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Opinion of the Committee for Medicinal Products for Veterinary Use pursuant to Article 30(3) of Regulation (EC) No 726/2004

On the risk to vultures and other necrophagous bird populations in the European Union in connection with the use of veterinary medicinal products containing the substance diclofenac

Basis for opinion

On 12 August 2014, the European Commission presented to the European Medicines Agency ('the Agency') a request for an opinion from the Committee for Medicinal Products for Veterinary Use, on a scientific matter concerning the risks to vultures and other necrophagous bird populations in the European Union in connection with the use of veterinary medicinal products containing the substance diclofenac, in accordance with Article 30(3) of Regulation (EC) No 726/2004.

In the European Union diclofenac, a non-steroidal anti-inflammatory substance, has been authorised for veterinary use since 1993 in Italy for cattle and pigs, and for horses not intended for human consumption. Since 2009 veterinary medicinal products containing diclofenac are authorised in a limited number of Member States. Following the national authorisation in 2013 of two veterinary medicinal products containing diclofenac (Dolofenac and Diclovet, respectively) by the Spanish competent authority, conservation organisations, members of the public and politicians wrote to the European Commission expressing their reservations on the risks that these products may represent to vultures and other necrophagous bird populations.

These concerns arose as a result of the decline of the vulture population in South East Asia following the use of diclofenac to treat livestock in this region in the 1990s. Vultures were exposed to it by scavenging on livestock carcasses, and consequently died as a result of diclofenac-induced kidney failure.

The dramatic decline in vulture populations, which was estimated to be more than 95%, led in 2006 to the prohibition of the sale of veterinary medicinal products containing diclofenac in India, Nepal, Pakistan and Bangladesh by the respective governments, while encouraging the development of safer alternatives and the use of substances that are less toxic to necrophagous birds.

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In the scientific opinion, the Committee was requested to address the following points:

- The risk that the use of veterinary medicinal products authorised in the Union containing the substance diclofenac may represent to vultures and to other necrophagous birds in the Union, taking into account the EU rules on animal by-products;
- If a risk is identified, any actions or mitigation measures that could be implemented to manage effectively the risk.

The procedure started on 10 September 2014.

Opinion

The Committee, having considered the matter, reviewed data from published literature, answers provided by stakeholders during the public consultation including data received from the marketing authorisation holders, information from the presentations that the Committee received from Fatro S.p.A, Fatro Ibérica S.L. and BirdLife International, and personal communications, came to the following conclusions:

The Committee confirmed that vultures and other necrophagous birds in the European Union may be at risk due to residues of diclofenac if they feed on carcasses of animals that have been treated with this medicine. In the European Union, there are two main scenarios in which necrophagous bird species can become exposed to diclofenac residues:

A. Exposure at feeding stations (place where animal by-products and/or carcasses of domestic livestock or wild mammals are put out for vultures and other scavengers).

- *A.1 Ingestion of animal by-products from slaughterhouses*
- *A.2 Ingestion of animals that have died from natural causes and are taken directly to feeding stations*

B. Exposure through fallen stock (animals that die in open pastures from natural causes and are left in fields to be disposed by vultures and other necrophagous birds and wild mammals).

In relation to the two main routes of exposure of necrophagous birds to diclofenac used in veterinary medicinal products in the European Union the following was considered in respect to the risk to vultures and other necrophagous bird populations in connection with the use of veterinary medicinal products containing the substance diclofenac:

- All populations of birds that display a necrophagous feeding behaviour in the European Union have been considered species of concern and fall within the scope of the assessment. The Oriental white-rumped vulture (*Gyps bengalensis*) has been chosen as the model organism for the risk assessment given that laboratory and field toxicity data are available for this species.
- As many of the species considered at risk from veterinary medicines containing diclofenac are included in the International Union for the Conservation of Nature Red List of Threatened Species, and also considering their reproductive strategy, the level of protection for the risk assessment has been established at the individual level (i.e. probability of death of a single individual). This is the common methodology adopted internationally for assessing environmental risk to endangered species.
- The assessment of the risks to vultures and other necrophagous birds from the use of veterinary medicinal products containing diclofenac, as a result of ingesting carcasses containing diclofenac

residues in feeding stations, or through fallen stock in pastures, is not a standard environmental risk assessment. Given that the CVMP guidelines for the assessment of environmental risks cannot be used for this particular environmental risk assessment, and in the absence of suitable default parameters, the Committee decided to apply an *ad-hoc* approach by identifying the most suitable species to use as a model organism for the assessment, as well as determining the most adequate inter- and intraspecies extrapolation factors based on expert judgement.

- Based on laboratory and field toxicity data from the Oriental white-rumped vulture and considering its feeding patterns, the maximum concentration of residues of diclofenac in tissues to ensure the safety of vultures and other necrophagous birds has been assessed to be 3 µg/kg.
- After the recommended three day treatment of pigs and cattle with veterinary medicinal products containing diclofenac, the highest residue concentrations are found in injection sites. Residue concentrations in tissues and in the injection site decline to below 3 µg/kg after 9 and 10 days for pigs and cattle, respectively. These conclusions are based on data from cattle weighing below 200 kg and pigs below 60 kg, and having no overlapping injection sites.
- The withdrawal periods for diclofenac products are 12 days for pigs and 15 days for cattle.

Based on the above the risk to vultures and other necrophagous birds from the use of veterinary medicinal products containing the substance diclofenac has been assessed as follows:

A. Exposure at feeding stations:

A.1. Ingestion of animal by-products from slaughterhouses

No risk to vultures and other necrophagous birds is identified from their feeding in stations supplied by animal by-products from slaughterhouses. Animals sent to slaughterhouses are intended for human consumption and therefore their withdrawal periods after being treated have to comply with those indicated in the SPC. For pigs and cattle the withdrawal periods are 12 and 15 days, respectively. Taking into account residue data, after 9 days for pigs and 10 days for cattle, diclofenac residue levels in animal by-products are below 3 µg/kg, the concentration established as safe and therefore considered not to pose a risk to vultures and other necrophagous birds if they are consumed.

A.2. Ingestion of animals that have died from natural causes and are taken directly to feeding stations

A risk to vultures and other necrophagous birds is identified if feeding in stations supplied by animals that have died from natural causes and are taken directly (by farmers) to feeding stations. In principle, the conditions that are treated with diclofenac are unlikely to lead to death. However, diclofenac can also be used in young animals for respiratory infections as a complimentary treatment to an antibacterial, and consequently the risk of mortality after treatment of these animals might be higher. These carcasses may be left in the field or be taken to a carcass dump by the farmer to avoid higher disposal costs. As a result the CVMP considers that in this scenario further regulatory action (e.g. additional risk management measures) are needed to ensure that necrophagous bird populations are not at risk if feeding from animals in feeding stations that are not coming from slaughterhouses. Also, non-food producing horses are generally categorised as farm animals and their carcasses might be taken to feeding stations. For older horses diclofenac might be used for palliative purposes, and thus with a higher risk of mortality.

B. Exposure through fallen stock:

A risk to vultures and other necrophagous birds is identified from their feeding on fallen stock in open pastures. A risk would exist in situations where extensively reared animals are treated with veterinary

medicinal products containing diclofenac and die in the field, or get lost and subsequently die shortly after treatment, in which case a vulture might spot the carcass before it is discovered by the owner. Some extensive producing farms can be authorised to leave dead animals in the field for the consumption of carrion birds. Animals that are kept in pastures are considered less likely to be treated with diclofenac given that the pathologies diclofenac is prescribed for are not common for animals under this farming practice. Moreover, conditions intended to be treated with diclofenac are unlikely to lead to death. In addition, the dosing regimen of the products, which requires injecting the animal on three consecutive days, is not very practical in free grazing animals. This would contribute to the infrequent use of veterinary medicinal products containing diclofenac in extensive farming conditions, and thus reduce the risk from exposure of necrophagous birds to toxic levels of diclofenac residues in fallen stock in the field. It is worth noting that common practice seems to indicate that when animals are sick, they are predominantly contained in pens rather than being treated and being left on pastures, as the treatment and the follow up of the condition of the animals would not be feasible to monitor in large open spaces. Based on the information provided by the marketing authorisation holders, approximately 10% of diclofenac is used for animals in extensive pastures. Although the risk through fallen stock is considered low, the Committee considers that additional regulatory action is needed (e.g. risk management measures) for this scenario.

Consequently, the Committee is of the opinion that based on field and laboratory data available from the Oriental white-rumped vulture, and residue data for cattle and pigs available from the marketing authorisation holders, a risk is identified for necrophagous birds feeding on carcasses of livestock that have been treated with diclofenac.

The crucial point in the assessment is whether it is likely that necrophagous birds in the European Union will be exposed to animal carcasses within 10 days (or longer) after treatment with diclofenac. Evidence of exposure in the European Union is lacking at the moment, given that no pharmacovigilance reports or any other type of communication is available that would indicate that a vulture in the European Union has been exposed or died as a result of feeding on carcasses from food-producing animals treated with diclofenac. This is a major data gap for the Committee's conclusions.

There are two exposure scenarios from the three identified above where a risk has been identified for vultures and other necrophagous birds (feeding stations from non-slaughterhouse material (A.2) and fallen stock (B)). Hence, the CVMP considers that for these two scenarios further regulatory action is needed (e.g. implementation of additional risk management measures).

Based on available peer reviewed data, the CVMP acknowledges that modelling studies have indicated that less than 1% of contaminated carcasses were needed in India to trigger the collapse of the vulture populations. Whether this value would be the same for the European populations is unknown, but this estimate is the result from considering a group feeding behaviour typical for European and Indian populations of vulture species.

The Committee considered a wide range of risk management measures (see Annex I) and discussed their practicalities and impact. The Committee was not in a position to evaluate the effectiveness of all of the proposed measures as several of them cannot be quantified at present or do not fall within the remit of the CVMP. Therefore, it was not possible to make a recommendation at this stage on which of them would be most appropriate.

In conclusion, the Committee is of the opinion that additional risk management measures are needed and efforts should focus on determining the most suitable and effective ones to ensure that contaminated carcasses do not end up in the food chain of vultures and other necrophagous birds.

The Icelandic and the Norwegian CVMP members agree with the above-mentioned recommendation of the CVMP.

This opinion is forwarded to all Member States, Iceland, Norway and to the European Commission together with its annex and appendix.

The opinion will be published on the Agency website with its annex and appendix.

London, 11 December 2014

Dr A. Holm,
Chair, on behalf of the CVMP

Appendix 1: CVMP assessment report

Annex I

Summary of considered risk management measures

Proposed risk management measure	CVMP considerations
Information to veterinarians	• The product might only be supplied with a veterinarian prescription. • Veterinarians should be knowledgeable about the risks of the product to necrophagous birds to ensure no exposure of vultures to carcasses from treated animals containing diclofenac residues. • Information should be transferred to the animal owners, as once the animal is medicated the fate of the carcass will not be under the control of the veterinarian.
Warnings in the product literature	• The SPC and package leaflet, which are addressed to the veterinarian and animal holder (farmer), respectively, should contain highlighted warnings indicating the desired protection, and restriction of use. Contraindications for extensive pasture animals could be considered. Additionally, horses not intended for human consumption are likely to end up in a feeding station, and this should be reflected. • Given that all current authorisations are by the national procedure, the national authorities would be responsible to implement this measure.
Change in the administration pattern of the VMP	• Exclusive administration of the product by the veterinarian (not only under his/her supervision) to prevent that animals at risk of being consumed by vultures receive treatment. • The veterinarian would have to visit the animal daily for 3-5 days. • Alternatively, only the exact dosage for the treatment could be kept in the farm for its administration by the farmer under veterinary supervision. • It is recognised that once the animal is medicated the fate of the carcass will not be under the control of the veterinarian.
Changes in the food chain information	• FCI[1] should contain additional information specifying if the animal has been treated with diclofenac during ts life. • The content of the FCI, detailed in EU legislation, should be amended. • It might be possible to involve the farm veterinarian by making it compulsory for him to issue the FCI instead of the farmer.

[1] FCI: Food chain information, as described in Regulation 853/2004 is a document that the farm operator has to fill in and sign in order to guarantee an adequate public health protection.

Proposed risk management measure	CVMP considerations
	• Slaughterhouse operators should be informed that if the withdrawal period of the animal has not been respected, the animal cannot be taken to a feeding station.
Increase controls in farms intentionally leaving dead animals in the field	• The Regulations 1069/2009 and 142/2011 allow farmers to leave fallen stock on fields • The farms that can do this have to meet certain requirements and have to be authorised to do so by the competent authorities. • As these farms are known and controlled, it would be a good measure to increase the frequency of controls in these farms and the checks of the farm book looking for the use of diclofenac. • Contraindications for extensive pasture animals could be considered. Additionally, horses not intended for human consumption are likely to end up in a feeding station, and this should be reflected as well.
Accompanying of document for by-products	• A new document can be developed to be prepared by the farmer (when supply was direct from the farm) or slaughterhouse operator (when supply was from the slaughterhouse) and to make it available to the responsible person/body in charge of the feeding station, which states that the by-products dispatched come from animals not treated with diclofenac. • This information could also be used to trace back the origin of the by-products in order to apply corrective actions if necessary.
Sampling scheme	• It would not be feasible to sample all the material used to feed necrophagous birds, but developing a sampling scheme with statistical purposes would be useful for detecting an eventual breach of the protocols and for applying the necessary corrective actions. • The information provided by this scheme would be able to provide a firm indication on whether exposure is likely and to predict its extent. • The sampling scheme could be included as a condition on the marketing authorisation of VMPs containing diclofenac, leaving the marketing authorisation holder to bear the costs, at least partly.
Withdraw diclofenac products from the EU market	• This measure would ensure a negligible risk. However, exposure under the 'cascade' by parenteral human medicinal products containing diclofenac might still be possible. • This measure would negatively affect the availability of medicines, however animal welfare will not be affected as alternatives are available. • The toxiciy of most other NSAIDs to negrophageous birds is unknown and the risk of their use cannot be estimated.

Proposed risk management measure	CVMP considerations
	• Up to now it has been clearly proven that diclofenac represents a potential threat to necrophagous birds, however no cases of diclofenac-related deaths of necrophagous birds have been reported so far in the European Union. • A withdrawal of the marketing authorisation should be based on a benefit/risk analysis. It should be considered that there is a limited availability of active substances for the relief of inflammation and pain.