of the VICH Guideline GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1), complete degradation has to be demonstrated either by total mineralisation or by the presence of degradation products all representing 5% or less of the total dose.

The Marketing Authorisation Holder provided a study to demonstrate that florfenicol degrades rapidly, with a DT_{50} of 14 hours (calculated using the Arrhenius equation to extrapolate from a DT_{50} of 5 hours measured at 20°C rather than at 10°C, as recommended in the CVMP guideline). The DT_{50} was further recalculated in accordance with a biphasic model. In the first phase the DT_{50} was calculated to be 4 hours, while it was 12 hours in the second phase.

Florfenicol concentrations were below the limit of quantification (LOQ) (0.4 mg/kg) by day 2 and below the limit of detection (LOD) (0.1 mg/kg) by day 27. All other potential degradation products of florfenicol were below the LOD by day 2.

The LOQ is equal to 11% of the dose added to manure (0.4/3.6) and the LOD is equal to 2.7% (0.1/3.6) of the dose added to manure. Therefore it was concluded that all extractable degradation products would represent less than 5% of the dose by day 27. However at the end of the study (27 days), 64% of the dose formed non-extractable residues.

As a result of the following weaknesses identified with this study the results could not be accepted:

- The nature and the biological activity of bound residues is not known,
- The nature of the binding is not known,
- The possibility of release into the environment has not been investigated.

However, given that the CVMP considers that no Phase II environmental risk assessment is required for this application (because the calculated PEC_{soil} values are below the trigger value), the manure degradation study is not pivotal to the environmental risk assessment.

3. Conclusions and Recommendations

The CVMP Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in Support of the VICH Guidelines GL8 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) provides default values for the proportion of animals in a herd which is treated, for use in the calculation of PEC_{soil}. The guidance document also allows for the use of alternative values if appropriately justified. In this case a number of studies were provided to demonstrate that the proportion of treated animals in a herd would not be greater than 38% for therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.*

Using the value of 38% for the proportion of treated animals in a herd, a maximum PEC_{soil} value of 88.6 µg/kg was calculated. As this is below the Phase II trigger value of 100 µg/kg no Phase II environmental risk assessment is required.

The CVMP therefore considers that the objections raised by Germany and The Netherlands should not prevent the granting of a Marketing Authorisation. The dossier as submitted in the referral procedure is considered to fulfil the necessary requirements with regards to the environmental risk assessment (as established in Article 12(3)(j) of Directive 2001/82/EC, as amended by Directive 2004/28/EC) provided that the product is used only for therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*. The CVMP considers that the therapeutic indication as currently authorised in the Reference Member State does not make the limitations of the approved use clear as the existing wording could be interpreted as allowing use of the product for preventative and therapeutic treatment of all diseases caused by florfenicol susceptible bacteria.

The CVMP therefore recommends that the two sentences of the therapeutic indication should be combined as follows:

> "Diseases caused by florfenicol susceptible bacteria: therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica*, *Pasteurella multocida* and *Hisophilus somni*"

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, Labelling and Package Leaflet are the final versions achieved during the Coordination Group procedure with the following amendment:

Section 4.2 of the SPC and Section 4 of the Package Leaflet:

"Diseases caused by florfenicol susceptible bacteria: therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni"*.