Annex I

Scientific conclusions and grounds for amendment of the summary of product characteristics and package leaflet
Overall summary of the scientific evaluation of veterinary medicinal products containing (fluoro)quinolones (see annex I)

1. Introduction

Quinolones including fluoroquinolones are very potent antimicrobials used in human and veterinary medicine which have a unique mechanism of action not related to conventional antimicrobials. They are well distributed in the body after administration and are active against a wide range of microorganisms.

The older generation of quinolones were licensed for use in food producing animals at the beginning of the 1980’s and the first fluoroquinolone (enrofloxacin) during the late 1980’s and early 1990’s. Since then additional fluoroquinolone molecules have been authorised and a number of different veterinary medicines are now available on the market.

(Fluoro) quinolones for use in food-producing species have been authorised in the European Union via the national, mutual recognition and centralised procedures. The number of authorised products containing (fluoro) quinolones varies between different European Union countries. Moreover the indications for use of the products are not the same in all countries and marketing authorisations can differ between countries.

Quinolones represent a class of antimicrobials that is most important in the treatment of severe and invasive infections in humans and animals and are therefore of special interest for public and animal health.

On 15 February 2007 the CVMP adopted a “Public Statement on the use of (fluoro)quinolones in food-producing animals in the European Union: Development of Resistance and Impact on Human Health” (EMEA/SAGAM/184651/2005) concluding that the use of (fluoro)quinolones in animals has selected for resistance in animal pathogens and food borne zoonotic pathogens and that there was a need for risk management interventions. The CVMP suggested that prudent use of fluoroquinolones should be strongly promoted through recommendations in the SPC and that there was a need to harmonise the prudent use instructions in the product literature of these products. Following a focus group meeting of the CVMP with Interested Parties and Member States, the CVMP adopted a 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) detailing the precautionary phrases to be included in the Summary of the Product Characteristics, as follows:

- **Fluoroquinolone products**

  “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.”
Quinolone products1 (e.g. flumequine, oxolinic acid)

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

“Whenever possible, quinolones 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 quinolones and may decrease the effectiveness of treatment with other (fluoro) quinolones due to the potential for cross resistance.”

The implementation of the CVMP recommendations was foreseen to be achieved following voluntary action and collaboration between national authorities and industry. The last analysis in late 2008 of the success of the agreed approach showed that the CVMP recommendations had not been fully implemented yet and that further action was necessary.

In the light of the increase in bacterial resistance to antimicrobial substances, the European Council has called upon the European Commission and Member States to take steps as regards food- and animal-borne resistance to promote the prudent use of antimicrobials. Subsequently, the European Commission invoked Community interest and referred all veterinary medicinal products containing quinolones including fluoroquinolones intended for use in food-producing species to the Agency in order to ensure that the warnings on prudent use included in the Summary of the Product Characteristics for these classes of products were harmonised in line with those recommended in the CVMP Reflection paper.

The European Commission clarified on 30 July 2009 that prudent use warnings already contained in the product literature of the concerned products could be maintained even if they were not an exact reproduction of the CVMP recommendation provided that they convey the same key messages.

The referral procedure involved 696 veterinary products containing (fluoro)quinolones as identified by the Member States (see Annex I). The fluoroquinolone products concerned contain the active substances enrofloxacin, marbofloxacin, danofloxacin and difloxacin, and the quinolone products contain flumequine and oxolinic acid.

2. Discussion

Summary of Product Characteristics concerning 564 products of the 696 included in the referral were submitted by the Applicant/Marketing Authorisation Holders and competent national authorities to the CVMP for review.

In order to evaluate the situation concerning the existing prudent use warnings in the concerned products the CVMP agreed to define the following groups:

Group 1. Veterinary medicinal products containing all the correct prudent use warnings in section 4 of the SPC (Special precautions for use), exactly as the CVMP recommendation and veterinary medicinal products containing all the prudent use warnings in section 4 of the SPC, which is however not exactly the text recommended by the CVMP, but conveys the same key messages;

Group 2. Veterinary medicinal products that contain prudent use warnings in section 4 of the SPC but which do not adequately reflect the CVMP recommendations;

Group 3. Veterinary medicinal products that do not contain prudent use warnings in section 4 of the SPC

1 Not for decoquinate.
Group 4  Products for which no information was submitted by the Applicants/Marketing Authorisation Holders or competent national authorities and for which no assessment of the existing SPC warnings was therefore possible.

Further to the evaluation of all information made available to the Committee the following conclusions were made concerning the inclusion of prudent use warnings in the Summary of the Product Characteristics of the concerned products:

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Veterinary medicinal products containing all the correct prudent use warnings in section 4 of the SPC, exactly as the CVMP recommendation and Veterinary medicinal products containing all the prudent use warnings in section 4 of the SPC, which are however not exactly the text recommended by the CVMP, but conveys the same key messages</td>
<td>318</td>
</tr>
<tr>
<td>2</td>
<td>Veterinary medicinal products that contain prudent use warnings in section 4 of the SPC but which do not adequately reflect the CVMP recommendations</td>
<td>163</td>
</tr>
<tr>
<td>3</td>
<td>Veterinary medicinal products that do not contain the prudent use warnings in section 4 of the SPC</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Veterinary medicinal products for which no information was submitted by the Applicants/Marketing Authorisation Holders or competent national authorities and for which no assessment of the existing SPC warnings was therefore possible</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>696</td>
</tr>
</tbody>
</table>

The (fluoro)quinolone SPC warnings were satisfactory for 318 products, and therefore no further action needs to be taken for these products.

For 163 products the SPC warnings were not adequate because they do not contain all the prudent use warnings in section 4 of the SPC or warnings for fluoroquinolone were used instead of quinolone warnings, or vice versa. Therefore, further action is required in order to ensure that adequate prudent use warnings are included.

In addition, for 83 products no prudent use warnings are included in the Summary of the Product Characteristics and therefore further action is required in order to ensure that adequate prudent use warnings in line with the recommendations from the Committee are included.

With regard to 132 products no information was submitted by the Applicants/Marketing Authorisation Holders or competent national authorities and therefore an assessment of the concerned Summary of the Product Characteristics could not be made.

The Committee also noted that not all veterinary medicinal products containing quinolones including fluoroquinolones authorised in the EEA-EU have been included in the scope of the referral as either some products were not notified to the Agency by the competent national authorities or the information was not received on time to allow the inclusion of these products in the referral procedure.
Grounds for amendment of the summary of product characteristics and package leaflet

Whereas:

- quinolones including fluoroquinolones are critical, efficient and valuable antimicrobials for animals and for some serious animal indications, fluoroquinolones are the only effective treatment available;
- the use of (fluoro)quinolones in animals has selected for antimicrobial resistance in animal pathogens and food borne zoonotic pathogens;
- there is a need for risk management interventions regarding the use of (fluoro)quinolones for humans and animals;
- the inclusion of specific warnings in the Summary of the Product Characteristics and Package Leaflet of the concerned products is intended to encourage prudent use and help maintain the positive benefit:risk balance for (fluoro)quinolone products;
- adequate precautionary phrases related to the use of (fluoro)quinolones intended for food-producing species have been included in Summary of the Product Characteristics for 318 products concerned by this referral;
- precautionary phrases related to the use of (fluoro)quinolones intended for food-producing species have been included in Summary of the Product Characteristics for 163 products which however do not adequately reflect the CVMP recommendations;
- no precautionary phrases related to the use of (fluoro)quinolones intended for food-producing species have been included in Summary of the Product Characteristics of 83 products concerned by this referral;
- for 132 the products identified by the Member States no or insufficient information was made available to the CVMP by the Applicants/Marketing Authorisation Holders or national authorities and therefore no conclusion on the availability or assessment the adequacy of precautionary phrases in the Summary of the Product Characteristics was possible;

the Committee recommends the variation of the terms of the marketing authorisations of products containing quinolones including fluoroquinolones intended for food producing species as referred in Annex I in order to amend the Summary of the Product Characteristics and Package Leaflets in those cases where there are not in line with the CVMP Reflection Paper (EMEA/CVMP/416168/2006). The warnings to be included in the Summary of the Product Characteristics and Package Leaflet should be reviewed to reflect the text set out in Annex III.

In addition the Committee notes that the list of products in Annex I does not include all veterinary medicinal products containing quinolones including fluoroquinolones authorised in the EEA-EU, as either some products were not notified to the Agency by the competent national authorities or the information was not received in time to include these products in the current referral. However, following the adoption of the Commission’s Decision on this referral, Member States should identify and review information on the outstanding products and consider whether any action is appropriate as regards products authorised by them, and should act accordingly.
Annex II

Amendment to the summary of product characteristics and package leaflet
Amendments to be included in the relevant sections of the summary of product characteristics
A. For products listed in Annex I containing fluoroquinolones (enrofloxacin, marbofloxacin, danofloxacin and difloxacin):

4.5 Special precautions for use

i) Special precautions for use in animals

Recommendations for prudent use

“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.”

“When ever 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.”

B. For products listed in Annex I containing quinolones (flumequine, oxolinic acid):

4.5 Special precautions for use

i) Special precautions for use in animals

Recommendations for prudent use

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

“When ever possible, quinolones 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 quinolones and may decrease the effectiveness of treatment with other (fluoro)quinolones due to the potential for cross resistance.”
Amendments to be included in the relevant sections of the package leaflet
A. For products listed in Annex I containing fluoroquinolones (enrofloxacin, marbofloxacin, danofloxacin and difloxacin):

12. Special warning(s)

“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.”

B. For products listed in Annex I containing quinolones (flumequine, oxolinic acid):

12. Special warning(s)

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

“Whenever possible, quinolones 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 quinolones and may decrease the effectiveness of treatment with other (fluoro)quinolones due to the potential for cross resistance.”