Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal product, animal species, route of administration, marketing authorisation holders in the Member States

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Austria	Bayer Austria GmbH Herbststraße 6-10 1160 Wien Austria	Baytril 25 mg/ml - Injektionslösung für Tiere	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats, rabbits, rodents (excluded: guinea pigs, hamster), exotic animals (reptiles, avian species), pigs (piglet, pigs < 30 kg bw)
Austria	Bayer Austria GmbH Herbststraße 6-10 1160 Wien Austria	Baytril 50 mg/ml - Injektionslösung für Tiere	Enrofloxacin	50 mg/ml	Solution for injection	Dogs, pigs, calves
Austria	Bayer Austria GmbH Herbststraße 6-10 1160 Wien Austria	Baytril 100 mg/ml - Injektionslösung für Rinder und Schweine	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs
Belgium	Bayer SA-NV J.E. Mommaertslaan 14 1831 Diegem (Machelen) Belgium	Baytril 2,5%	Enrofloxacin	25 mg/ml	Solution for injection	Cats, dogs
Belgium	Bayer SA-NV J.E. Mommaertslaan 14 1831 Diegem (Machelen) Belgium	Baytril Piglet	Enrofloxacin	25 mg/ml	Solution for injection	Pigs
Belgium	Bayer SA-NV J.E. Mommaertslaan 14 1831 Diegem (Machelen) Belgium	Baytril 5%	Enrofloxacin	50 mg/ml	Solution for injection	Cattle, pigs

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Belgium	Bayer SA-NV J.E. Mommaertslaan 14 1831 Diegem (Machelen) Belgium	Baytril 10%	Enrofloxacin	100 mg/ml	Solution for injection	Cattle
Belgium	Bayer SA-NV J.E. Mommaertslaan 14 1831 Diegem (Machelen) Belgium	Baytril Swine	Enrofloxacin	100 mg/ml	Solution for injection	Pigs
Bulgaria	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Байтрил 5% инжективен разтвор	Enrofloxacin	50 mg/ml	Solution for injection	Calves, pigs, dogs
Cyprus	Bayer Animal Health GmbH D-51368 Leverkusen Germany	BAYTRIL INJECTION 5%	Enrofloxacin	50 mg/ml	Solution for injection	Calves, pigs, dogs
Czech Republic	BAYER s.r.o. Siemensova 2717/4 155 00 Praha 5 Czech Republic	BAYTRIL 2,5% (w/v) injekční roztok	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats
Czech Republic	BAYER s.r.o. Siemensova 2717/4 155 00 Praha 5 Czech Republic	BAYTRIL 5% (w/v) injekční roztok	Enrofloxacin	50 mg/ml	Solution for injection	Dogs, pigs, calves

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Denmark	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril Vet.	Enrofloxacin	50 mg/ml	Solution for injection	Dogs, cats, cattle, poultry, pigs
Denmark	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril Vet.	Enrofloxacin	100 mg/ml	Solution for injection	Dogs, cats, cattle poultry, pigs
Finland	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril 5% inj.	Enrofloxacin	50 mg/ml	Solution for injection	Cats, dogs, sheep, cattle, pigs, goats
Finland	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril 10% inj.	Enrofloxacin	100 mg/ml	Solution for injection	Sheep, cattle, pigs, goats
France	Bayer Sante 220 Avenue de la Recherche 59120 Loos France	BAYTRIL 2,5 %	Enrofloxacin	25 mg/ml	Solution for injection	Pigs
France	Bayer Sante 220 Avenue de la Recherche 59120 Loos France	BAYTRIL 5 %	Enrofloxacin	50 mg/ml	Solution for injection	Cattle, pigs, dogs
France	Bayer Sante 220 Avenue de la Recherche 59120 Loos France	BAYTRIL 10%	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Germany	Bayer Vital GmbH Kaiser-Wilhelm-Allee D-51373 Leverkusen Germany	Baytril - Das Original - 2,5% Injektionslösung für Hunde, Katzen, Schweine und Kaninchen	Enrofloxacin	25 mg/ml	Solution for injection	Pig, rabbits, dogs, cats
Germany	Bayer Vital GmbH Kaiser-Wilhelm-Allee D-51373 Leverkusen Germany	Baytril - Das Original - 5% Injektionslösung	Enrofloxacin	50 mg/ml	Solution for injection	Cattle (calves), pigs, dogs
Germany	Bayer Vital GmbH Kaiser-Wilhelm-Allee D-51373 Leverkusen Germany	Baytril - Das Original - 10% Injektionslösung für Rinder und Schweine	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs
Greece	Bayer Animal Health GmbH D-51368 Leverkusen Germany	BAYTRIL 2,5% inj.sol	Enrofloxacin	25 mg/ml	Solution for injection	Dogs
Greece	Bayer Animal Health GmbH D-51368 Leverkusen Germany	BAYTRIL 5% inj.sol	Enrofloxacin	50 mg/ml	Solution for injection	Calves, cattle, pigs, dogs
Hungary	Bayer Hungária Kft. Alkotás u. 50 1123 Budapest Hungary	Baytril 2,5% injekció A.U.V.	Enrofloxacin	25 mg/ml	Solution for injection	Pigs, rabbit, dogs, cats, exotic animals (mammals, birds, reptiles)

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Hungary	Bayer Hungária Kft. Alkotás u. 50 1123 Budapest Hungary	Baytril 5% injekció A.U.V.	Enrofloxacin	50 mg/ml	Solution for injection	Cattle, pigs, dogs
Hungary	Bayer Hungária Kft. Alkotás u. 50 1123 Budapest Hungary	Baytril 10% injekció A.U.V.	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs
Iceland	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril vet	Enrofloxacin	50 mg/ml	Solution for injection	Calves, pigs, poultry, dogs, cats
Iceland	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril vet	Enrofloxacin	100 mg/ml	Solution for injection	Calves, pigs, poultry, dogs, cats
Ireland	Bayer Limited Animal Health Division The Atrium Blackthorn Road Dublin 18 Ireland	Baytril 2.5% Solution for Injection	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats, exotic animals (small mammals, reptiles and avian species)

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Ireland	Bayer Limited Animal Health Division The Atrium Blackthorn Road Dublin 18 Ireland	Baytril 5% Solution for Injection	Enrofloxacin	50 mg/ml	Solution for injection	Cattle, pigs, dogs, cats
Ireland	Bayer Limited Animal Health Division The Atrium Blackthorn Road Dublin 18 Ireland	Baytril 10% Solution for Injection	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs
Italy	Bayer S.p.A. Viale Certosa, 130 20156 Milano Italy	Baytril	Enrofloxacin	25 mg/ml and 50 mg/ml	Solution for injection	Cattle, dogs, sheep, goats, cats, rabbits, pigs
Italy	Bayer S.p.A. Viale Certosa, 130 20156 Milano Italy	Baytril 10%	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs, sheep, goats
Norway	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril vet	Enrofloxacin	25 mg/ml	Solution for injection	Pigs, cattle, dogs, cats

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Norway	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril vet	Enrofloxacin	100 mg/ml	Solution for injection	Pigs, cattle, dogs, cats
Poland	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril 2,5% inj., 25 mg/ml roztwór do wstrzykiwań dla psów i kotów	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats
Poland	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril 5% inj., enrofloksacyna 50 mg/ml, roztwór do wstrzykiwań dla bydła i świń	Enrofloxacin	50 mg/ml	Solution for injection	Cattle, pigs
Portugal	Bayer Portugal S.A. Rua Quinta do Pinheiro, 5 2794-003 Carnaxide Portugal	BAYTRIL 2,5% solução injectável	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats
Portugal	Bayer Portugal S.A. Rua Quinta do Pinheiro, 5 2794-003 Carnaxide Portugal	Baytril 5% solução injectável	Enrofloxacin	50 mg/ml	Solution for injection	Dogs, cattle, pigs
Portugal	Bayer Portugal S.A. Rua Quinta do Pinheiro, 5 2794-003 Carnaxide Portugal	Baytril 10% solução injectável	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Romania	Bayer Health Care AG D-51368 Leverkusen Germany	Baytril 5%	Enrofloxacin	50 mg/ml	solution for injection	Calves, pigs, dogs
Romania	Bayer Health Care AG D-51368 Leverkusen Germany	Baytril 10%	Enrofloxacin	100 mg/ml	solution for injection	Cattle, pigs
Slovakia	Bayer s.r.o. Litvínovská 609/3 190 21 Praha 9 Czech Republic	Baytril 2.5 %	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats
Slovakia	Bayer s.r.o. Litvínovská 609/3 190 21 Praha 9 Czech Republic	Baytril 5 %	Enrofloxacin	50 mg/ml	Solution for injection	Dogs, pigs, calves
Slovenia	Bayer d.o.o. Bravničarjeva 13 Ljubljana Slovenia	Baytril® 5 % raztopina za injiciranje	Enrofloxacin	50 mg/ml	Solution for injection	Calves, pigs, dogs
Slovenia	Bayer d.o.o. Bravničarjeva 13 Ljubljana Slovenia	Baytril® 10 % raztopina za injiciranje	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Spain	Bayer Hispania S.L. Avda Baix LLObregat, 3-5 08970, Saint Joan Despí Barcelona Spain	Baytril 2.5% solución inyectable	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats and other exotic species (rodents, rabbits, cage birds and reptiles (snakes, turtles and iguana))
Spain	Bayer Hispania S.L. Avda Baix LLObregat, 3-5 08970, Saint Joan Despí Barcelona Spain	Baytril 5% solución inyectable	Enrofloxacin	50 mg/ml	Solution for injection	Dogs, cattle, pigs
Spain	Bayer Hispania S.L. Avda Baix LLObregat, 3-5 08970, Saint Joan Despí Barcelona Spain	Baytril 10% solución inyectable	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs
Sweden	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril®vet	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, pigs, cattle, cats
Sweden	Bayer Animal Health GmbH D-51368 Leverkusen Germany	Baytril®vet	Enrofloxacin	100 mg/ml	Solution for injection	Dogs, pigs, cattle, cats
The Netherlands	Bayer BV Energieweg 1 3641 RT Mijdrecht The Netherlands	Baytril Piglet 25 mg/ml inspuitbare oplossing	Enrofloxacin	25 mg/ml	Solution for injection	Pigs

Member State EU / EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
The Netherlands	Bayer BV Energieweg 1 3641 RT Mijdrecht The Netherlands	BAYTRIL 2,5% INJEKTIEVLOEISTOF	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats
The Netherlands	Bayer BV Energieweg 1 3641 RT Mijdrecht The Netherlands	BAYTRIL 5 % INJECTIEOPLOSSING	Enrofloxacin	50 mg/ml	Solution for injection	Cattle, pigs, dogs
The Netherlands	Bayer BV Energieweg 1 3641 RT Mijdrecht The Netherlands	BAYTRIL 5% INJEKTIEVLOEISTOF	Enrofloxacin	50 mg/ml	Solution for injection	Cattle, pigs, dogs
The Netherlands	Bayer BV Energieweg 1 3641 RT Mijdrecht The Netherlands	BAYTRIL 10 % INJECTIEOPLOSSING	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs
The Netherlands	Bayer BV Energieweg 1 3641 RT Mijdrecht The Netherlands	BAYTRIL INJEKTIEVLOEISTOF 10%	Enrofloxacin	100 mg/ml	Solution for injection	Pigs, cattle

Member State EU/EEA	Marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Animal species
United Kingdom	Bayer plc Animal Health Division Bayer House Strawberry Hill Newbury, Berkshire RG14 1JA United Kingdom	Baytril 2.5% Solution for Injection	Enrofloxacin	25 mg/ml	Solution for injection	Dogs, cats and exotic animals (small mammals, reptiles and avian species)
United Kingdom	Bayer plc Animal Health Division Bayer House Strawberry Hill Newbury, Berkshire RG14 1JA United Kingdom	Baytril 5% Solution for Injection	Enrofloxacin	50 mg/ml	Solution for injection	Cattle, pigs, dogs, cats
United Kingdom	Bayer plc Animal Health Division Bayer House Strawberry Hill Newbury, Berkshire RG14 1JA United Kingdom	Baytril 10% Solution for Injection	Enrofloxacin	100 mg/ml	Solution for injection	Cattle, pigs

Annex II

Scientific conclusions and grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Overall summary of the scientific evaluation of Baytril 2.5% injectable, Baytril 5% injectable and Baytril 10% injectable and their associated names (see Annex I)

1. Introduction

Baytril 2.5% injectable, Baytril 5% injectable and Baytril 10% injectable and their associated names are solutions for injection containing enrofloxacin at 25 mg/ml, 50 mg/ml and 100 mg/ml respectively. Enrofloxacin is a synthetic chemotherapeutic agent from the class of the fluoroquinolone carboxylic-acid derivatives. It has antibacterial activity against a broad spectrum of Gram-negative and Gram-positive bacteria. Enrofloxacin is for veterinary use only.

On 26 October 2012, France sent a referral notification under Article 34(1) of Directive 2001/82/EC, as amended, to the CVMP/European Medicines Agency for Baytril 2.5% injectable, Baytril 5% injectable and Baytril 10% injectable and their associated names. France referred the issue due to divergent national decisions having been taken by the Member States (EU/EEA) resulting in discrepancies in the product information for Baytril 2.5% injectable, Baytril 5% injectable and Baytril 10% injectable and their associated names.

The main areas of disharmony in the existing product information relate to:

- Target species;
- Indications;
- Posology;
- Withdrawal periods.

2. Discussion of data available

Target species, indications and posology

Calves (50 mg/ml strength)

Cattle (100 mg/ml strength)

Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of Pasteurella multocida, Mannheimia haemolytica, Mycoplasma spp. and Histophilus somni (50 mg/ml and 100 mg/ml strengths)

- *Dosage: 5 mg/kg body weight (bw), once daily for 3 to 5 days.*

The efficacy against *M. haemolytica* and *Mycoplasma bovis* has been justified with several experimental studies in which induced infection with *M. haemolytica* and *M. bovis* was produced. However, the provided results do not allow assessing the efficacy of the products for each one of these agents individually because only data about *M. haemolytica* have been provided. The results from the pharmacokinetic/pharmacodynamic (PK/PD) analysis with *M. haemolytica* were not fully predictive of clinical efficacy. However, several experimental controlled studies were conducted employing both 2.5 and 5 mg/kg body weight (bw) parenteral doses, but more consistent data on the higher dose were presented. Confirmatory field trials showed clinical efficacy of the dose of 5 mg/kg bw/day rather than the lower dose.

Data regarding *Pasteurella* spp. are sparse. A dose-confirmation study and a field study showed clinical efficacy of the dose of 5 mg/kg bw/day against enzootic pneumonia caused by *M. haemolytica* and

P. multocida. In addition, a PK/PD analysis was conducted with this pathogen, obtaining values considered as predictive of clinical efficacy.

As regards to *Mycoplasma bovis*, this microorganism is difficult to be identified and assessed since it is often involved in mixed infections. Several controlled experimental studies were conducted with induced infection (all of them together with *M. haemolytica*). The results of these trials demonstrated good clinical evolution of animals at the tested doses, but microbiological results were not provided or they indicated an incomplete elimination of the pathogen.

Taking into account all (clinical, PK/PD and antimicrobial resistance) data, the CVMP considered that this indication can be accepted.

Regarding *Histophilus somni*, only susceptibility data originated in Canada, USA and Europe were provided, showing the high susceptibility of the bacterium to enrofloxacin. However, clinical efficacy of the recommended dose for respiratory infection has not been demonstrated. Therefore the CVMP recommended the removal of the target pathogen *Histophilus somni* from the product information.

Treatment of infections of the alimentary tract and septicaemia caused by enrofloxacin susceptible strains of Escherichia coli (50 mg/ml and 100 mg/ml strengths)

- *Dosage: 5 mg/kg bw, once daily for 3 to 5 days.*

The results from an experimental study and a field study were provided. In these studies different doses were administered (overall range 1–6 mg/kg bw/day) and the study design did not allow evaluating the efficacy of each dose individually. In the field study, calves (from 15 kg to 150 kg bw) with naturally occurring gastrointestinal infections due to *E.coli*, were treated every day with enrofloxacin either orally, by a parenteral (intramuscular, subcutaneous or intravenous) route followed by oral, or only parenteral route. Cure or improvement was observed in 85% to 90% of animals treated by enrofloxacin, the best results being obtained when parenteral administration is followed by oral administration. From the results obtained, it was not possible to confirm whether the lower dose (2.5 mg/kg bw) produced cure or improvement in the animals. Therefore only the dose of 5 mg/kg bw for 3-5 days is supported.

Regarding the 'septicaemia' indication, this was present in the experimental study only. PK/PD and antimicrobial resistance data have been taken into account to justify this indication.

Taking into account all data, the CVMP considered that both indications can be accepted.

Arthritis caused by Mycoplasma bovis (50 mg/ml and 100 mg/ml strengths)

- *Dosage: 5 mg/kg bw, once daily for 5 days*

A field study compared 2 different durations of treatments (5 mg/kg bw for 3 or 5 days), but it did not compare the efficacy against an authorised product with a recognised efficacy for this indication. The overall recovery rate was 46.7%. The highest success rate was observed in calves ≤ 2 years old (71.4%), but it decreased in older animals. Taking into account all the documentation provided, the CVMP considered that this indication can be accepted, but in the 50 mg/ml strength it should be stated as "Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis"*. In the 100 mg/ml strength, this indication should be restricted to cattle less than 2 years old.

Acute severe mastitis caused by Escherichia coli (100 mg/ml strength)

- *Dosage: 5 mg/kg bw, once daily for two consecutive days*

Regarding *E. coli*, a PK/PD study was conducted at the proposed dose. The critical PK parameters in milk were determined following intravenous administration of the 100 mg/ml strength and used to

calculate the predictive PK/PD ratios together with MIC_{90} values for *E. coli*. These data are supported by published literature. Dose determination and dose confirmation studies demonstrated the efficacy of the recommended dose. A field study showed the efficacy of the proposed dose comparing it with a reference product containing cefquinome. Non-inferiority of the test product was demonstrated.

Taking into account all data, the CVMP considered that this indication can be accepted.

Acute severe mastitis caused by Staphylococcus aureus (100 mg/ml strength)

Taking into account the available data, the CVMP concluded that the poor bacteriological results obtained *in vivo* and the results from the PK/PD analysis do not sufficiently support this indication. The CVMP recommended the removal of the indication from the product information.

Piglets (25 mg/ml strength)

Pigs (50 mg/ml and 100 mg/ml strengths)

Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of Actinobacillus pleuropneumoniae, Pasteurella multocida and Mycoplasma spp.

- *Dosage: 2.5 mg/kg bw, once daily for 3 days by intramuscular injection.*

A systematic review and meta-analysis of more than 50 studies showed a high efficacy of enrofloxacin in treating porcine respiratory disease complex although the etiological agents were no detailed. An enrofloxacin intramuscular injection at 2.5 mg/kg bw, administered once daily until the clinical signs of respiratory disease decreased, resulted in a 94.5% success rate. Additionally, the efficacy was demonstrated in several studies conducted in the USA with an arginin formulation of enrofloxacin at a 7.5 mg/kg bw dose.

Regarding *Pasteurella multocida*, no particular conclusion could be drawn from the documentation provided, in view of the lack of precise microbiological data and considering that extrapolation of data from other formulations is not justified in this case. Therefore PK/PD and resistance data were taken into account when considering the efficacy of enrofloxacin against *Pasteurella multocida*.

Similarly, for *Mycoplasma* spp. no particular conclusion could be drawn from the documentation provided, in view of the lack of precise microbiological data (not allowing to assess the efficacy of the product against each of the isolated microorganisms specifically) or the lack of complete elimination of *M. hyopneumoniae*. Therefore PK/PD and resistance data were taken into account when considering the efficacy of enrofloxacin against *Mycoplasma* spp.

In the case of *Actinobacillus pleuropneumoniae* several references were reviewed with experimental and field studies conducted in piglets and pigs. The provided data on efficacy are adequate to demonstrate efficacy against this bacteria.

Taking into account all data available (clinical, PK/PD and antimicrobial resistance data), the CVMP considered that this indication can be accepted.

Treatment of post-partum dysgalactiae syndrome (PDS), mastitis, metritis, agalactia (MMA syndrome) caused by enrofloxacin susceptible strains of Escherichia coli, Klebsiella spp. (100 mg/ml strength)

- *Dosage: 2.5 mg/kg bw, once daily for 3 days by intramuscular injection.*

Several publications and proprietary studies were reviewed. Clinical outcome was demonstrated on sows with MMA/PDS treated with enrofloxacin. The high efficacy of enrofloxacin in the MMA-syndrome therapy has been confirmed by meta-analysis and systematic review of 6 clinical and susceptibility studies on MMA/PDS and enrofloxacin from the period 1990 to 1998. In another study after five

months at the end of the study, no enrofloxacin resistant bacteria could be isolated from the treated sows.

In conclusion, this indication in sows can be accepted for the 100 mg/ml strength, but not for the 50 mg/ml strength, as the administration of the lower strength product is not practicable in heavy animals. Moreover, the excessive volume of injection needed with the 50 mg/ml strength could lead to violation of allowed residues. Thus, the indication should be removed from the product information for the 50 mg/ml strength.

Treatment of infections of the urinary tract caused by enrofloxacin susceptible strains of Escherichia coli.

- *Dosage: 2.5 mg/kg bw, once daily for 3 days by intramuscular injection.*

A multi-centric comparative field trial in sows has been provided. The efficacy at the dosage of 2.5 mg/kg bw daily for 3 days was compared to the one of a trimetroprim-sulfamid fixed combination (30 mg/kg bw daily for 3 days). The bacteriological success was the first criteria of efficacy. The success rate was 76% on day 3 and 50% on day 10 in the test group *versus* 14.3% and 9.5%, respectively, for the same days, for the reference product. On the basis of the available data the CVMP considered that this indication can be accepted.

Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of Escherichia coli.

- *Dosage: 5 mg/kg bw, once daily for 3 days by intramuscular injection.*

The results of different well controlled studies with natural enteric infection were reviewed. The results of different field studies in piglets with enteritis were summarised. All animals were treated intramuscularly with enrofloxacin at 2.5 mg/kg bw once daily. The clinical response rate was 92%. Results of a dose-titration study with experimentally induced infection with enterotoxigenic *E. coli* in suckling piglets and weaners were also reported.

A second dose-titration trial was conducted in Japan with natural infection caused by *E. coli* in suckling piglets. Three different doses of enrofloxacin were administered: 1.25, 2.5 or 5 mg/kg bw/day for 3 days. A positive control group treated with oxytetracyclin and an untreated group were included. Enrofloxacin showed better clinical results than oxytetracyclin at all dose levels, with a more rapid decrease of total clinical scores and faecal consistency scores. Intestinal bacterial counts were significantly reduced by treatment with 2.5 mg/kg bw/day.

A field study was conducted to evaluate effect of enrofloxacin against pathogens related to the alimentary tract in suckling and weaning piglets with diarrhoea. The presence of bacteria including *E. coli* was determined. Enrofloxacin was administered at 2.5 and 5 mg/kg bw/day intramuscularly for 3 days and by oral route. An untreated group was included. Injectable enrofloxacin decreased diarrhoea incidence up to 70% in suckling piglets. Lower isolation index of *E. coli* in treated animals was observed.

In another study piglets were challenged with *E. coli* and displayed signs of diarrhoea and enterotoxaemia. The animals were split into four groups. A dose of 2.5 mg/kg bw/day intramuscularly for 1 or 3 days was tested comparing with oral administration. The results showed that all groups of medicated piglets increased in weight thus contrasting the control animals that were not treated with enrofloxacin. Treatment with enrofloxacin significantly reduced the incidence and severity of diarrhoea. Intramuscular administration of enrofloxacin showed to be effective especially in cases of enterotoxaemia. No mortality was observed in the treatment groups.

However, taking into account the available PK/PD and resistance data it has been concluded that the dose for this indication can be accepted only at 5 mg of enrofloxacin per kg bw once daily for 3 days by intramuscular injection.

Treatment of septicaemia caused by enrofloxacin susceptible strains of E. coli.

- *Dosage: 5 mg/kg bw, once daily for 3 days by intramuscular injection.*

The available data does fully demonstrate the efficacy of this veterinary medicinal product for the treatment of septicaemia. Nevertheless, taking into account the available PK/PD and resistance data it has been concluded that the dose for this indication can be accepted only at 5 mg of enrofloxacin per kg bw once daily for 3 days by intramuscular injection.

Sheep and Goats (50 mg/ml and 100 mg/ml strengths)

Both strengths share the same indications, but differences exist in terms of target animal species i.e. in the 50 mg/ml strength the species were stated as dairy ewes/lambs and dairy goats/kids whereas in the 100 mg/ml strength the species were sheep and goats. The documentation provided was exactly the same, and both strengths (50 mg/ml and 100 mg/ml) have the same withdrawal periods. Thus, it was considered that for consistency the target animal species for both strengths should harmonised to “Sheep” and “Goats”. These terms will apply to all age ranges and physiological status, as well as for both meat and/or milk production animals.

Sheep (50 mg/ml and 100 mg/ml strengths)

Treatment of mastitis caused by enrofloxacin susceptible strains of Staphylococcus aureus, Escherichia coli.

- *Dosage: 5 mg/kg bw, once daily for 3 days by subcutaneous administration.*

The efficacy of enrofloxacin for the treatment of acute mastitis was investigated in a field trial in sheep with clinical signs of acute mastitis. In the milk samples the pathogens *Staph. aureus* and *E. coli* were identified. Two different enrofloxacin treatment schemes were investigated: 5 mg/kg bw for 3 days and 2.5 mg/kg for 5 days. All treated animals showed a rapid improvement in mammary gland functions, and no clinical differences were found between the two treatment schedules. Clinical and bacteriological cure were obtained.

In another study the efficacy against *Staph. aureus* in commercial dairy herds was investigated. Two different doses were examined: 2.5 mg/kg bw and 5 mg/kg bw, twice daily for 3 consecutive days. The clinical parameters improved. The percentage of bacteriological cure (*Staph. aureus*) was 39.5% in the 2.5 mg/kg group and 82% in the 5 mg/kg group.

On the basis of the available data the CVMP considered that this indication can be accepted.

Treatment of Escherichia coli infections of the alimentary tract or septicaemia caused by enrofloxacin susceptible strains of Escherichia coli.

- *Dosage: 5 mg/kg bw, once daily for 3 days by subcutaneous administration.*

Two field studies were provided to demonstrate the efficacy of enrofloxacin in the treatment of infections of the alimentary tract caused by *E.coli* and septicaemia caused by *E.coli*.

In the first study two groups of lambs suffering from coli-enteritis were treated intramuscularly with enrofloxacin, at the dosage of 2.5 mg/kg bw for 5 days or 5 mg/kg bw for 4 days. Most of the animals recovered within 2-3 days.

In the second study, lambs with septicaemia caused by *E. coli* and *Cl. perfringens* were treated intramuscularly at the dosage of 5 mg/kg bw for 5 days. Better clinical results were observed in 3-4 weeks old animals compared to 1-2 weeks old animals.

On the basis of the available data the CVMP considered that these indications can be accepted.

Goats (50 mg/ml and 100 mg/ml strengths)

The CVMP position paper regarding availability of products for minor uses and minor species (EMEA/CVMP/477/03)[1] establishes that cattle (dairy and meat animals) and sheep (meat animals) are considered as major food-producing species. Sheep intended for milk production and goats do not fall into the category of major species, are by default are classified as minor species and, thus, assessed in the context of the CVMP guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/EWP/117899/2004)[2].

Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of Pasteurella multocida and *Mannheimia haemolytica.*

Treatment of mastitis caused by enrofloxacin susceptible strains of Staphylococcus aureus and *Escherichia coli.*

Treatment of Escherichia coli infections of the alimentary tract or septicaemia caused by enrofloxacin susceptible strains of Escherichia coli.

- *Dosage: 5 mg/kg bw, once daily for 3 days by subcutaneous administration.*

In a study the pharmacokinetics of enrofloxacin were compared in Desert sheep and Nubian goats after intravenous and intramuscular administration at 5 mg/kg bw dose. The study results indicate that the pharmacokinetics of enrofloxacin did not differ significantly between sheep and goats.

No field studies were submitted to support the indications in goats. The respiratory indications were extrapolated from the ones existing in cattle. The remaining indications i.e. mastitis, alimentary tract infections and septicaemia were extrapolated from sheep. These extrapolations were considered acceptable as goats are considered as minor species.

Data on the MIC of different isolates of *M.haemolytica* confirms the high susceptibility of this pathogen to enrofloxacin, as well as a very low resistance rate.

Although limited data were available the percentage of resistance of *Staph. aureus* isolated from goat mastitis was also very low.

The 2012 RESAPATH annual report indicated that more than 90% of *Pasteurella* in goats are sensitive to enrofloxacin.

In view of above the CVMP considered that these indications can be accepted.

Dogs and Cats (25 mg/ml and 50 mg/ml strengths)

Dogs: *Treatment of infections of the alimentary, respiratory and urogenital tracts (including prostatitis, adjunctive antibiotic therapy for pyometra), skin and wound infections, otitis caused by susceptible strains of: Staphylococcus spp., Escherichia coli, Pasteurella spp., Klebsiella spp., Bordetella spp., Pseudomonas spp., Proteus spp.*

[1] CVMP position paper regarding availability of products for minor uses and minor species (EMEA/CVMP/477/03) - http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2009/10/WC500005163.pdf

[2] CVMP guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/EWP/117899/2004) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004678.pdf

Cats: *Treatment of infections of the alimentary, respiratory and urogenital tracts (as adjunctive antibiotic therapy for pyometra), skin and wound infections, caused by susceptible strains of: Staphylococcus spp., Escherichia coli, Pasteurella spp., Klebsiella spp., Bordetella spp., Pseudomonas spp., Proteus spp.*

- *Dosage: 5 mg/kg bw, once daily by subcutaneous injection for up to 5 days.*

Several proprietary studies and numerous scientific publications, documenting the efficacy of enrofloxacin, either by injectable and/or oral route of administration, were provided to demonstrate the efficacy against the above specified bacteria for the intended indications in both dogs and cats

The data provided consist of studies performed with several posology regimens where the more frequent dose of 5 mg/kg bw was used. In other cases, a combination of parenteral and oral administration or the parenteral route alone was used. However, the analysis of the results did not allow differentiating the efficacy data and attribute to a particular posology regimen. In support of the efficacy data, published literature was provided, but, generally, lacking specific data and employing variable posology regimens. Therefore for the justification of the posology, a PK/PD were taken into account. The PK/PD analysis shows that the PK/PD ratios are largely exceeded for Gram-negative pathogens. The C_{max}/MIC and AUC/MIC ratios for *Staphylococcus* spp. are also appropriate for Gram-positive infection in both species as well.

Therefore the CVMP considered that these indications can be accepted for dogs and cats, when taking into account that the PK/PD data shown are theoretically predictive of good clinical efficacy in the treatment of the bacterial infections for which the products are intended, and the efficacy of the products has been confirmed by field studies and good clinical experience since more than two decades.

Rabbits (25 mg/ml strength)

Treatment of infections of the alimentary and respiratory tracts caused by enrofloxacin susceptible strains of: Escherichia coli, Pasteurella multocida and Staphylococcus spp.

Treatment of skin and wound infections caused by enrofloxacin susceptible strains of: Staphylococcus aureus.

- Dosage: 10 mg/kg bw, once daily for 5 to 10 consecutive days by subcutaneous administration.

Rabbits are classified as minor species and thus the available data is assessed in the context of the CVMP guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/EWP/117899/2004).

The available data showed that enrofloxacin is one of the most commonly used antimicrobials in lagomorphs to manage many different bacterial diseases because of its efficacy and safety.

Documentation that describes the uses of the injectable veterinary medicinal product in the treatment of infections of both the alimentary and respiratory tract, as well as for the treatment of skin and wound infections was provided. All available clinical data referred to pet rabbits only.

Enrofloxacin is also authorised for administration by oral route in farm rabbits all over Europe, and therefore CVMP considered that the use of an injectable solution could lead to a lesser exposure than the oral route as it can be individually administered to sick animals (with more precise dosage based on individual weights of animals) and can prevent the use in mass treatment.

Thus, the indications in farm rabbits should be considered as an extrapolation from other data (oral route for farm rabbits and/or pet rabbits with the injectable route).

The documentation provided was considered acceptable to support the efficacy of enrofloxacin against infections of the alimentary and respiratory tracts *caused by Escherichia coli, Pasteurella multocida* and *Staphylococcus* spp.

Regarding the indication for treatment of skin and wound infections caused by *Staphylococcus aureus*, the available data were suggestive of a non-complete bacteriological cure, and no PK/PD data were available.

The Committee is aware that (i) the use of enrofloxacin in rabbit production could lead to an increase in *Staph. aureus* resistance, (ii) isolates of *Staph. aureus* multi-resistant to several types of antimicrobials are currently documented and (iii) that there can be a transfer of resistant bacteria from animals to humans, involving both consumers and handlers of rabbits.

The following information addressing the concern of the risk to public health (consumers and handlers) due to the potential for selection of antibiotic resistant strains of *Staph. aureus* following use of the product in food rabbits was considered:

- In a study 4.2% of 71 isolates of *Staph. aureus* collected between 2006-2007 in Germany were resistant to enrofloxacin.
- In another study 56 *Staph. aureus* strains were isolated from commercial rabbit farms in different Member States and tested for resistance. The authors concluded that resistance to antimicrobial agents in *Staph. aureus* isolates originating from rabbits is relatively rare compared to resistance in *Staph. aureus* isolates originating from other animals and humans.
- In another referral for an enrofloxacin oral solution (Hipralona Enro-S (EMEA/V/A/79))[3] the Committee concluded that the risk is likely to be minor, in rabbits, in comparison with the other species due to the size of rabbit's production and no measures have been deemed necessary to minimize the risk for spread of *methicillin resistant Staphylococcus aureus* (MRSA) from those. The risk on individual level might be increased for rabbit as compared to other species. Rabbits are raised in continuous systems where resistant bacteria might be persistent over time, however the overall risk would remain low due to the low consumption of rabbit meat.
- A study, conducted in intensive rabbit farms in Spain, has demonstrated a high prevalence of *Staph. aureus* strains, 17.2% of which were found to be methicillin-resistant[4]. The study also unveiled very high resistance to quinolones (around 38% for ciprofloxacin).
- A study described the first case of livestock-associated methicillin-resistant *Staph. aureus* LA-MRSA (ST398, spa types t034 and t5210) occurring in rabbits raised intensively for meat production and involving farm workers or their family members[5].

As stated in CVMP reflection paper on the use of fluoroquinolones in food producing animals - Precautions for use in the SPC regarding prudent use guidance[6], fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/referrals/Hipralona_Enro-S/vet_referral_000067.jsp&mid=WC0b01ac05805c5170
[4] Ortega et al. Characterisation and public health risks of antimicrobial resistance in *Staphylococcus aureus* in intensive rabbit breeding. Rev Sci Tech Off Int Epiz 2009;28:1119-1128
[5] Agnoletti et al. First reporting of methicillin-resistant *Staphylococcus aureus* (MRSA) ST398 in an industrial rabbit holding and in farm-related people. Vet Microbiol 2014;170:172-177
[6] CVMP reflection paper on the use of fluoroquinolones in food producing animals - Precautions for use in the SPC regarding prudent use guidance (EMEA/CVMP/416168/2006) - http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500005173.pdf

For some serious animal indications, fluoroquinolones could be the only alternative available (EMEA/CVMP/SAGAM/184651/2005)[7]. In the case of dermatitis caused by *Staph. aureus* in rabbits, no other veterinary medicinal products are authorised for this indication in this animal species in the EU.

Although the scientific justification for this indication is not as robust as desirable, a clinical cure (response to treatment) of 87.5% was obtained in infections involving *Staph. aureus*, together with a bacteriological cure of 66.67%.

In view of the lack of therapeutic alternatives, if this indication was not accepted, this product as well as many other antimicrobial products, could be used off-label (under the so-called cascade). Off-label use, leaves the decision on the posology of use to the veterinary practitioner and bears a potential risk of misuse, thus it could increase the risk for developing antimicrobial resistance. Furthermore, the veterinary practitioner will be left without an authorised product for the treatment of skin and wound infections caused by *Staph. aureus* in rabbits. This might potentially lead to problems of animal welfare. It is expected that the use of these products for this indication may not be high, as the product is to be administered parenterally to rabbits with a frequency of daily injection for a period of 5 to 10 days.

In conclusion the Committee can accept this indication considering that it is an injectable formulation, and that necessary restrictions provided in the SPC, together with the withdrawal period, would be in favour of a more adequate use of the veterinary medicinal product in rabbits compared to the use under the cascade.

Rodents, reptiles and ornamental birds (25 mg/ml strength)

Treatment of infections of the alimentary and respiratory tracts where clinical experience, if possible supported by sensitive testing of the causal organism, indicates enrofloxacin as the substance of choice.

- *Dosage for rodents: 10 mg/kg bw, once daily by subcutaneous injection for 5–10 consecutive days*
- *Dosage for reptiles: 5-10 mg/kg bw, once daily by intramuscular injection for 5 consecutive days.*
- *Dosage for ornamental birds: 20 mg/kg bw, once daily by intramuscular injection for 5-10 consecutive days.*

Supporting literature for use of enrofloxacin was provided in rodents (e.g. hamsters, gerbils, guinea pigs), in reptiles (snakes, lizards and chelonia) and in ornamental birds.

The CVMP considered the target species and associated indications and dosages can be accepted because all species are considered as minor species, and no concern on safety or on efficacy has been reported in the Member States where these target species are authorised.

Contraindications

This section takes into account a possible hypersensitivity to fluoroquinolones or to any excipients of the product.

As enrofloxacin is known to cause CNS stimulation, the contraindications in epileptic animals or in animals that suffer from seizures are justified.

[7] CVMP public statement on the use of (fluoro)quinolones in food-producing animals in the European Union: development of resistance and impact on human and animal health (2007) (EMEA/CVMP/SAGAM/184651/2005) - http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/10/WC500005152.pdf

Because of known effects of quinolones on articular joints in growing dogs, the contraindication in such animals is justified.

Because the safety and the efficiency of the product have not been assessed in cats less than 8 weeks, the contraindication in such animals is justified.

Enrofloxacin is reported to have deleterious effect on articular cartilage in growing horses. Although horses are not authorised as target species the Committee considered that a contraindication for use in growing horses should be included in the product information for the 50 mg/ml and 100 mg/ml strengths.

Special warnings and precautions

The warning regarding possible degenerative changes of articular cartilage in calves is supported by a study in which calves (2 weeks old) were orally administered with 0, 30 or 90 mg/kg bw of enrofloxacin per day for 14 days. Primary degenerative lesions were noted in stifle joints of all calves that were treated with 90 mg/kg bw and in one calf that was treated with 30 mg/kg bw.

The use of enrofloxacin in growing lambs at the recommended dose for 15 days caused histological changes in the articular cartilage, not associated to clinical signs.

The specific properties of enrofloxacin regarding both its use in animals with renal disorders and retinal toxicity in cats are also stated.

Warning sentences are sufficient to ensure the safe use of the product by the person who administers the product.

Detrimental effects on developing eggs of avian scavengers were reported when these birds ingest livestock meat from animals previously administered with fluoroquinolone. Then in countries where feeding of fallen stock to scavenger bird populations is permitted as a conservation measure special warnings have to be keep in order to reduce the risk for these birds.

Adverse reactions

Digestive tract disorders (e.g. diarrhoea) may occur in very rare cases. These signs are generally mild and transient.

Mild and transient digestive tract disorders are common with many antibiotics, including fluoroquinolones.

The local tolerance was followed during tolerance and/or clinical studies in pigs, calves and dogs.

Interaction with other medicinal products

The section on interactions takes into account for all relevant interactions between enrofloxacin and other substances.

Use in pregnancy and lactation

Depending on species, the safety of the veterinary medicinal product has been established through specific studies in pregnant and/or lactating animals (cows, sows).

In other species, the safety of the veterinary medicinal product has not been established during pregnancy and lactation. The use should be done only accordingly to the benefit-risk assessment by the responsible veterinarian.

Overdose

In cases of accidental overdoses digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

Cats have been shown to suffer ocular damage after receiving doses of more than 15 mg/kg bw once daily for 21 consecutive days. Doses of 30 mg/kg bw given once daily for 21 consecutive days have been shown to cause irreversible ocular damage. At 50 mg/kg bw given once daily for 21 consecutive days, blindness can occur. In dogs, cattle, sheep and goats, overdose has not been documented.

In accidental overdose there is no antidote and treatment should be symptomatic.

Withdrawal periods

Cattle meat and offal (50 mg/ml and 100 mg/ml strengths)

Residue depletion data were made available and supported a cattle meat and offal withdrawal period of 5 days following an intravenous injection at the recommended dose of 5 mg/kg bw.

Residue depletion data were made available and supported a cattle meat and offal withdrawal period of 10 days following a subcutaneous injection at the recommended dose of 5 mg/kg bw.

Cattle milk (100 mg/ml strength)

Residue depletion data were made available and supported a cattle milk withdrawal period of 3 days following an intravenous injection at the recommended dose of 5 mg/kg bw.

Residue depletion data were made available and supported a cattle milk withdrawal period of 4 days following a subcutaneous injection at the recommended dose of 5 mg/kg bw.

Sheep meat and offal (50 mg/ml and 100 mg/ml strengths)

Residue depletion data were made available and supported a sheep meat and offal withdrawal period of 4 days following a subcutaneous injection at the recommended dose of 5 mg/kg bw.

Sheep milk (50 mg/ml and 100 mg/ml strengths)

Residue depletion data were made available and supported a sheep milk withdrawal period of 3 days following a subcutaneous injection at the recommended dose of 5 mg/kg bw.

Goat meat and offal (50 mg/ml and 100 mg/ml strengths)

No residue depletion data were made available. Based on the available data in sheep and with the addition of an uncertainty factor of 1.5 a goat meat and offal withdrawal period of 6 days is supported following a subcutaneous injection at the recommended dose of 5 mg/kg bw.

Goat milk (50 mg/ml and 100 mg/ml strengths)

No residue depletion data were made available. A withdrawal period of 4 days following a subcutaneous injection at the recommended dose of 5 mg/kg bw is recommended based on extrapolation of the withdrawal period established for cattle milk.

Pigs (25 mg/ml, 50 mg/ml and 100 mg/ml strengths)

Residue depletion data were made available and supported a pig meat and offal withdrawal period of 13 days following an intramuscular administration at the recommended dose of 5 mg/kg bw.

Rabbits (25 mg/ml strength)

Residue depletion data were made available and supported a rabbit meat and offal withdrawal period of 6 days following a subcutaneous injection at the recommended dose of 10 mg/kg bw.

3. Benefit-risk assessment

The data provided are insufficient to justify two indications in cattle (i) 'treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Histophilus somni*' and (ii) 'treatment of acute severe mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus'.* Further to the concerns expressed by the CVMP regarding the aforementioned two indications CVMP recommended the removal of these from the product information.

During this referral and considering the scope of the procedure, adequate data have been submitted to support the following posology (depending on the indications):

Sheep and goats: 5 mg of enrofloxacin/kg bw once daily by subcutaneous injection for 3 days.

Dogs and cats: 5 mg of enrofloxacin/kg bw once daily by subcutaneous injection for up to 5 days.

Rabbits and rodents: 10 mg of enrofloxacin/kg bw once daily by subcutaneous injection for 5-10 days.

Reptiles: 5-10 mg of enrofloxacin/kg bw once daily by intramuscular injection for 5 days.

Ornamental birds: 20 mg of enrofloxacin/kg bw once daily by intramuscular injection for 5-10 days.

Concerning target species cattle and pigs a risk has been identified regarding an insufficient dose rate against target pathogens in cattle and pigs. The overall evaluation of the submitted data (clinical, PK/PD and resistance data) show that the dose of 2.5 mg/kg bw/day may not allow for a complete elimination of bacteria and it could lead to an increased resistance development.

Therefore in order to optimise the dosage and to avoid development of resistance it has been concluded, that the dose rate of 2.5 mg/kg bw/day should be deleted for all the indications in cattle. The latter also applies for alimentary tract infections and septicaemia caused by *E. coli* in pigs.

Further to the assessment of the available data withdrawal periods were established and several contraindications and warning sentences are recommended to ensure the safe use of the products.

The overall benefit-risk balance of the products was deemed positive subject to the recommended changes in the product information (see Annex III).

Grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Whereas:

- the CVMP considered the scope of the referral was the harmonisation of the summaries of product characteristics, labelling and package leaflets;
- the CVMP reviewed the summaries of product characteristics, labelling and package leaflets proposed by the marketing authorisation holders and considered all the overall submitted data;

the CVMP has recommended variations of the marketing authorisations for Baytril 2.5% injectable, Baytril 5% injectable and Baytril 10% injectable and their associated names as referred in Annex I for which the summaries of the product characteristics, labelling and package leaflets are set out in Annex III.

Annex III

Summaries of product characteristics, labelling and package leaflets

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 25 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains:
Active substance:
Enrofloxacin 25 mg

Excipient:
n-Butyl alcohol 30 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear light-yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs, cats, pigs (piglets), rabbits, rodents, reptiles and ornamental birds.

4.2 Indications for use, specifying the target species

Dogs
Treatment of infections of the alimentary, respiratory and urogenital tracts (including prostatitis, adjunctive antibiotic therapy for pyometra), skin and wound infections, otitis (externa/media) caused by enrofloxacin susceptible strains of: *Staphylococcus* spp., *Escherichia coli*, *Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.

Cats
Treatment of infections of the alimentary, respiratory and urogenital tracts (as adjunctive antibiotic therapy for pyometra), skin and wound infections, caused by enrofloxacin susceptible strains of: *Staphylococcus* spp., *Escherichia coli, Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.

Pigs (piglets)
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of: *Pasteurella multocida, Mycoplasma* spp., *Actinobacillus pleuropneumoniae*.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*

Rabbits
Treatment of infections of the alimentary and respiratory tracts caused by enrofloxacin susceptible strains of: *Escherichia coli*, *Pasteurella multocida* and *Staphylococcus* spp.
Treatment of skin and wound infections caused by enrofloxacin susceptible strains of *Staphylococcus aureus.*

Rodents, reptiles and ornamental birds
Treatment of infections of the alimentary and respiratory tracts where clinical experience, if possible, supported by susceptibility testing of the causal organism, indicates enrofloxacin as the substance of choice.

4.3 Contraindications

Do not use in the case of known hypersensitivity to fluoroquinolones or to any of the excipients.
Do not use in animals that are epileptic or suffer from seizures since enrofloxacin may cause CNS stimulation.

Do not use in young dogs during their growth, i.e. in small breeds of dogs less than 8 months of age, in big breeds of dogs less than 12 months of age, in giant breeds of dogs less than 18 months of age.
Do not use in cats less than 8 weeks of age.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Official and local antimicrobial policies should be taken into account when the product is used.

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.

Whenever possible fluoroquinolones should only be used based on susceptibility testing.

Use of the product including use deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to enrofloxacin and may decrease the effectiveness of treatment with all fluoroquinolones due to the potential for cross-resistance.

Special caution should be taken when using enrofloxacin in animals with impaired renal function.
Special caution should be taken when using enrofloxacin in cats because higher doses than recommended can cause retinal damage and blindness (see section 4.10).

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to fluoroquinolones should avoid any contact with the product.
Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.
Wash hands after use. Do not eat, drink or smoke whilst handling the product.

Care should be taken to avoid accidental self-injection. If accidental self-injection occurs seek medical advice immediately.

Other precautions
In countries where feeding of fallen stock to scavenger bird populations is permitted as a conservation measure (see Commission Decision 2003/322/EC), the possible risk to hatching success should be considered before feeding carcasses of livestock recently treated with this product.

4.6 Adverse reactions (frequency and seriousness)

Digestive tract disorders (e.g. diarrhoea) may occur in very rare cases. These signs are generally mild and transient.

Local reactions at injection site
In pigs, after intramuscular administration of the product, inflammatory reactions may occur. They may persist up to 28 days after the injection.

In dogs, a moderate and transient local reaction (such as oedema) may occur.

In rabbits, reactions (from reddening to ulcerative lesions with deep loss of tissue), may occur. They may persist at least up to 17 days after the injection.

In reptiles and birds, muscle bruising may occur in very rare cases.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic effects but have shown evidence of foetotoxic effects at maternotoxic doses.

Mammals
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

Birds and reptiles
The safety of the veterinary medicinal product has not been established during lay. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Do not use enrofloxacin concomitantly with antimicrobial substances acting antagonistically to quinolones (e.g. macrolides, tetracyclines or phenicols).
Do not use concurrently with theophylline as the elimination of theophylline may be delayed.
Care should be taken during the concomitant use of flunixin and enrofloxacin in dogs to avoid adverse drug reactions. The decrease in drug clearances as a result of co-administration of flunixin and enrofloxacin indicates that these substances interact during the elimination phase. Thus, in dogs, the co-administration of enrofloxacin and flunixin increased the AUC and the elimination half-life of flunixin and increased the elimination half-life and reduced the Cmax of enrofloxacin.

4.9 Amounts to be administered and administration route

Subcutaneous or intramuscular use.
Repeated injections should be made at different injection sites.
To ensure a correct dosage, body weight (bw) should be determined as accurately as possible to avoid underdosing.

Dogs and cats

5 mg of enrofloxacin/kg bw, corresponding to 1 ml/5 kg bw, daily by subcutaneous injection for up to 5 days.
Treatment may be initiated with injectable product and maintained with enrofloxacin tablets. Duration of treatment should be based on the duration of treatment approved for the appropriate indication in the product information of the tablet product.

Pigs (piglets)
2.5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by intramuscular injection for 3 days.

Alimentary tract infection or septicaemia caused by *Escherichia coli*: 5 mg of enrofloxacin/kg of bw, corresponding to 2 ml/10 kg bw, once daily by intramuscular injection for 3 days.

In pigs, the injection should be made in the neck at the ear base.
Not more than 3 ml should be administered at one intramuscular injection site.

Rabbits
10 mg/kg bw, corresponding to 2 ml/5 kg bw, once daily by subcutaneous injection for 5 to 10 consecutive days.

Rodents
10 mg/kg bw, corresponding to 0.4 ml/kg bw, once daily by subcutaneous injection for 5 to 10 consecutive days. If necessary, depending on the severity of clinical signs, this dosage can be doubled.

Reptiles
Reptiles are ectothermic, relying on external heat sources to maintain their body temperature at the optimum level for correct function of all body systems. Metabolism of substances and activity of the immune system are, thus, critically dependent on the body temperature. Therefore, the veterinarian must be aware of the correct temperature requirements of the respective reptile species and the hydration status of the individual patient. Furthermore, it has to be considered that large differences exist in the pharmacokinetic behaviour of enrofloxacin among different species, which additionally will influence the decision about the correct dosage of "*product name (to be completed nationally)*". Therefore, the recommendations made here can only be used as a starting point for individual dose setting.

5–10 mg/kg bw, corresponding to 0.2–0.4 ml/kg bw, once daily by intramuscular injection for 5 consecutive days.
An extension of the treatment interval to 48 hours may be necessary in individual cases. In complicated infections, higher dosages and longer treatment courses may be necessary. The presence of the renal portal system in reptiles means it is prudent to administer substances in the front half of the body wherever possible.

Ornamental birds
20 mg/kg bw, corresponding to 0.8 ml/kg bw**,** once daily by intramuscular injection for 5 to 10 consecutive days. In case of complicated infections higher doses may be necessary.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

In cases of accidental overdose digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

Cats have been shown to suffer ocular damage after receiving doses of more than 15 mg/kg once daily for 21 consecutive days. Doses of 30 mg/kg given once daily for 21 consecutive days have been shown to cause irreversible ocular damage. At 50 mg/kg given once daily for 21 consecutive days, blindness can occur.

In dogs, rabbits, small rodents, reptiles and birds, overdose has not been documented.
In accidental overdose there is no antidote and treatment should be symptomatic.

4.11 Withdrawal period(s)

Pigs:
Meat and offal: 13 days.

Rabbits:
Meat and offal: 6 days.

Do not use in birds intended for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, fluoroquinolones.
ATCvet code: QJ01MA90.

5.1 Pharmacodynamic properties

Mode of action
Two enzymes essential in DNA replication and transcription, DNA gyrase and topoisomerase IV, have been identified as the molecular targets of fluoroquinolones. Target inhibition is caused by non-covalent binding of fluoroquinolone molecules to these enzymes. Replication forks and translational complexes cannot proceed beyond such enzyme-DNA-fluoroquinolone complexes, and inhibition of DNA and mRNA synthesis triggers events resulting in a rapid, drug concentration-dependent killing of pathogenic bacteria. The mode of action of enrofloxacin is bactericidal and bactericidal activity is concentration dependent.

Antibacterial spectrum
Enrofloxacin is active against many Gram-negative bacteria such as *Escherichia coli*, *Klebsiella* spp., *Actinobacillus pleuropneumoniae*, *Pasteurella* spp. (e.g. *Pasteurella multocida*), *Bordetella* spp., *Proteus* spp., *Pseudomonas* spp., against Gram-positive bacteria such as *Staphylococcus* spp. (e.g. *Staphylococcus aureus*) and against *Mycoplasma* spp. at the recommended therapeutic doses.

Types and mechanisms of resistance
Resistance to fluoroquinolones has been reported to arise from five sources, (i) point mutations in the genes encoding for DNA gyrase and/or topoisomerase IV leading to alterations of the respective enzyme, (ii) alterations of drug permeability in Gram-negative bacteria, (iii) efflux mechanisms, (iv) plasmid mediated resistance and (v) gyrase protecting proteins. All mechanisms lead to a reduced susceptibility of the bacteria to fluoroquinolones. Cross-resistance within the fluoroquinolone class of antimicrobials is common.

5.2 Pharmacokinetic particulars

Enrofloxacin is rapidly absorbed after parenteral injection. Bioavailability is high (approximately 100% in pigs) with a low to moderate plasma protein binding (approximately from 20 to 50%). Enrofloxacin is metabolized to the active substance ciprofloxacin at approximately 40% in dogs and less than 10% in cats and pigs.
African Grey Parrots serum ciprofloxacin concentrations were 3–78% of the enrofloxacin dose, with an increasing ciprofloxacin/enrofloxacin ratio with multiple doses.

Enrofloxacin and ciprofloxacin distribute well into all target tissues, e.g. lung, kidney, skin, and liver, reaching 2- to 3-fold higher concentrations than in plasma. Parent substance and active metabolite are cleared from the body via urine and faeces.
Accumulation in plasma does not occur following a treatment interval of 24 h.

	Dogs	Cats	Rabbits	Pigs	Pigs
Dose rate (mg/kg bw)	5	5	10	2.5	5
Route of administration	sc	sc	sc	im	im
T_{max} (h)	0.5	2	/	2	2
C_{max} (µg/ml)	1.8	1.3	/	0.7	1.6
AUC (µg·h/ml)	/	/	/	6.6	15.9
Terminal half-life (h)	/	/	/	13.12	8.10
Elimination half-life (h)	4.4	6.7	2.5	7.73	7.73
F (%)	/	/	/	95.6	/

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

n-Butyl alcohol
Potassium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products

6.3 Shelf life

Shelf life of the veterinary product as packaged for sale: 4 years.
Shelf life after the first opening of the immediate packaging: 28 days.

6.4. Special precautions for storage

Advice for handling: Do not refrigerate or freeze.

6.5 Nature and composition of immediate packaging

Brown glass (type I) vials with a chlorobutyl polytetrafluoroethylene (PTFE) stopper and with a flip-off cap with aluminium case and plastic flip-off button.

Pack-sizes:
50 ml and 100 ml in a cardboard box.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.
{Name and address}
<{Tel.}>
<{Fax}>
<{E-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.
<Date of first authorisation:> <{DD/MM/YYYY}><{DD month YYYY}.>

10 DATE OF REVISION OF THE TEXT

To be completed nationally.
<{MM/YYYY}>

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 25 mg/ml solution for injection
Enrofloxacin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One ml solution contains:
Enrofloxacin 25 mg.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml

5. TARGET SPECIES

Dogs, cats, pigs (piglets), rabbits, rodents, reptiles and ornamental birds

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Pigs:
Meat and offal: 13 days.
Rabbits:
Meat and offal: 6 days.
Do not use in birds intended for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached use within 28 days.

11. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and address}
<{Tel.}>
<{Fax}>
<{E-mail}>

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Glass vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 25 mg/ml solution for injection
Enrofloxacin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One ml solution contains:
Enrofloxacin 25 mg.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml

5. TARGET SPECIES

Dogs, cats, pigs (piglets), rabbits, rodents, reptiles and ornamental birds

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

SC, IM
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Pigs:
Meat and offal: 13 days.
Rabbits:
Meat and offal: 6 days.
Do not use in birds intended for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached use by …

11. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and address}
<{Tel.}>
<{Fax}>
<{E-mail}>

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:
<Invented name> 25 mg/ml solution for injection

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
To be completed nationally

Manufacturer responsible for batch release:
To be completed nationally

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 25 mg/ml solution for injection

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

One ml solution contains 25 mg enrofloxacin and 30 mg n-butyl alcohol as preservative.

4. INDICATION(S)

Dogs
Treatment of infections of the alimentary, respiratory and urogenital tracts (including prostatitis, adjunctive antibiotic therapy for pyometra), skin and wound infections, otitis (externa/media) caused by enrofloxacin susceptible strains of: *Staphylococcus* spp., *Escherichia coli, Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.

Cats
Treatment of infections of the alimentary, respiratory and urogenital tracts (as adjunctive antibiotic therapy for pyometra), skin and wound infections, caused by enrofloxacin susceptible strains of: *Staphylococcus* spp., *Escherichia coli, Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.

Pigs (piglets)
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of: *Pasteurella multocida, Mycoplasma* spp., *Actinobacillus pleuropneumoniae*.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.

Rabbits
Treatment of infections of the alimentary and respiratory tracts caused by enrofloxacin susceptible strains of: *Escherichia coli, Pasteurella multocida* and *Staphylococcus* spp.
Treatment of skin and wound infections caused by enrofloxacin susceptible strains of *Staphylococcus aureus.*

Rodents, reptiles and ornamental birds
Treatment of infections of the alimentary and respiratory tracts where clinical experience, if possible, supported by susceptibility testing of the causal organism, indicates enrofloxacin as the substance of choice.

5. CONTRAINDICATIONS

Do not use in the case of known hypersensitivity to fluoroquinolones or to any of the excipients.
Do not use in animals that are epileptic or suffer from seizures since enrofloxacin may cause CNS stimulation.

Do not use in young dogs during their growth, i.e. in small breeds of dogs less than 8 months of age, in big breeds of dogs less than 12 months of age, in giant breeds of dogs less than 18 months of age.
Do not use in cats less than 8 weeks of age.

6. ADVERSE REACTIONS

Digestive tract disorders (e.g. diarrhoea) may occur in very rare cases. These signs are generally mild and transient.

Local reactions at injection site
In pigs, after intramuscular administration of the product, inflammatory reactions may occur. They may persist up to 28 days after the injection.

In dogs, a moderate and transient local reaction (such as oedema) may occur.

In rabbits, reactions (from reddening to ulcerative lesions with deep loss of tissue), may occur. They may persist at least up to 17 days after the injection.

In reptiles and birds, muscle bruising may occur in very rare cases.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs, cats, pigs (piglets), rabbits, rodents, reptiles and ornamental birds

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Subcutaneous or intramuscular use.
Repeated injections should be made at different injection sites.

Dogs and cats
5 mg of enrofloxacin/kg body weight (bw), corresponding to 1 ml/5 kg bw, daily by subcutaneous injection for up to 5 days.
Treatment may be initiated with injectable product and maintained with enrofloxacin tablets. Duration of treatment should be based on the duration of treatment approved for the appropriate indication in the product information of the tablet product.

Pigs (piglets)

2.5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by intramuscular injection for 3 days.

Alimentary tract infection or septicaemia caused by *Escherichia coli*: 5 mg of enrofloxacin/kg of bw, corresponding to 2 ml/10 kg bw, once daily by intramuscular injection for 3 days.

In pigs, the injection should be made in the neck at the ear base.
- Not more than 3 ml should be administered at one intramuscular injection site.

Rabbits
10 mg/kg bw, corresponding to 2 ml/5 kg bw, once daily by subcutaneous injection for 5 to 10 consecutive days.

Rodents
10 mg/kg bw, corresponding to 0.4 ml/kg bw, once daily by subcutaneous injection for 5 to 10 consecutive days. If necessary, depending on the severity of clinical signs, this dosage can be doubled.

Reptiles
Reptiles are ectothermic, relying on external heat sources to maintain their body temperature at the optimum level for correct function of all body systems. Metabolism of substances and activity of the immune system are, thus, critically dependent on the body temperature. Therefore, the veterinarian must be aware of the correct temperature requirements of the respective reptile species and the hydration status of the individual patient. Furthermore, it has to be considered that large differences exist in the pharmacokinetic behaviour of enrofloxacin among different species, which additionally will influence the decision about the correct dosage of "*product name (to be completed nationally)*". Therefore, the recommendations made here can only be used as a starting point for individual dose setting.

5–10 mg/kg bw, corresponding to 0.2–0.4 ml/kg bw, once daily by intramuscular injection for 5 consecutive days.
An extension of the treatment interval to 48 hours may be necessary in individual cases. In complicated infections, higher dosages and longer treatment courses may be necessary. The presence of the renal portal system in reptiles means it is prudent to administer substances in the front half of the body wherever possible.

Ornamental birds
20 mg/kg bw, corresponding to 0.8 ml/kg bw**,** once daily by intramuscular injection for 5 to 10 consecutive days. In case of complicated infections higher doses may be necessary.

9. ADVICE ON CORRECT ADMINISTRATION

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

10. WITHDRAWAL PERIOD

Pigs:
Meat and offal: 13 days.

Rabbits:
Meat and offal: 6 days.

Do not use in birds intended for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not refrigerate or freeze.
Do not use this veterinary medicinal product after the expiry date which is stated on the vial after {abbreviation used for expiry date}.
Shelf life after first opening the container: 28 days.
The discard date should be recorded on the label of the glass vial after the vial was broached for the first time.

12. SPECIAL WARNING(S)

Special precautions for use in animals:
Official and local antimicrobial policies should be taken into account when the product is used.

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.

Whenever possible fluoroquinolones should only be used based on susceptibility testing.

Use of the product including use deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to enrofloxacin and may decrease the effectiveness of treatment with all fluoroquinolones due to the potential for cross-resistance.

Special caution should be taken when using enrofloxacin in animals with impaired renal function.
Special caution should be taken when using enrofloxacin in cats because higher doses than recommended can cause retinal damage and blindness (see Overdose).

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to fluoroquinolones should avoid any contact with the product.
Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.
Wash hands after use. Do not eat, drink or smoke whilst handling the product.

Care should be taken to avoid accidental self-injection. If accidental self-injection occurs seek medical advice immediately.

Other precautions
In countries where feeding of fallen stock to scavenger bird populations is permitted as a conservation measure (see Commission Decision 2003/322/EC), the possible risk to hatching success should be considered before feeding carcasses of livestock recently treated with this product.

Pregnancy and lactation and lay:
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic effects but have shown evidence of foetotoxic effects at maternotoxic doses.
Mammals
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.
Birds and reptiles
The safety of the veterinary medicinal product has not been established during lay. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
Do not use enrofloxacin concomitantly with antimicrobial substances acting antagonistically to quinolones (e.g. macrolides, tetracyclines or phenicols).
Do not use concurrently with theophylline as the elimination of theophylline may be delayed.
Care should be taken during the concomitant use of flunixin and enrofloxacin in dogs to avoid adverse drug reactions. The decrease in drug clearances as a result of co-administration of flunixin and enrofloxacin indicates that these substances interact during the elimination phase. Thus, in dogs, the co-administration of enrofloxacin and flunixin increased the AUC and the elimination half-life of flunixin and increased the elimination half-life and reduced the C_{max} of enrofloxacin.

Overdose (symptoms, emergency procedures, antidotes):
In cases of accidental overdoses digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

Cats have been shown to suffer ocular damage after receiving doses of more than 15 mg/kg once daily for 21 consecutive days. Doses of 30 mg/kg given once daily for 21 consecutive days have been shown to cause irreversible ocular damage. At 50 mg/kg given once daily for 21 consecutive days, blindness can occur.
In dogs, rabbits, small rodents, reptiles and birds, overdose has not been documented.
In accidental overdose there is no antidote and treatment should be symptomatic.

Incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

To be completed nationally.

15. OTHER INFORMATION

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 50 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains:
Active substance:
Enrofloxacin: 50 mg

Excipient(s):
n-Butyl alcohol: 30 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear light-yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (calves), sheep, goats, pigs, dogs and cats.

4.2 Indications for use, specifying the target species

Calves
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma* spp.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis*

Sheep
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Goats
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida* and *Mannheimia haemolytica*.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Pigs

Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mycoplasma* spp. and *Actinobacillus pleuropneumoniae*.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*

Dogs
Treatment of infections of the alimentary, respiratory and urogenital tracts (including prostatitis, adjunctive antibiotic therapy for pyometra), skin and wound infections, otitis (externa/media) caused by enrofloxacin susceptible strains of *Staphylococcus* spp.*, Escherichia coli, Pasteurella* spp.*, Klebsiella* spp.*, Bordetella* spp.*, Pseudomonas* spp. and *Proteus* spp.

Cats
Treatment of infections of the alimentary, respiratory and urogenital tracts (as adjunctive antibiotic therapy for pyometra), skin and wound infections, caused by enrofloxacin susceptible strains of, e.g.: *Staphylococcus* spp.*, Escherichia coli, Pasteurella* spp.*, Klebsiella* spp.*, Bordetella* spp.*, Pseudomonas* spp. and *Proteus* spp.

4.3 Contraindications

Do not use in animals with known hypersensitivity to enrofloxacin or other fluoroquinolones or to any of the excipients.
Do not use in animals that are epileptic or suffer from seizures since enrofloxacin may cause CNS stimulation.

Do not use in young dogs during their growth, i.e. in small breeds of dogs less than 8 months of age, in big breeds of dogs less than 12 months of age, in giant breeds of dogs less than 18 months of age.
Do not use in cats less than 8 weeks of age.

Do not use in growing horses because of possible deleterious damage on articular cartilage.

4.4 Special warnings for each target species

None**.**

4.5 Special precautions for use

Special precautions for use in animals

Official and local antimicrobial policies should be taken into account when the product is used.

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.

Whenever possible fluoroquinolones should only be used based on susceptibility testing.

Use of the product including use deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to enrofloxacin and may decrease the effectiveness of treatment with all fluoroquinolones due to the potential for cross-resistance.

Special caution should be taken when using enrofloxacin in animals with impaired renal function.

Special caution should be taken when using enrofloxacin in cats because higher doses than recommended can cause retinal damage and blindness. For cats weighting less than 5 kg, the dosage of 25 mg/ml is more appropriate to avoid risk of overdosage (see section 4.10).

Degenerative changes of articular cartilage were observed in calves treated orally with 30 mg enrofloxacin/kg body weight during 14 days.

The use of enrofloxacin in growing lambs at the recommended dose for 15 days caused histological changes in the articular cartilage, not associated to clinical signs.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to fluoroquinolones should avoid any contact with the product.
Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.
Wash hands after use. Do not eat, drink or smoke whilst handling the product.

Care should be taken to avoid accidental self-injection. If accidental self-injection occurs seek medical advice immediately.

Other precautions
In countries where feeding of fallen stock to scavenger bird populations is permitted as a conservation measure (see Commission Decision 2003/322/EC), the possible risk to hatching success should be considered before feeding carcasses of livestock recently treated with this product.

4.6 Adverse reactions (frequency and seriousness)

Digestive tract disorders (e.g. diarrhoea) may occur in very rare cases. These signs are generally mild and transient.

Local reactions at injection site
In calves, transient local tissue reactions may occur in very rare cases and may be observed up to 14 days.
In pigs, after intramuscular administration of the product, inflammatory reactions may occur. They may persist up to 28 days after the injection
In dogs, a moderate and transient local reaction (such as oedema) may occur.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic effects but have shown evidence of foetotoxic effects at maternotoxic doses.
Mammals
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Do not use enrofloxacin concomitantly with antimicrobial substances acting antagonistically to quinolones (e.g. macrolides, tetracyclines or phenicols).
Do not use concurrently with theophylline as the elimination of theophylline may be delayed.
Care should be taken during the concomitant use of flunixin and enrofloxacin in dogs to avoid adverse drug reactions. The decrease in drug clearances as a result of co-administration of flunixin and enrofloxacin indicates that these substances interact during the elimination phase. Thus, in dogs, the

co-administration of enrofloxacin and flunixin increased the AUC and the elimination half-life of flunixin and increased the elimination half-life and reduced the C_{max} of enrofloxacin.

4.9 Amounts to be administered and administration route

Intravenous, subcutaneous or intramuscular use.
Repeated injections should be made at different injection sites.
To ensure a correct dosage, body weight (bw) should be determined as accurately as possible to avoid underdosing.
II
Calves
5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily for 3-5 days.

Acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis*: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily for 5 days.

The product can be administered by slow intravenous or subcutaneous administration.
Not more than 10 ml should be administered at one subcutaneous injection site.

Sheep and goats
5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by subcutaneous injection for 3 days.
Not more than 6 ml should be administered at one subcutaneous injection site.

Pigs
2.5 mg of enrofloxacin/kg bw, corresponding to 0.5 ml/10 kg bw, once daily by intramuscular injection for 3 days.

Alimentary tract infection or septicaemia caused by *Escherichia coli*: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by intramuscular injection for 3 days.

In pigs, the injection should be made in the neck at the ear base.
Not more than 3 ml should be administered at one intramuscular injection site.

Dogs and cats
5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by subcutaneous injection for up to 5 days.
Treatment may be initiated with injectable product and maintained with enrofloxacin tablets. Duration of treatment should be based on the duration of treatment approved for the appropriate indication in the product information of the tablet product.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

In cases of accidental overdoses digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

Cats have been shown to suffer ocular damage after receiving doses of more than 15 mg/kg once daily for 21 consecutive days. Doses of 30 mg/kg given once daily for 21 consecutive days have been shown to cause irreversible ocular damage. At 50 mg/kg given once daily for 21 consecutive days, blindness can occur.

In dogs, cattle, sheep and goats, overdose has not been documented.

In accidental overdose there is no antidote and treatment should be symptomatic.

4.11 Withdrawal period(s)

Calves:
Following intravenous injection: Meat and offal: 5 days.
Following subcutaneous injection: Meat and offal: 10 days.
Not authorised for use in animals producing milk for human consumption.

Sheep:
Meat and offal: 4 days.
Milk: 3 days.

Goats:
Meat and offal: 6 days.
Milk: 4 days.

Pigs:
Meat and offal: 13 days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, fluoroquinolones.
ATCvet code: QJ01MA90.

5.1 Pharmacodynamic properties

Mode of action
Two enzymes essential in DNA replication and transcription, DNA gyrase and topoisomerase IV, have been identified as the molecular targets of fluoroquinolones. Target inhibition is caused by non-covalent binding of fluoroquinolone molecules to these enzymes. Replication forks and translational complexes cannot proceed beyond such enzyme-DNA-fluoroquinolone complexes, and inhibition of DNA and mRNA synthesis triggers events resulting in a rapid, drug concentration-dependent killing of pathogenic bacteria. The mode of action of enrofloxacin is bactericidal and bactericidal activity is concentration dependent.

Antibacterial spectrum
Enrofloxacin is active against many Gram-negative bacteria such as *Escherichia coli, Klebsiella* spp., *Actinobacillus pleuropneumoniae*, *Mannheimia haemolytica, Pasteurella* spp. (e.g. *Pasteurella multocida*), *Bordetella* spp., *Proteus* spp., *Pseudomonas* spp., against Gram-positive bacteria such as *Staphylococcus* spp. (e.g. *Staphylococcus aureus*) and against *Mycoplasma* spp. at the recommended therapeutic doses.

Types and mechanisms of resistance
Resistance to fluoroquinolones has been reported to arise from five sources, (i) point mutations in the genes encoding for DNA gyrase and/or topoisomerase IV leading to alterations of the respective enzyme, (ii) alterations of drug permeability in Gram-negative bacteria, (iii) efflux mechanisms, (iv) plasmid mediated resistance and (v) gyrase protecting proteins. All mechanisms lead to a reduced susceptibility of the bacteria to fluoroquinolones. Cross-resistance within the fluoroquinolone class of antimicrobials is common.

5.2 Pharmacokinetic particulars

Enrofloxacin is rapidly absorbed after parenteral injection. Bioavailability is high (approximately 100% in pig and cattle) with a low to moderate plasma protein binding (approximately 20 to 50%). Enrofloxacin is metabolized to the active substance ciprofloxacin at approximately 40 % in dogs and ruminants, less than 10 % in pigs and cats.

Enrofloxacin and ciprofloxacin distribute well into all target tissues, e.g. lung, kidney, skin, and liver, reaching 2- to 3-fold higher concentrations than in plasma. Parent substance and active metabolite are cleared from the body via urine and faeces.
Accumulation in plasma does not occur following a treatment interval of 24 h.
In milk, most of drug activity consists on ciprofloxacin. Overall drug concentrations peak at 2 hours after treatment showing an approximately 3-fold higher total exposure over the 24 hours dosing interval compared to plasma.

	Dogs	Cats	Pigs	Pigs	Cattle	Calves
Dose rate (mg/kg bw)	5	5	2.5	5	5	5
Route of administration	sc	sc	im	im	iv	sc
T_{max} (h)	0.5	2	2	2	/	1.2
C_{max} (µg/ml)	1.8	1.3	0.7	1.6	/	0.73
AUC (µg·h/ml)	/	/	6.6	15.9	7.11	3.09
Terminal half-life (h)	/	/	13.12	8.10	/	2.34
Elimination half-life (h)	4.4	6.7	7.73	7.73	2.2	/
F (%)	/	/	95.6	/	/	/

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

n-Butyl alcohol
Potassium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products

6.3 Shelf life

Shelf life of the veterinary product as packaged for sale: 4 years.
Shelf life after the first opening of the immediate packaging: 28 days.

6.4. Special precautions for storage

Advice for handling: Do not refrigerate or freeze

6.5 Nature and composition of immediate packaging

Brown glass (type I) vials with a chlorobutyl polytetrafluoroethylene (PTFE) stopper and with a flip-off cap with aluminium case and plastic flip-off button.

Pack-sizes:
50 ml and 100 ml in a cardboard box.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.
{Name and address}
<{Tel.}>
<{Fax}>
<{E-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.<Date of first authorisation:> <{DD/MM/YYYY}><{DD month YYYY}.>

10 DATE OF REVISION OF THE TEXT

To be completed nationally.
<{MM/YYYY}>

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 50 mg/ml solution for injection
Enrofloxacin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One ml solution contains:
Enrofloxacin 50 mg

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml

5. TARGET SPECIES

Cattle (calves), sheep, goats, pigs, dogs and cats

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Calves:
IV: Meat and offal: 5 days.
SC: Meat and offal: 10 days.
Not authorised for use in animals producing milk for human consumption.

Sheep:
Meat and offal: 4 days.
Milk: 3 days.

Goats:
Meat and offal: 6 days.
Milk: 4 days.

Pigs:
Meat and offal: 13 days.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached use within 28 days.

11. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and address}
<{Tel.}>
<{Fax}>
<{E-mail}>

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Glass vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 50 mg/ml solution for injection
Enrofloxacin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One ml solution contains:
Enrofloxacin 50 mg.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml

5. TARGET SPECIES

Cattle (calves), sheep, goats, pigs, dogs and cats

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

IV, SC, IM
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Calves:
IV: Meat and offal: 5 days.
SC: Meat and offal: 10 days.
Not authorised for use in animals producing milk for human consumption.

Sheep:
Meat and offal: 4 days.
Milk: 3 days.

Goats:
Meat and offal: 6 days.
Milk: 4 days.

Pigs:
Meat and offal: 13 days.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached use by …

11. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and address}
<{Tel}>
<{Fax}>
<{E-mail}>

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:
<Invented name> 50 mg/ml solution for injection

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
To be completed nationally

Manufacturer responsible for batch release:
To be completed nationally

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 50 mg/ml solution for injection

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

One ml solution contains 50 mg enrofloxacin and 30 mg n-butyl alcohol as preservative.

4. INDICATION(S)

Calves
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma* spp.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis*.

Sheep
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Goats
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida* and *Mannheimia haemolytica*.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Pigs
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mycoplasma* spp. and *Actinobacillus pleuropneumoniae*.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.

Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*

Dogs
Treatment of infections of the alimentary, respiratory and urogenital tracts (including prostatitis, adjunctive antibiotic therapy for pyometra), skin and wound infections, otitis (externa/media) caused by enrofloxacin susceptible strains of *Staphylococcus* spp., *Escherichia coli*, *Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.

Cats
Treatment of infections of the alimentary, respiratory and urogenital tracts (as adjunctive antibiotic therapy for pyometra), skin and wound infections, caused by enrofloxacin susceptible strains of, e.g.: *Staphylococcus* spp., *Escherichia coli, Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.

5. CONTRAINDICATIONS

Do not use in animals with known hypersensitivity to enrofloxacin or other fluoroquinolones or to any of the excipients.

Do not use in animals that are epileptic or suffer from seizures since enrofloxacin may cause CNS stimulation.

Do not use in young dogs during their growth, i.e. in small breeds of dogs less than 8 months of age, in big breeds of dogs less than 12 months of age, in giant breeds of dogs less than 18 months of age.
Do not use in cats less than 8 weeks of age.

Do not use in growing horses because of possible deleterious damage on articular cartilage.

6. ADVERSE REACTIONS

Digestive tract disorders (e.g. diarrhoea) may occur in very rare cases. These signs are generally mild and transient.

Local reactions at injection site
In calves, transient local tissue reactions may occur in very rare cases and may be observed up to 14 days.
In pigs, after intramuscular administration of the product, inflammatory reactions may occur. They may persist up to 28 days after the injection.
In dogs, a moderate and transient local reaction (such as oedema) may occur.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Cattle (calves), sheep, goats, pigs, dogs and cats.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Intravenous, subcutaneous or intramuscular use.

Repeated injections should be made at different injection sites.
III
Calves
5 mg of enrofloxacin/kg bodyweight (bw), corresponding to 1 ml/10 kg bw, once daily for 3-5 days.

Acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis*.*:* 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily for 5 days.

The product can be administered by slow intravenous or subcutaneous administration.
Not more than 10 ml should be administered at one subcutaneous injection site.

Sheep and goats
5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by subcutaneous injection for 3 days.
Not more than 6 ml should be administered at one subcutaneous injection site.

Pigs
2.5 mg of enrofloxacin/kg bw, corresponding to 0.5 ml/10 kg bw, once daily by intramuscular injection for 3 days.

Alimentary tract infection or septicaemia caused by *Escherichia coli*: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by intramuscular injection for 3 days.

In pigs, the injection should be made in the neck at the ear base.
Not more than 3 ml should be administered at one intramuscular injection site.

Dogs and cats
5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by subcutaneous injection for up to 5 days.
Treatment may be initiated with injectable product and maintained with enrofloxacin tablets. Duration of treatment should be based on the duration of treatment approved for the appropriate indication in the product information of the tablet product.

9. ADVICE ON CORRECT ADMINISTRATION

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

10. WITHDRAWAL PERIOD

Calves:
Following intravenous injection: Meat and offal: 5 days.
Following subcutaneous injection: Meat and offal: 10 days.
Not authorised for use in animals producing milk for human consumption.

Sheep:
Meat and offal: 4 days.
Milk: 3 days.

Goats:
Meat and offal: 6 days.
Milk: 4 days.

Pigs:
Meat and offal: 13 days.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not refrigerate or freeze.
Do not use this veterinary medicinal product after the expiry date which is stated on the vial after {abbreviation used for expiry date}.
Shelf life after first opening the container: 28 days.
The discard date should be recorded on the label of the glass vial after the vial was broached for the first time.

12. SPECIAL WARNING(S)

Special precautions for use in animals:
Official and local antimicrobial policies should be taken into account when the product is used.

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.

Whenever possible fluoroquinolones should only be used based on susceptibility testing.

Use of the product including use deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to enrofloxacin and may decrease the effectiveness of treatment with all fluoroquinolones due to the potential for cross-resistance.

Special caution should be taken when using enrofloxacin in animals with impaired renal function.

Special caution should be taken when using enrofloxacin in cats because higher doses than recommended can cause retinal damage and blindness. For cats weighting less than 5 kg, the dosage of 25 mg/ml is more appropriate to avoid risk of overdosage (see Overdose).

Degenerative changes of articular cartilage were observed in calves treated orally with 30 mg enrofloxacin/kg body weight during 14 days.

The use of enrofloxacin in growing lambs at the recommended dose for 15 days caused histological changes in the articular cartilage, not associated to clinical signs.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to fluoroquinolones should avoid any contact with the product.
Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.
Wash hands after use. Do not eat, drink or smoke whilst handling the product.

Care should be taken to avoid accidental self-injection. If accidental self-injection occurs seek medical advice immediately.

Pregnancy and lactation and lay:
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic effects but have shown evidence of foetotoxic effects at maternotoxic doses.

Mammals
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
Do not use enrofloxacin concomitantly with antimicrobial substances acting antagonistically to quinolones (e.g. macrolides, tetracyclines or phenicols).
Do not use concurrently with theophylline as the elimination of theophylline may be delayed.
Care should be taken during the concomitant use of flunixin and enrofloxacin in dogs to avoid adverse drug reactions. The decrease in drug clearances as a result of co-administration of flunixin and enrofloxacin indicates that these substances interact during the elimination phase. Thus, in dogs, the co-administration of enrofloxacin and flunixin increased the AUC and the elimination half-life of flunixin and increased the elimination half-life and reduced the C_{max} of enrofloxacin.

Overdose (symptoms, emergency procedures, antidotes):
In cases of accidental overdoses digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

Cats have been shown to suffer ocular damage after receiving doses of more than 15 mg/kg once daily for 21 consecutive days. Doses of 30 mg/kg given once daily for 21 consecutive days have been shown to cause irreversible ocular damage. At 50 mg/kg given once daily for 21 consecutive days, blindness can occur.
In dogs, cattle, sheep and goats, overdose has not been documented.
In accidental overdose there is no antidote and treatment should be symptomatic.

Incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

To be completed nationally.

15. OTHER INFORMATION

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 100 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains:
Active substance:
Enrofloxacin: 100 mg

Excipient:
n-Butyl alcohol: 30 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear light-yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle, sheep, goats and pigs.

4.2 Indications for use, specifying the target species

Cattle
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma* spp.
Treatment of acute severe mastitis caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis* in cattle less than 2 years old.

Sheep
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Goats
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida* and *Mannheimia haemolytica.*
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Pigs
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mycoplasma* spp. and *Actinobacillus pleuropneumoniae.*
Treatment of infections of the urinary tract caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of post-partum dysgalactiae syndrome, PDS (MMA syndrome) caused by enrofloxacin susceptible strains of *Escherichia coli* and *Klebsiella* spp.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*

4.3 Contraindications

Do not use in animals with known hypersensitivity to enrofloxacin or other fluoroquinolones or to any of the excipients.

Do not use in growing horses because of possible deleterious damage on articular cartilage.

4.4 Special warnings for each target species

None**.**

4.5 Special precautions for use

Special precautions for use in animals

Official and local antimicrobial policies should be taken into account when the product is used.

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.

Whenever possible fluoroquinolones should only be used based on susceptibility testing.

Use of the product including use deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to enrofloxacin and may decrease the effectiveness of treatment with all fluoroquinolones due to the potential for cross-resistance.

Degenerative changes of articular cartilage were observed in calves treated orally with 30 mg enrofloxacin/kg body weight during 14 days.

The use of enrofloxacin in growing lambs at the recommended dose for 15 days caused histological changes in the articular cartilage, not associated to clinical signs.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to fluoroquinolones should avoid any contact with the product.
Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.
Wash hands after use. Do not eat, drink or smoke whilst handling the product.

Care should be taken to avoid accidental self-injection. If accidental self-injection occurs seek medical advice immediately.

Other precautions
In countries where feeding of fallen stock to scavenger bird populations is permitted as a conservation measure (see Commission Decision 2003/322/EC), the possible risk to hatching success should be considered before feeding carcasses of livestock recently treated with this product.

4.6 Adverse reactions (frequency and seriousness)

Digestive tract disorders (e.g. diarrhoea) may occur in very rare cases. These signs are generally mild and transient.

In very rare cases intravenous treatment of cattle can cause shock reactions, presumably as a result of circulatory impairment.

Local reactions at injection site
In pigs, after intramuscular administration of the product, inflammatory reactions may occur. They may persist up to 28 days after the injection.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Cattle
The safety of the veterinary medicinal product has been established in pregnant cows during the 1st quarter of pregnancy. The product can be used in pregnant cows during the 1st quarter of pregnancy. The use of the product in cows during the 3 last quarters of pregnancy should be based on a benefit-risk assessment by the responsible veterinarian.
The product can be used in cows during lactation.

Sheep and goats
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Pigs
The safety of the veterinary medicinal product has not been established during pregnancy. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.
The product can be used in sows during lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Do not use enrofloxacin concomitantly with antimicrobial substances acting antagonistically to quinolones (e.g. macrolides, tetracyclines or phenicols).

Do not use concurrently with theophylline as the elimination of theophylline may be delayed.

4.9 Amounts to be administered and administration route

Intravenous, subcutaneous or intramuscular use.
Repeated injections should be made at different injection sites.
To ensure a correct dosage, body weight (bw) should be determined as accurately as possible to avoid underdosing.

Cattle
5 mg of enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, once daily for 3–5 days.

Acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis* in cattle less than 2 years old: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, once daily for 5 days.

The product can be administered by slow intravenous or subcutaneous administration.

Acute mastitis caused by *Escherichia coli*: 5 mg enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, by slow intravenous injection once daily for two consecutive days.
The second dose may be administered by the subcutaneous route. In this case, the withdrawal period following subcutaneous injection applies.

Not more than 10 ml should be administered at one subcutaneous injection site.

Sheep and goats
5 mg of enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, once daily by subcutaneous injection for 3 days.
Not more than 6 ml should be administered at one subcutaneous injection site.

Pigs
2.5 mg of enrofloxacin/kg bw, corresponding to 0.5 ml/20 kg bw, once daily by intramuscular injection for 3 days.

Alimentary tract infection, or septicaemia caused by *Escherichia coli*: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, once daily by intramuscular injection for 3 days.
In pigs, the injection should be made in the neck at the ear base.
Not more than 3 ml should be administered at one intramuscular injection site.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

In cases of accidental overdoses digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

In cattle, sheep and goat, overdose has not been documented.

In accidental overdose there is no antidote and treatment should be symptomatic.

4.11 Withdrawal period(s)

Cattle:
Following intravenous injection:
Meat and offal: 5 days.
Milk: 3 days.
Following subcutaneous injection:
Meat and offal: 10 days.
Milk: 4 days.

Sheep:
Meat and offal: 4 days.
Milk: 3 days.

Goats:
Meat and offal: 6 days.
Milk: 4 days.

Pigs:
Meat and offal: 13 days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, fluoroquinolones.
ATCvet code: QJ01MA90.

5.1 Pharmacodynamic properties

Mode of action
Two enzymes essential in DNA replication and transcription, DNA gyrase and topoisomerase IV, have been identified as the molecular targets of fluoroquinolones. Target inhibition is caused by non-covalent binding of fluoroquinolone molecules to these enzymes. Replication forks and translational complexes cannot proceed beyond such enzyme-DNA-fluoroquinolone complexes, and inhibition of DNA and mRNA synthesis triggers events resulting in a rapid, drug concentration-dependent killing of pathogenic bacteria. The mode of action of enrofloxacin is bactericidal and bactericidal activity is concentration dependent.

Antibacterial spectrum
Enrofloxacin is active against many Gram-negative bacteria such as *Escherichia coli, Klebsiella* spp., *Actinobacillus pleuropneumoniae*, *Mannheimia haemolytica, Pasteurella* spp. (e.g. *Pasteurella multocida*), against Gram-positive bacteria such as *Staphylococcus* spp. (e.g. *Staphylococcus aureus*) and against *Mycoplasma* spp. at the recommended therapeutic doses.

Types and mechanisms of resistance
Resistance to fluoroquinolones has been reported to arise from five sources, (i) point mutations in the genes encoding for DNA gyrase and/or topoisomerase IV leading to alterations of the respective enzyme, (ii) alterations of drug permeability in Gram-negative bacteria, (iii) efflux mechanisms, (iv) plasmid mediated resistance and (v) gyrase protecting proteins. All mechanisms lead to a reduced susceptibility of the bacteria to fluoroquinolones. Cross-resistance within the fluoroquinolone class of antimicrobials is common.

5.2 Pharmacokinetic particulars

Enrofloxacin is rapidly absorbed after parenteral injection. Bioavailability is high (approximately 100% in pig and cattle) with a low to moderate plasma protein binding (approximately 20 to 50%). Enrofloxacin is metabolized to the active substance ciprofloxacin at approximately 40% in ruminants and less than 10% in pigs.
Enrofloxacin and ciprofloxacin distribute well into all target tissues, e.g. lung, kidney, skin and liver, reaching 2- to 3-fold higher concentrations than in plasma. Parent substance and active metabolite are cleared from the body via urine and faeces.

Accumulation in plasma does not occur following a treatment interval of 24 h.
In milk, most of drug activity consists on ciprofloxacin. Overall drug concentrations peak at 2 hours after treatment showing an approximately 3-fold higher total exposure over the 24 hours dosing interval compared to plasma.

	Pigs	Pigs	Cattle	Cattle
Dose rate (mg/kg bw)	2.5	5	5	5
Route of administration	im	im	iv	sc
T_{max} (h)	2	2	/	3.5
C_{max} (µg/ml)	0.7	1.6	/	0.733
AUC (µg·h/ml)	6.6	15.9	9.8	5.9
Terminal half-life (h)	13.12	8.10	/	7.8
Elimination half-life (h)	7.73	7.73	2.3	
F (%)	95.6	/	/	88.2

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

n-Butyl alcohol
Potassium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products

6.3 Shelf life

Shelf life of the veterinary product as packaged for sale: 4 years.
Shelf life after the first opening of the immediate packaging: 28 days.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Brown glass (type I) vials with a chlorobutyl polytetrafluoroethylene (PTFE) stopper and with a flip-off cap with aluminium case and plastic flip-off button.

Pack-sizes:
50 ml and 100 ml in a cardboard box.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.
{Name and address}
<{Tel.}>
<{Fax}>
<{E-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.
<Date of first authorisation:> <{DD/MM/YYYY}><{DD month YYYY}.>

10 DATE OF REVISION OF THE TEXT

To be completed nationally.
<{MM/YYYY}>

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 100 mg/ml solution for injection
Enrofloxacin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One ml solution contains:
Enrofloxacin 100 mg.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml

5. TARGET SPECIES

Cattle, sheep, goats and pigs.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Cattle:

IV: Meat and offal: 5 days.
Milk: 3 days.
SC: Meat and offal: 10 days.
Milk: 4 days.

Sheep:
Meat and offal: 4 days.
Milk: 3 days.

Goats:
Meat and offal: 6 days.
Milk: 4 days.

Pigs:
Meat and offal: 13 days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached use within 28 days.

11. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and address}
<{Tel.}>
<{Fax}>
<{E-mail}>

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER*/*

Batch{number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Glass vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 100 mg/ml solution for injection
Enrofloxacin

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One ml solution contains:
Enrofloxacin 100 mg

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml

5. TARGET SPECIES

Cattle, sheep, goats and pigs.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

IV, SC, IM
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Cattle:
IV: Meat and offal: 5 days.
Milk: 3 days.
SC: Meat and offal: 10 days.
Milk: 4 days.

Sheep:
Meat and offal: 4 days.

Milk: 3 days.

Goats:
Meat and offal: 6 days.
Milk: 4 days.

Pigs:
Meat and offal: 13 days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached use by …

11. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.
To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and address}
<{Tel.}>
<{Fax}>
<{E-mail}>

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch{number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:
<Invented name> 100 mg/ml solution for injection

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
To be completed nationally
Manufacturer responsible for batch release:
To be completed nationally

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 100 mg/ml solution for injection

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

One ml solution contains 100 mg enrofloxacin and 30 mg n-butyl alcohol as preservative.

4. INDICATION(S)

Cattle
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mannheimia haemolytica* and *Mycoplasma* spp.
Treatment of acute severe mastitis caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis* in cattle less than 2 years old.

Sheep
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Goats
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida* and *Mannheimia haemolytica.*
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli.*
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Pigs
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida, Mycoplasma* spp. and *Actinobacillus pleuropneumoniae.*
Treatment of infections of the urinary tract caused by enrofloxacin susceptible strains of *Escherichia coli.*

Treatment of post-partum dysgalactiae syndrome, PDS (MMA syndrome) caused by enrofloxacin susceptible strains of *Escherichia coli* and *Klebsiella* spp.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.

5. CONTRAINDICATIONS

Do not use in animals with known hypersensitivity to enrofloxacin or other fluoroquinolones or to any of the excipients.
Do not use in growing horses because of possible deleterious damage on articular cartilage.

6. ADVERSE REACTIONS

Digestive tract disorders (e.g. diarrhoea) may occur in very rare cases. These signs are generally mild and transient.

In very rare cases intravenous treatment of cattle can cause shock reactions, presumably as a result of circulatory impairment.

Local reactions at injection site
In pigs, after intramuscular administration of the product, inflammatory reactions may occur. They may persist up to 28 days after the injection.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Cattle, sheep, goats and pigs.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Intravenous, subcutaneous or intramuscular use.
Repeated injections should be made at different injection sites.

Cattle
5 mg of enrofloxacin/kg body weight (bw), corresponding to 1 ml/20 kg bw, once daily for 3–5 days.

Acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis* in cattle less than 2 years old: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, once daily for 5 days.

The product can be administered by slow intravenous or subcutaneous administration.

Acute mastitis caused by *Escherichia coli*: 5 mg enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, by slow intravenous injection once daily for two consecutive days.
The second dose may be administered by the subcutaneous route. In this case, the withdrawal period following subcutaneous injection applies.

Not more than 10 ml should be administered at one subcutaneous injection site.

Sheep and goats
5 mg of enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, once daily by subcutaneous injection for 3 days.
Not more than 6 ml should be administered at one subcutaneous injection site.

Pigs
2.5 mg of enrofloxacin/kg bw, corresponding to 0.5 ml/20 kg bw, once daily by intramuscular injection for 3 days.

Alimentary tract infection, or septicaemia caused by *Escherichia coli*: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/20 kg bw, once daily by intramuscular injection for 3 days.
In pigs, the injection should be made in the neck at the ear base.
Not more than 3 ml should be administered at one intramuscular injection site.

9. ADVICE ON CORRECT ADMINISTRATION

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

10. WITHDRAWAL PERIOD

Cattle**:**
Following intravenous injection:
Meat and offal: 5 days.
Milk: 3 days.
Following subcutaneous injection:
Meat and offal: 10 days.
Milk: 4 days.

Sheep:
Meat and offal: 4 days.
Milk: 3 days.

Goats:
Meat and offal: 6 days.
Milk: 4 days.

Pigs:
Meat and offal: 13 days.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not refrigerate or freeze.
Do not use this veterinary medicinal product after the expiry date which is stated on the vial after {abbreviation used for expiry date}
Shelf life after first opening the container: 28 days.

The discard date should be recorded on the label of the glass vial after the vial was broached for the first time.

12. SPECIAL WARNING(S)

Special precautions for use in animals:
Official and local antimicrobial policies should be taken into account when the product is used.

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.

Whenever possible fluoroquinolones should only be used based on susceptibility testing.

Use of the product including use deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to enrofloxacin and may decrease the effectiveness of treatment with all fluoroquinolones due to the potential for cross-resistance.

Degenerative changes of articular cartilage were observed in calves treated orally with 30 mg enrofloxacin/kg body weight during 14 days.

The use of enrofloxacin in growing lambs at the recommended dose for 15 days caused histological changes in the articular cartilage, not associated to clinical signs.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to fluoroquinolones should avoid any contact with the product.
Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.
Wash hands after use. Do not eat, drink or smoke whilst handling the product.

Care should be taken to avoid accidental self-injection. If accidental self-injection occurs seek medical advice immediately.

Pregnancy and lactation and lay:
Cattle
The safety of the veterinary medicinal product has been established in pregnant cows during the 1st quarter of pregnancy. The product can be used in pregnant cows during the 1st quarter of pregnancy.
The use of the product in cows during the 3 last quarters of pregnancy should be based on a benefit/risk assessment by the responsible veterinarian.
The product can be used in cows during lactation.
Sheep and goats
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.
Pigs
The safety of the veterinary medicinal product has not been established during pregnancy. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.
The product can be used in sows during lactation.

Interaction with other medicinal products and other forms of interaction:
Do not use enrofloxacin concomitantly with antimicrobial substances acting antagonistically to quinolones (e.g. macrolides, tetracyclines or phenicols).

Do not use concurrently with theophylline as the elimination of theophylline may be delayed.

Overdose (symptoms, emergency procedures, antidotes):
In cases of accidental overdoses digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

In cattle, sheep and goat, overdose has not been documented.
In accidental overdose there is no antidote and treatment should be symptomatic.

Incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

To be completed nationally.

15. OTHER INFORMATION

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.