

Annex I

List of the name, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, marketing authorisation holder in the Member States

Member State EU/EEA	Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Austria	Intervet GesmbH Siemensstrasse 107 1210 Wien Austria	RESFLOR 300/16.5 mg/mL Lösung zur Injektion für Rinder	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Belgium	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor 300, 16,5 mg/mL solution injectable pour bovines	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Bulgaria	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	РЕСФЛОР 300/16,5 мг/мл Разтвор за инжективно приложение при едри преживни животни	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Cyprus	Schering-Plough S.A. 63, Agiou Dimitriou street 17456 Alimos Greece	RESFLOR 300/16.5 mg/mL Ενέσιμο Διάλυμα για βοοειδή	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Czech Republic	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor injekční roztok pro skot	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Denmark	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor vet. injection, solution for Injection for Cattle	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous

Member State EU/EEA	Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Estonia	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor vet. injection, solution for Injection for Cattle	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Finland	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor vet. injection, solution for Injection for Cattle	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
France	Intervet MSD Santé Animale 7 Rue Olivier de Serres Angers Technopole CS 17144 49071 Beaucouzé France	RESFLOR SOLUTION INJECTABLE	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Germany	Intervet Deutschland GmbH Feldstraße 1a D-85716 Unterschleißheim Germany	RESFLOR 300/16.5 mg/mL Lösung zur Injektion für Rinder	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Greece	Intervet Hellas S.A. 63, Agiou Dimitriou street 17456 Alimos Greece	RESFLOR 300/16.5 mg/mL Ενέσιμο Διάλυμα για βοοειδή	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Hungary	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	RESFLOR INJEKCIÓS OLDAT	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous

Member State EU/EEA	Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Ireland	Intervet Ireland Ltd. Magna Drive Magna Business Park Citywest Rd. Dublin 24 Ireland	RESFLOR 300/16.5 mg/mL Solution for Injection for Cattle	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Italy	Intervet MSD Santé Animale 7 Rue Olivier de Serres Angers Technopole CS 17144 49071 Beaucouzé France	RESFLOR 300/ 16,5 mg/mL SOLUZIONE INIETTABILE per bovini	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Latvia	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor vet. injection, solution for Injection for Cattle	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Lithuania	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor vet. injection, solution for Injection for Cattle	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Luxembourg	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor 300, 16,5 mg/mL solution injectable pour bovines	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
The Netherlands	Intervet Nederland B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor 300, 16,5 mg/mL oplossing voor injectie voor runderen	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous

Member State EU/EEA	Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Norway	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor vet. injection, solution for Injection for Cattle	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Poland	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor 300/16,5 mg/mL roztwór do wstrzykiwań dla bydła	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Portugal	MSD Animal Health, Lda. Quinta da Fonte Edifício Vasco da Gama 19 2770-192 Paço de Arcos Portugal	RESFLOR 300/16,5 mg/mL Solução Injectável para Bovinos	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Romania	Intervet Romania s.r.l. Soseua de Centura no. 13A Comuna Chiajna Judet Ilfov Romania	RESFLOR 300/16.5 mg/mL solutie injectabila pentru bovine	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Slovakia	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor injekčný roztok pre hovädzí dobytok	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
Slovenia	Intervet International B.V. Wim de Koerverstraat 35 5831 AN Boxmeer The Netherlands	Resflor 300/16,5 mg/mL raztopina za injiciranje za govedo	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous

Member State EU/EEA	Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Spain	Merck Sharp & Dohme Animal Health S.L. Polígono Industrial El Montalvo I c/Zeppelin nº 6, parcela 38 37008 Carbajosa de la Sagrada – Salamanca Spain	RESFLOR SOLUCIÓN INYECTABLE	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous
United Kingdom	Intervet UK Ltd. Walton Manor, Walton Milton Keynes MK7 7AJ United Kingdom	RESFLOR 300/16.5 mg/mL Solution for Injection for Cattle	Florfenicol, flunixin	Solution for injection	300 mg/ml 16.5 mg/ml	Cattle	Subcutaneous

Annex II

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

Overall summary of the scientific evaluation of Resflor solution injectable and associated names (see annex I)

1. Introduction

Resflor solution injectable (thereafter called 'Resflor') is a solution for injection for use in cattle containing florfenicol and flunixin as active substances. It is indicated for the treatment of respiratory infections caused by *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* associated with pyrexia. A single subcutaneous injection of 40 mg florfenicol and 2.2 mg flunixin per kg body weight (bw) is recommended (2 ml/15 kg bw).

The marketing authorisation holder Intervet International BV, submitted an application for a type II variation to add *Mycoplasma bovis* as a target pathogen. The application was submitted to France as reference Member State and to Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and the United Kingdom as concerned Member States. The variation procedure (FR/V/0167/01/II/017) started on 28 January 2013.

During the variation procedure at the veterinary coordination group for mutual recognition and decentralised procedure (CMDv) a potential serious risk to animal health was identified by Denmark and Germany regarding the demonstration of efficacy in the clinical trials and the justification of the recommended treatment dose of Resflor in the treatment of respiratory infections caused by *Mycoplasma bovis*, which may be associated with an increased risk of development of antimicrobial resistance.

This issue remained unsolved and therefore a CMDv procedure under Article 13(1) of Commission Regulation (EC) No 1234/2008 has started on 6 November 2013. As the reference and concerned Member States were not able to reach an agreement in respect of the variation, on 24 January 2014, France referred the matter to the CVMP under Article 13(2) of Commission Regulation (EC) No 1234/2008.

2. Assessment of the data submitted

In order to address the concerns raised by Denmark and Germany, the marketing authorisation holder was requested to provide all available efficacy data for Resflor, together with a justification for the recommended treatment dose and the appropriateness of the study design for the pivotal challenge study performed in 2012. In addition, the marketing authorisation holder had to address the potential for the use of the product against *M. bovis* to contribute to, or increase the risk of, emergence of antimicrobial resistance.

MIC data and evolution of resistance of *M. bovis* towards florfenicol

Currently there is no standardised method to determine the minimum inhibitory concentration (MIC) of florfenicol against *M. bovis*. Nevertheless, based on the pre-clinical data provided by the marketing authorisation holder, MICs of florfenicol against *M. bovis* strains isolated in several EU Member States between 2007 and 2013 ranged between 0.5 and >64 µg/ml. The MIC₉₀ of the total population of *M. bovis* was 4 µg/ml.

M. bovis has been exposed to florfenicol at the exposure rate recommended for Resflor for nearly two decades. It cannot be concluded from the data available that the susceptibility of *M. bovis* has decreased during this period.

No particular risk of increase of *M. bovis* susceptibility to florfenicol is expected from the use of Resflor at the recommended dose. However, any use of antibiotic will lead to increase of resistance and therefore, prudent use should always be recommended.

Clinical data

The efficacy of Resflor against respiratory infection caused by *M. bovis* was demonstrated in two experimental models (performed in 2008 and 2012) and two clinical field trials (performed in 2004 and 2005).

The experimental study performed in 2008 was blinded, randomised, and compliant with good clinical practice (GCP). The tested product Resflor was compared to a negative control group (saline) to ensure the internal validity of the trial. Another positive control group treated with a florfenicol monoproduct was used, however it should be noted that this product is not approved for the treatment of respiratory infections caused by *M. bovis*. The study confirmed the superiority of Resflor to placebo (saline) for the treatment of *M. bovis*-induced bovine respiratory disease (BRD). Additionally, calves treated with Resflor had a quicker decrease in fever and demeanour score over the first 9 hours when compared to calves treated with florfenicol alone. Therefore, the trial also showed the therapeutic benefit of using a fixed combination of 40 mg florfenicol and 2.2 mg flunixin per kg bw (Resflor) compared to 40 mg florfenicol per kg bw alone.

The pivotal challenge model performed in 2012 was randomised, blinded and GCP compliant. The tested group was compared to two control groups, one negative control (saline) and a positive control. The reference product in the positive control group contains tulathromycin and is approved for the treatment and prevention of BRD associated with *M. bovis*. However, it could not be used alone in this study, as this would have given an advantage to the tested product which is a combined product of florfenicol and flunixin. Therefore, a flunixin product was co-administered with the tulathromycin product to ensure comparability of treatment groups. This is in line with the recommendations of the CVMP guideline on statistical principles (EMA/CVMP/EWP/81976/2010)¹ for avoiding bias.

The follow up of animals was sufficiently long as to observe the same clinical disease progression in the control group as in the field. The final outcome and the risk for relapse was assessed when the antimicrobial effect of Resflor has ceased. The success rate on Day 4 and Day 7 (primary endpoints) were significantly higher in the Resflor than in the saline group (Day 4: Resflor 96.9% versus saline 61.9%; Day 7: Resflor 92.2% versus saline 47.6%; $p < 0.0001$ - Fischer exact test). The non-inferiority in success rate of Resflor to tulathromycin was demonstrated on Day 4 and Day 7 since the lower boundary of the 97.5% confidence interval was less than 15%. Resflor is therefore considered superior to the saline treatment and non-inferior to the combination tulathromycin-flunixin.

The field trial study performed in 2004 was a GCP study comparing a florfenicol monoproduct (40 mg/kg) and Resflor administered as a single subcutaneous dose for the treatment of bovine respiratory disease. This study demonstrated the efficacy of Resflor in the treatment of BRD associated with major pathogens. *Mannheimia haemolytica* was the most prevalent pathogen pre-treatment (142 isolates). *Mycoplasma bovis* was next with 63 isolates followed by *Pasteurella multocida* (50 isolates). Even if the florfenicol monoproduct which was used as a comparator is not approved for *M. bovis* infections, it had been shown effective in the *M. bovis* experimental model performed in 2008. Resflor was shown to be significantly superior over florfenicol alone with higher reduction in pyrexia, lower incidence of depression, and better respiratory score at 6 hours post-treatment. No significant difference could be shown in the cumulative success rate 4 to 10 days after treatment (79.4% with florfenicol alone versus 83.5% with Resflor).

¹ CVMP guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/01/WC500120834.pdf

The marketing authorisation holder retrospectively re-analysed this study with the subset of cases that tested positive for *M. bovis* upon enrolment. Enrolled calves had been sampled on Day 0 prior to treatment by deep, protected pharyngeal swabs. The results show that the success rate in both treated groups of this subset (84%) was close to the success rate of the overall population (83.5% in the Resflor group and 79.4% in the florfenicol monoproduct group).

The multicentre trial performed in 2005 compared the efficacy of the florfenicol monoproduct to tulathromycin in naturally occurring outbreaks of BRD. As only the florfenicol-monoproduct was tested, the antimicrobial effect of florfenicol could be compared with the one of tulathromycin only. The antipyretic response to tulathromycin or florfenicol treatment was clinically similar with statistically significant differences in favour of florfenicol on Days 2 and 3. By the end of the study (Day 18), 61 of 87 cases (70.1%) were successfully treated with florfenicol compared to 68 out of 89 cases (76.4%) treated with tulathromycin. The differences in daily failure rates from Day 5 to Day 18 between the two treatment groups were not statistically significant at any of these days nor was the overall difference in cumulative failure rates from Day 5 to Day 18 (29.9% vs. 23.6%; $p = 0.3682$).

An additional statistical analysis has been carried out to demonstrate non-inferiority of florfenicol in comparison to the positive control with regards to the clinical cure rate on Day 7. Treatment failures between Day 8 and Day 18 were considered relapses. The clinical cure rate in the florfenicol group (88.5%) was compared to the tulathromycin group (82%) and significant non-inferiority on Day 7 was confirmed.

Discussion

There is little information on how pharmacokinetic and pharmacodynamic data should be applied in the treatment of *M. bovis* infections. Based on the fact that susceptibility testing for *Mycoplasma* in animals is not currently standardised (the "true" MIC₉₀ cannot be determined with certainty), that no MIC breakpoint values for *Mycoplasma* spp. have been approved by the Clinical and Laboratory Standards Institute (CLSI) and that there is no well-established pharmacokinetic/pharmacodynamic (PK/PD) relationship, no conclusion can be drawn on the predictive efficacy of this approach. There are too many uncertainties in the PK/PD analysis to justify the dose. Therefore, the justification of the recommended treatment dose of a single injection of 40 mg florfenicol and 2.2 mg flunixin per kg bw for the treatment of BRD associated with *M. bovis* is based on the clinical data. The two experimental studies and the retrospective analyses on field trials show that the dose and duration of treatment of Resflor is adequate for the treatment of BRD associated with *M. bovis*. The submitted studies are considered to be well conducted.

Based on the absence of standardised method to determine MIC, it is difficult to follow resistance evolution in the different publications. From the data currently available, no particular risk of increase of *M. bovis* susceptibility to florfenicol is expected from the use of Resflor. However, any use of antibiotic will lead to increase of resistance and therefore, prudent use should always be recommended.

3. Benefit-risk assessment

Benefit assessment

The two experimental studies and the retrospective analyses on field trials show that the recommended dose and duration of treatment of Resflor is adequate for the treatment of BRD associated with *M. bovis*.

The authorisation of florfenicol for the treatment of respiratory disease caused by *M. bovis* would avoid the use of Critically Important Antimicrobials and consequently could decrease the selection pressure

for emergence of resistant strains from the usage of other classes of antibiotics such as macrolides and fluoroquinolones.

Based on the current knowledge on *Mycoplasma* infections the use of the combination of florfenicol with flunixin will improve the clinical success rate over an antibiotic alone. Flunixin is one of the most potent anti-inflammatory substances on the market and exerts important effects on the pathophysiology of *M. bovis* pneumonia, as well as clinical parameters (quicker decrease in rectal temperature and demeanour score over the first 9 hours compared to florfenicol alone).

Risk assessment

Quality, target animal safety, user safety, environmental risk and residues were not assessed in this referral procedure.

Resistance

Based on the absence of standardised method to determine the MIC, it is difficult to follow resistance evolution of *M. bovis* toward florfenicol.

Mycoplasma bovis has been exposed to florfenicol at the exposure rate recommended for Resflor for nearly two decades. It cannot be concluded from the data available that the susceptibility of *M. bovis* has decreased during this period.

No particular risk of decrease of *M. bovis* susceptibility to florfenicol is expected from the use of Resflor. However, any use of antibiotic will lead to increase of resistance and therefore, prudent use should always be recommended.

Risk management or mitigation measures

The warnings in the product information remain appropriate. No further risk management or mitigation measures are required as a consequence of this referral procedure.

Evaluation of the benefit-risk balance

The clinical benefit of Resflor in the treatment of BRD associated with *M. bovis* has been demonstrated and no specific risk of antimicrobial resistance or any other kind have been identified with the use of this product.

Conclusion on the benefit-risk balance

The benefit-risk ratio for the addition of *M. bovis* as a fourth BRD pathogen to the indication of Resflor is considered favourable.

Grounds for the variation to the terms of the marketing authorisations

Whereas

- the CVMP considered that based on clinical results of the data package (two experimental study and two field trials), the dose and duration of treatment of Resflor in the treatment of BRD associated with *M. bovis* are appropriate;
- the CVMP considered that no specific risk of antimicrobial resistance has been identified with the use of this product at the recommended dose;

the CVMP concluded that the overall benefit-risk balance is positive and recommended the granting of the variation to the terms of the marketing authorisation for Resflor solution injectable (see annex I)

for which the valid summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in annex III.

Annex III

Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

The valid summary of product characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.