Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal products, animal species, route of administration, applicant / marketing authorisation holders in the Member States

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
Belgium	GLOBAL VET HEALTH SL C/Capçanes nº12-bajos Polígono Agro-Reus 43206 Reus SPAIN	QUINOFLOX 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Chickens (Broilers, replacement chickens, broiler breeders), Rabbits
Cyprus	LABORATORIOS KARIZOO, S.A. Polígono Industrial La Borda Mas Pujades, 11-12 08140 Caldes de Montbui Barcelona SPAIN	K-Flox 100mg/ml Πόσιμο διάλυμα για ορνίθια κρεοπαραγωγής και κουνέλια	Enrofloxacin	100 mg/ml	Oral solution	Chickens (broilers), Rabbits
Spain	LABORATORIOS HIPRA, S.A.Avda. La Selva,135 17170 Amer SPAIN	HIPRALONA ENRO - S	Enrofloxacin	100 mg/ml	Oral solution	Poultry (Chicken and Turkeys), Rabbits
Spain	UNIVERSAL FARMA,S.L. Gran Via Carlos III 98 - 7ª 08028 Barcelona SPAIN	LEVOFLOK® 100 mg/ml Oral solution for chickens and rabbits	Enrofloxacin	100 mg/ml	Oral solution	Chickens, Rabbits
Spain	LABORATORIOS KARIZOO, S.A. Polígono Industrial La Borda Mas Pujades, 11-12 08140 Caldes de Montbui Barcelona SPAIN	K-FLOX 100 mg/ml Oral Solution for chickens and rabbits.	Enrofloxacin	100 mg/ml	Oral solution	Chickens, Rabbits
Spain	Global Vet Health, SL Capcanes, 12 bajos Poligono Agro-Reus 43206 Reus SPAIN	QUINOFLOX 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Chickens, Rabbits
Spain	SP VETERINARIA Ctra.Reus-Vinyols, Km, 43330 Ruidoms SPAIN	COLMYC -C	Enrofloxacin	100 mg/ml	Oral solution	Poultry (Chicken and Turkeys), Rabbits

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
France	GLOBAL VET HEALTH SL c/Capçanes, nº12-bajos. Polígon Agro-Reus. 43206 Reus SPAIN	Quinoflox 100 mg/ml solution for use in drinking water, chicken and rabbits	Enrofloxacin	100 mg/ml	Oral solution	Chickens (Broilers, replacement chickens, broiler breeders), Rabbits
Italy	GLOBAL VET HEALTH, S.L. Capsanes, 12 - Polígono Agro-Reus E-43206 - REUS (Tarragona) SPAIN	QUINOLCEN	Enrofloxacin	100 mg/ml	Oral solution	Chickens, Rabbits
Italy	LABORATORIOS KARIZOO, S.A. Polígono Industrial La Borda Mas Pujades, 11-12 08140 – CALDES DE MONTBUI (Barcelona) SPAIN	K-FLOX 100mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Chickens, Rabbits
Italy	VETPHARMA ANIMAL HEALTH, S.L. Les Corts, 23 08028 – BARCELONA SPAIN	NIFLOX 100mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Chickens, Rabbits
Poland	Medivet S.A. Szkolna 17 63-100 Śrem POLAND	MEDOXIL ORAL 100 mg/ml roztwór doustny dla kur i królików	Enrofloxacinum	100mg/ml	Oral solution	Chickens, Rabbits
Portugal	GLOBAL VET HEALTH SL C / Capçanes n º 12-bajos Polígono Agro-Reus 43206 Reus SPAIN	Quinoflox 100 mg / ml solução para administração na água de bebida para frangos e coelhos	Enrofloxacin	100 mg	Oral solution	Chickens (Broilers, replacement chickens, broiler breeders) and rabbits
Portugal	VETPHARMA ANIMAL HEALTH, S.L. Les Corts, 23 08028 Barcelona SPAIN	LEVOFLOK® 100 mg/ml Solução oral para frangos de carne e coelhos	Enrofloxacin	100 mg	Oral solution	Chickens (broilers), Rabbits

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
Portugal	LABORATORIOS KARIZOO, S.A. Polígono Industrial La Borda Mas Pujades, 11-12 08140 Caldes de Montbui Barcelona SPAIN	K-FLOX 100 mg/ml Solução oral para frangos de carne e coelhos	Enrofloxacin	100 mg	Oral solution	Chickens (broilers), Rabbits
Portugal	Prodivet-Zn, Nutrição e Comércio de Produtos Químicos Farmacêuticos e Cosméticos SA Av. Infante D. Henrique nº333 H 3º Piso Esc. 411800-282 Lisboa PORTUGAL	Prodirox 100 mg/ml solução oral para frangos e coelhos	Enrofloxacin	100 mg	Oral solution	Chickens (broilers), Rabbits
Portugal	VETLIMA Sociedade Distr. Produtos Agro-Pecuários LDA. Centro Empresarial da Rainha Lote 27 2050-501 Vila Nova Da Rainha PORTUGAL	VETAFLOX 100 mg/ml solução oral para frangos de engorda e coelhos	Enrofloxacin	100 mg	Oral solution	Chickens (broilers), Rabbits
United Kingdom	Global Vet Health S.L. Calle Capcanes n12 Bajos Poligono Agro-Reus 43206 Reus SPAIN	Quinoflox 100 mg/ml Solution for Use in Drinking Water, Chicken and Rabbits	Enrofloxacin	100 mg/ml	Oral solution	Chickens, Rabbits

Annex II

Scientific conclusions

Overall summary of the scientific evaluation of HIPRALONA ENRO-S and its generics intended for use in rabbits *(see Annex I)*

1. Introduction

HIPRALONA ENRO-S, and its generics, contain enrofloxacin as active ingredient, and are indicated in rabbits for the treatment of respiratory infections due to *Pasteurella multocida*. The pharmaceutical form is an oral solution administered via the drinking water. The dosage is 10 mg enrofloxacin per kg bodyweight (bw) during 5 days. Enrofloxacin is for veterinary use only.

On 30 September 2011, France initiated a referral under Article 35 of Directive 2001/82/EC, as amended, for the veterinary medicinal product HIPRALONA ENRO-S and its generics indicated for use in rabbits.

The concerns raised by France were that the use of HIPRALONA ENRO-S and its generics in rabbit production would increase *Escherichia coli* and *Staphylococcus aureus* resistance to enrofloxacin. France considered that these resistances would possibly be directly or indirectly transmitted to humans and may represent a potential serious risk to public health as enrofloxacin belongs to the fluoroquinolones family which is considered a highly critical class of antimicrobials for human health.

The CVMP was requested to give its opinion as to whether the benefit-risk ratio for HIPRALONA ENRO-S and its generics is positive when the products are administered to rabbits and whether the introduction of such highly critical antibiotics in a food production species, used via oral route, is in line with the current recommendations to implement prudent use of antimicrobials (EMEA/CVMP/SAGAM/184651/2005)[1]. The Committee was also asked to recommend whether the marketing authorisations should be maintained, varied, suspended or withdrawn.

2. Discussion

The enrofloxacin is an antimicrobial belonging to the class of fluoroquinolones, which are listed by the WHO as a critically important class of antimicrobials for human health (Critically important antimicrobials for human medicine, WHO/AGISAR, Copenhagen, 2009). It is very important that those antimicrobials are used in veterinary and human medicine according to responsible use principles to safeguard the efficacy of these substances and minimise the development of and dissemination of antimicrobial resistance.

The development of antimicrobial resistance is a risk for target animal species resulting in lack of efficacious treatment and for humans by transferring resistant bacteria from animals to humans. The evaluation of the risk related antimicrobial resistance has to consider both effects; on the target animal species and in humans.

The transfer of resistant bacteria from animals to humans may occur via consumption of meat carrying enteric zoonotic bacteria e.g. *E. coli* or by direct contact with animals, e.g. *Staph. aureus* (skin disease).

[1] 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

Available data

Efficacy in target animals

The pharmacokinetic/pharmacodynamic relationship was discussed in relation to the dosage regimens for the clinical trials provided.

The conclusion of a comparative study of plasma levels of enrofloxacin and its metabolite ciprofloxacin during treatment with the product at doses equivalent to 5 and 10 mg/kg bw of enrofloxacin administered in drinking water for 5 consecutive days was that the effective dose regimen of enrofloxacin for the treatment of respiratory infections caused by *P. multocida* in rabbits is 10 mg/kg bw. The treatment did not affect the estimated water consumption of animals (about 100 ml/kg body weight). Thus, it was possible for the animals to receive the indicated dose of antibiotic.

A second pharmacokinetic study was carried out in order to confirm the dose. The conclusion of this study was that the optimal dose for the treatment of respiratory infections caused by *P. multocida* in rabbits is 10 mg/kg bw for 5 consecutive days.

The efficacy of the product has been demonstrated in a well conducted GCP compliant trial.

A comprehensive review of the published data was provided. The data from published literature (RESAPATH annual reports) show that the sensitivity of *P. multocida* strains to enrofloxacin in rabbits was high (100% and 99% in 2009 and 2010, respectively). Unfortunately, there is insufficient information on the interpretation criteria used on the RESAPATH annual reports.

Furthermore, several studies were presented in order to address the susceptibility of different field strains of *P. multocida* to enrofloxacin. Data on susceptibility of enrofloxacin from a study conducted in Spain in 2005 showed a MIC_{90} of 0.06 µg/ml. Several MIC data on *P. multocida* isolated from clinical samples from 30 Spanish rabbit farms in 2006 and 2007 were provided. Most of the MICs obtained were above the range expected for wild-type isolates, data from EUCAST (European Committee on Antimicrobial Susceptibility Testing) indicate that the distribution of MICs of enrofloxacin for the wild type of the target pathogen, *P. multocida*, is between 0.004 and 0.03 µg/ml. Sensitivity of various strains of *P. multocida* was analysed in Spain between 2009 and 2011 and the antibiogram results showed that of a total of 61 *P. multocida* isolates all 61 strains were sensitive. In another study carried out in Spain in 2011 to address the evolution of the level of resistances the MIC_{50} and the MIC_{90} of the *P. multocida* strains examined were 0.125 and 0.380 µg/ml, respectively. Of the strains examined, 86.67% were susceptible to enrofloxacin, 10% were intermediate and 3.33% were resistant. This observed decrease of susceptibility could either be explained by methodological factors, or it could reflect a true emergence of decreased susceptibility, that could be related to the use of enrofloxacin in rabbits or other animal species.

In summary it may be concluded that today there is sufficient susceptibility to allow adequate treatment against the target animal pathogen *Pasteurella*. However, data indicates that in the long run treatment could result in a decrease of efficacy of the treatment of the disease in rabbits and thus it is important that use is limited to cases where it is clearly needed and should be combined with good husbandry practices.

Risk to public health due to spread of resistant bacteria from treated animals

Data from the RESAPATH 2009 and 2010 annual reports (French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin) were provided. From the RESAPATH annual reports, the highest susceptibility levels to enrofloxacin in *E. coli* in rabbits were 90% (2009) and 85% (2010). Regarding *S. aureus*, 89% (2009) and 82% (2010) of the bacterial isolates were susceptible to enrofloxacin. Unfortunately, there is insufficient information on the interpretation criteria used on the

RESAPATH annual reports to reach a conclusion on the trends of resistance to enrofloxacin in *E. coli* in rabbits compared to other resistance studies provided.

Horizontal and vertical resistance transmission in poultry and pigs has been studied taking into account the specific characteristic of each animal production (Petersen. A et al[2], 2006, Belloc et al[3], 2005, Lurette A. et al[4], 2009, Mathieu. A[5], 2011). The current knowledge regarding the occurrence of antimicrobial resistance in food animals and the influence of the animal production on its transmission is incomplete. Resistance transmission has not been studied specifically in rabbits.

Therefore, there are no data available to characterise the risk to public health specifically linked to intake of rabbit meat or contact with food producing rabbits.

In the absence of specific data concerning transmission of resistant bacteria from rabbits to humans, the risk analysis from other animal species where enrofloxacin is used (poultry and pigs) is extrapolated to rabbits.

In intensive reared rabbits the treatment will be of the flock and not individual animals which may increase the risk of development of resistant bacteria, this is similar to poultry production where flocks of animals are treated. The route of administration for rabbits is oral via drinking water, similar to the route of administration for poultry. The route of administration for pigs is injectable or oral. From the route of administration it can be concluded that the risk of rabbit treatment would be similar to that of poultry.

The practice of coprophagy (consumption of faeces) that is part of rabbits behaviour/physiology may hypothetically have an impact on development of antimicrobial resistance. The use of fluoroquinolones in rabbits may therefore have a higher risk on development of antimicrobial resistance, however this risk is theoretical. It should also be noted that coprophagy involves the ingestion of the own rabbit faeces and that there are no data to assess if this would have any impact on increase of resistance. In addition this process seems to be immediate which means that the overall time during which faeces of rabbits are exposed to enrofloxacin during treatment is not significantly higher than without the coprophagy practice.

Fluoroquinolones are also authorised for use in cattle, pigs and poultry. These species account for 85% of the animal (meat) production whilst e.g. rabbits only account for 0.7% of the French animal production (EMA, 2011)[6], France being one of the biggest rabbit producers in the EU. Therefore it could be considered that the use of enrofloxacin in rabbits should not significantly increase overall use of enrofloxacin in the EU when compared to its use in other animal species.

3. Benefit-Risk Assessment

Benefit assessment

HIPRALONA ENRO-S and its generics contain 100 mg enrofloxacin per ml oral solution for use in drinking water. The products are authorised for use in the target species chickens, turkeys and rabbits.

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[2] Petersen A, Christensen JP, Kuhnert P, Bisgaard M, Olsen JE, 2006. Vertical transmission of a fluoroquinolone-resistant Escherichia coli within an integrated broiler operation. Vet Microbiol. (1-3):120-8. Epub 2006 May 2.

[3] Belloc et al, 2005. Effect of quinolone treatment on selection and persistence of quinolone-resistant Escherichia coli in swine faecal flora. J. Appl. Microbiolo., 99, 954-959

[4] Lurrete. A. et al,. Sensitivity analysis to identify key parameters influencing Salmonella infection dynamics in a pig batch. 2009, May 7, 258(1):43-52. Epub 2009 Feb 6

[5] Mathieu Andraud, Nicolas Rose, Michel Laurentie, Pascal Sanders, Aurélie Le Roux, Roland Cariolet, Claire Chauvin and Eric Jouy 2011. Estimation of transmission parameters of a fluoroquinolone-resistant Escherichia coli strain between pigs in experimental conditions. Veterinary Research, 42:44 - http://www.veterinaryresearch.org/content/42/1/44/#ins1

[6] EMA document on Trends in the sales of veterinary antimicrobial agents in nine European countries (2005-2009)' (EMA/238630/2011). (2011) - http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf

The indication for rabbits is the treatment of respiratory diseases due to *P. multocida* strains susceptible to enrofloxacin.

In order to confirm the adequate dose for rabbits two studies were carried out showing that the optimal dose for the treatment of respiratory infections caused by *P. multocida* in rabbits is 10 mg/kg bw for 5 consecutive days. The safety and efficacy of the product have been demonstrated in a well conducted GCP compliant trial that fulfils the requirements of Directive 2001/82/EC and the relevant guidelines using a dose of 10 mg/kg bw for 5 consecutive days.

Risk to animals health

No specific risk to animal health was identified.

Risk for public health

There are two risks for public health identified with the use of enrofloxacin in rabbits: (i) the risk for spread of *methicillin resistant Staphylococcus aureus* (MRSA) from rabbits to people in contact with these animals and (ii) the risk of spread of resistant zoonotic bacteria and transmissible resistance genes via food, e.g. *Salmonella* and *E. coli.*

In relation to the first risk, the use of fluoroquinolones is identified as a risk factor for spread of MRSA but this would be an issue mainly in case of high prevalence of MRSA in animals and/or close contact between animals and humans. The species for which spread of MRSA would be important is therefore mainly swine (high prevalence) and companion animals (close contact). Fluoroquinolones have been authorised for use in these species for many years. With regard to intensively reared rabbits, the risk is likely to be minor in comparison with the other species due to the size of rabbits production and no measures have been deemed necessary to minimise the risk for spread of MRSA from those.

Regarding the second risk, spread of resistant zoonotic bacteria and resistance genes via food, this is a well characterised risk for which CVMP in November 2006 recommended risk mitigation measures[7]. There are no data available that would allow the Committee to estimate the risk for rabbits alone but it seems adequate to allow for the extrapolation of information from poultry and pigs.

It is anticipated that 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 less well characterised and possibly slightly higher risk as compared to other species could be acceptable in case of a minor species.

Overall benefit-risk

Taking into account the above reasoning the Committee considered that withdrawing or not authorising the use of these products in rabbit was considered not proportionate as this would create a negative impact on the availability of tools to treat respiratory diseases in this minor species, in cases when other antibiotics cannot be used or would not be sufficiently effective. Restrictions on availability of antimicrobials for rabbits may cause animal health and welfare concerns.

Furthermore, as a consequence of restriction on availability, off-label use could be anticipated and this would compromise correct monitoring of use and reporting of adverse reactions. It is acknowledged that the limited availability of authorised veterinary medicinal products containing first line antimicrobials as active substance make it difficult to comply with the responsible use recommendations for fluoroquinolones and the recommendation that it is desirable that antimicrobials

[7] 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

that are less likely to produce resistances of public health concern are used as a first option instead of fluoroquinolones.

HIPRALONA ENRO-S and its generics were involved in the referral under Article 35 of Directive 2001/82/EC for all veterinary medicinal products containing quinolones including fluoroquinolones intended for use in food-producing species (EMEA/V/A/049) and the adequate prudent use warnings were recommended for these products.

The antimicrobial prudent use recommendations and warnings that are included in the product information are as follows:

- 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 deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross resistance.

The prudent use recommendations and warnings that are listed in the product information for these products should be strictly followed and the products should not be used as a first line treatment.

Taking into account all available data it was considered that the use of HIPRALONA ENRO-S and its generics in rabbits would represent a comparable or lower risk for public health compared to the use of enrofloxacin in other animal species (e.g. poultry or pigs).

Grounds for maintaining the marketing authorisations

Whereas

- the CVMP considered whether the benefit-risk ratio for HIPRALONA ENRO-S and its generics is positive when the products are administered to rabbits and whether the use of such highly critical antibiotics in a food producing species, used via oral route, is in line with the current recommendations to implement responsible use of antimicrobials.
- on the basis of the available data on antimicrobial resistance, and taking into account the very limited data on resistance that are available in rabbit production, the CVMP considered that the use of the concerned products in rabbits would not represent a higher risk for public health when compared with use in other animals species;
- prudent use warnings for fluoroquinolones were recommended by the CVMP for the products concerned and should be strictly followed;
- no additional risk management or mitigation measures nor prohibition of enrofloxacin in rabbits was considered proportionate;
- the CVMP considered that the overall benefit-risk balance is positive for the products concerned by this procedure;

the CVMP recommended the maintenance of the marketing authorisations for the veterinary medicinal product HIPRALONA ENRO-S and its generics (see Annex I) in accordance with the previously approved product information.