Questions for CVMP

in relation to EMA's recommendations under Article 107(6) and Article 114(3)

SUBSTANCES [assessed in scientific advice under Article 114(3)]: enrofloxacin, flumequine, oxolinic acid

GROUP [assessed in scientific advice under Article 107(6)]: Quinolones (including fluoroquinolones)

ENROFLOXACIN, FLUMEQUINE and OXOLINIC ACID are widely authorised, e.g:

- In fish, for group administration via feed
- In cattle, pigs and chicken, for group administration via water.

EMA recommendation under Article 114(3)

Enrofloxacin, flumequine and oxolinic acid to be included in the list with the following condition:

- B – blanket condition ensuring the use of less environmentally hazardous substances/ routes of administration and the use in 'closed' setups, if possible.

Relevant EMA recommendations under Article 107(6)

- For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible.
- When the proposed route of administration is outside the terms of the SPC, or when using an extemporaneous formulation, the product should be administered to individual animals, only.
- Human medicinal products should be administered to individual animals, only.

Proposed set of conditions

1. **Implementing act under Article 114(3):**

- enrofloxacin, flumequine, oxolinic acid to be included in the list with the proposed condition B (blanket).

2. **Amendment of Regulation (EU) 2024/1973 to expand the scope to Article 114:**

- not to restrict the use of enrofloxacin, flumequine, oxolinic acid to individual animals only.
- to impose condition B (blanket) to the use of extemporaneous VMPs containing the three substances.

Rationale

- The VMPs authorised for fish are already being used in groups by virtue of their marketing authorisations.
- The scientific advice under Article 107(6) does not recommend restricting the use of the three substances to individual food-producing aquatic animals except for the use cases below: a route of administration different form the one covered by the terms of the marketing authorisation of VMPs, medicinal products for human use, extemporaneous products.

- The VMPs authorised for food-producing aquatic animals are outside the scope of Article 114(3) and are to be used outside the terms of their marketing authorisations in groups of food-producing aquatic animals, without any condition mitigating the environmental exposure.
- The VMPs authorised for food-producing terrestrial species or medicinal products for human use will be used in food-producing aquatic animals only where the VMPs authorised for such animals are not available.
- The scientific advice under Article 114(3) concludes that if the three substances cannot be used in groups of animals the impact on animal health is considered high.
- Condition B (blanket) is understood to mitigate not only environmental risks but also AMR risks by minimising the exposure. To mitigate risks and for consistency in the use of each substance, condition B (blanket) should also apply to extemporaneous VMPs containing the three substances.

Questions for the CVMP

1. Would the proposed set of conditions (see above) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of enrofloxacin, flumequine and oxolinic acid under Article 114(1)(b) and (c)?
2. In the negative, what conditions would be recommended?

SUBSTANCES [assessed in scientific advice under Article 114(3)]: difloxacin

GROUP [assessed in scientific advice under Article 107(6)]: Quinolones (including fluoroquinolones)

DIFLOXACIN: Authorised for group administration in water in chicken and turkeys

EMA recommendation under Article 114(3)

Difloxacin to be included in the list with the following conditions:

- B – blanket condition ensuring the use of less environmentally hazardous substances/ routes of administration and the use in 'closed' setups, if possible.

Relevant EMA recommendations under Article 107(6)

- For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible.
- When the proposed route of administration is outside the terms of the SPC, or when using an extemporaneous formulation, the product should be administered to individual animals, only.
- Human medicinal products should be administered to individual animals, only.

Proposed set of conditions

1. **Implementing act under Article 114(3):**
   - difloxacin to be included in the list with the proposed condition B (blanket).
2. **Amendment of Regulation (EU) 2024/1973 to expand the scope to Article 114:**
   - not to restrict the use of difloxacin to individual animals only.
   - to impose condition B (blanket) to the use of extemporaneous VMPs containing difloxacin.

Rationale

- Difloxacin is authorised for group administration in water in food-producing terrestrial species (chickens and turkeys), only turkeys considered limited market.
- In accordance with Commission Implementing Regulation (EU) (EU) 2024/1973, the difloxacin-containing VMP can also be administered via water to groups of any other food-producing terrestrial animal species under Article 113(1)(a).
- The scientific advice under Article 114(3) concludes that difloxacin is needed to treat or prevent infectious diseases, for which there is lack of availability of other treatments or measures in food-producing aquatic species, and if difloxacin cannot be used in groups of animals the impact on animal health is considered high.
- Condition B (blanket) is understood to mitigate not only environmental risks but also AMR risks by minimising environmental exposure to microbiologically active effluent. To mitigate risks and for consistency in the use of difloxacin, condition B (blanket) should also apply to extemporaneous VMPs containing difloxacin.
- The total biomass of finfish in the EU represents 0.52% of the total biomass of food-producing animals, while chicken represent 18.64% of the total biomass of food-producing animals in the EU.

Questions for the CVMP

1. Would the proposed set of conditions (see above) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of difloxacin under Article 114(1)(b) and (c)?
2. In the negative, what conditions would be recommended?

SUBSTANCES [assessed in scientific advice under Article 114(3)]: danofloxacin and marbofloxacin

GROUP [assessed in scientific advice under Article 107(6)]: Quinolones (including fluoroquinolones)

DANOFLOXACIN: authorised for injection in cattle and pigs

MARBOFLOXACIN: Authorised for injection in cattle and in pigs

EMA recommendation under Article 114(3)

Danofloxacin and marbofloxacin to be included in the list with the following conditions:

- B – blanket condition ensuring the use of less environmentally hazardous substances/ routes of administration and the use in 'closed' setups, if possible.

Relevant EMA recommendations under Article 107(6)

- For those indications not included in the SPC of the concerned product, use must be based on target pathogen identification and antimicrobial susceptibility testing that demonstrates that (fluoro)quinolones are likely to be effective and that antimicrobials from a lower AMEG category would not be effective, unless it can be justified that this is not possible.
- When the proposed route of administration is outside the terms of the SPC, or when using an extemporaneous formulation, the product should be administered to individual animals, only.
- Human medicinal products should be administered to individual animals, only.

Proposed set of conditions

1. **Implementing act under Article 114(3):**
   - danofloxacin and marbofloxacin to be included in the list with:
     - condition B (blanket) and
     - condition S (use restricted to individual animals only).
2. **Amendment of Regulation (EU) 2024/1973 to expand the scope to Article 114:**
   - the restrictions to use in individual animals only, which, by virtue of Commission Implementing Regulation (EU) 2024/1973, are currently applicable to the use of *Quinolones (including Fluoroquinolones*) under Articles 112 and 113 of Regulation (EU) 2019/6, to apply also to the uses of danofloxacin and marbofloxacin under Article 114.

Rationale

- Danofloxacin and marbofloxacin are authorised for individual administration only.
- It is understood that the extent of additional exposure (and associated AMR risks) due to group administration under Article 114(1)(b) and (c) can be relatively big. Therefore, the restrictions to use in individual animals only, which are currently applicable to *Quinolones (including Fluoroquinolones)*, should apply also to the uses of danofloxacin and marbofloxacin under Article 114.
- The scientific advice under Article 107(6) when assessing AMR risks related to the use in aquaculture seems to have considered mainly 'open' aquaculture systems.
- Condition B (blanket) is understood to mitigate not only environmental risks but also AMR risks by

minimising the exposure.

- It is understood that the treatment of individual food-producing aquatic animals will likely take place in 'closed' setups where the effluent can be confined and controlled and consequently, environmental exposure to microbiologically active effluent is likely to be limited.
- The scientific advice under Article 114(3) concludes that danofloxacin and marbofloxacin are needed to treat or prevent infectious diseases, for which there is lack of availability of other treatments or measures in food-producing aquatic species, and if danofloxacin and marbofloxacin cannot be used in groups of animals the impact on animal health is considered high.

Questions for the CVMP

1. If other quinolones (difloxacin, enrofloxacin, flumequine, oxolinic acid) were to be included in the list under Article 114(3) without restriction to be used only in individual food-producing aquatic animals, would you consider that restricting the use of marbofloxacin and danofloxacin under Article 114(1)(b) and (c) only to individual food-producing aquatic animals no longer has a high impact on animal health?
2. In the negative, what would be recommended?

SUBSTANCE [assessed in scientific advice under Article 114(3)]: cefoperazone, cefquinome, ceftiofur

GROUP [assessed in scientific advice under Article 107(6)]: 3rd- & 4th-generation cephalosporins

EMA recommendations under Article 114(3)	**Relevant EMA recommendation under Article 107(6)**
Cefoperazone, cefquinome, ceftiofur to be included in the list with the following conditions: • B – blanket condition ensuring the use of less environmentally hazardous substances/ routes of administration and the use in 'closed' setups, if possible, • S – use restricted to individual animals only, • C – not to be used in combination with BLI	• 3rd- and 4th-generation cephalosporins not to be used in food-producing aquaculture.

Proposed set of conditions

1. **Implementing act under Article 114(3):**
   - cefoperazone, cefquinome, ceftiofur to be included in the list with:
     - condition B (blanket) and
     - condition S (use restricted to individual animals only).
2. **Amendment of Commission Implementing Regulation (EU) 2024/1973 to expand the scope to Article 114:**
   - 3rd- and 4th-generation cephalosporins to be allowed for use only in individual food-producing aquatic animals.
   - to specify that the conditions in Commission Implementing Regulation (EU) 2024/1973 are without prejudice to the conditions laid down in the implementing act under Article 114(3).
   - to explain in the recitals that the conditions imposed by the various regulations, such as Commission Implementing Regulation (EU) 2022/1255, should be seen as cumulative/complementary.
3. **Commission Implementing Regulation (EU) 2022/1255 already prohibits the use in all animals of cefoperazone, cefquinome, ceftiofur in combination with beta-lactamase inhibitors.**

Rationale

- For food-producing terrestrial species, cefoperazone, cefquinome and ceftiofur are authorised for individual use only.
- The scientific advice under Article 114(3) recommends allowing use in individual food-producing aquatic animals only.
- The scientific advice under Article 107(6), when assessing AMR risks related to the use in aquaculture, seems to have considered mainly 'open' aquaculture systems.
- Condition B (blanket) is understood to mitigate not only environmental risks but also AMR risks by minimising the exposure.
- It is understood that the treatment of individual food-producing aquatic animals will likely take place in 'closed' setups where the effluent can be confined and controlled and consequently, environmental exposure to microbiologically active effluent is likely to be limited.
- The scientific advice under Article 114(3) concludes that cefoperazone, cefquinome, ceftiofur are needed to treat or prevent infectious disease, for which there is lack of availability of other

treatments or measures in food-producing aquatic species.

Questions for the CVMP

1. Would the proposed set of conditions (see above) satisfactorily mitigate the risks to animal or public health from AMR, as identified in the scientific advice under Article 107(6), associated with the use of cefoperazone, cefquinome and ceftiofur under Article 114(1)(b) and (c)?
2. In the negative, what conditions would be recommended?