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***Diclofenac* in Europe – current situation, legal aspects, potential impacts and required actions**

February 2014

Executive summary

Veterinary *diclofenac* kills vultures and caused a dramatic (99%) and rapid decline in the vultures in the Indian subcontinent – significant effort has been spent to successfully ban the marketing of this drug in that region, as non-toxic alternatives exist.

The appearance of this drug in Europe – it is now legally on sale in Spain and Italy – represents a new and significant threat to the European vulture populations, and creates a precedent that can have global impact on the world's vultures.

The Vulture Conservation Foundation (VCF), BirdLife International, the Royal Society for the Protection of Birds, SEO/BirdLife and the IUCN Vulture Specialist Group ask now the EU and members states to take decisive action to ban this veterinary drug, by initiating a referral procedure.

Introduction

Diclofenac is a non-steroid anti-inflammatory drug (NSAID) whose veterinary use has been the main cause of the catastrophic decline of several species of vultures in South Asia, due to its extreme toxicity to this group of wild scavengers (see below). BirdLife International has been leading an initiative to ban its sale and use in that part of the world, and to recover the now almost depleted vulture populations ([see here](#)). This represents a global priority in terms of nature conservation and locally represents a serious health issue as well.

In spring 2013 the Spanish Agency for Medicines (AEM) approved two products containing *diclofenac* to be used on pigs and bovine cattle. The information was released in August 2013. SEO/BirdLife started coordinating in September with the biodiversity department at the Spanish Ministry of Agriculture and Environment in order to get information from AEM. It now clear that the drug is available for sale in at least two EU Member States.



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The marketing of this veterinary drug in Europe not only represents an immediate and tangible threat to European vulture populations, but also sets a very dangerous precedent and an alternative channel for the veterinary use of the drug in Africa and Asia, which could have much wider consequences. This situation is starting to have repercussion in the scientific circles (Margalida *et al.* 2014, Camina *et al.*, submitted).

The VCF, BirdLife International, the Royal Society for the Protection of Birds, SEO/BirdLife and the IUCN Vulture Specialist Group are calling for an immediate ban the legal sale of veterinary *diclofenac* in the EU.

This technical brief summarizes all the known information about this threat, and lists the necessary steps that will need to be taken to prevent a catastrophic decline of all European species.

Impact of *diclofenac* on vultures – the known science

Until the mid-1990s, tens of millions of vultures occurred in the Indian subcontinent. Now less than 1% of them remain. Population declines in of vultures in India over the period between the 1992 and 2007 ranged between 97.5% and 99.9%, depending on the species (Prakash *et al.* 2012).

These declines are attributable to unintentional poisoning from *diclofenac*. Old world vulture species (mainly, but not only, *Gyps* spp.) have been shown to die from kidney failure within a few days of eating tissues of cattle treated with a veterinary dose of *diclofenac* shortly before death (Oaks *et al.* 2004, Swan *et al.* 2006, Green *et al.* 2006).

Diclofenac causes kidney necrosis in vultures, leading to reduced excretion of uric acid and the deposition of uric acid crystals in tissues. Death usually occurs within two days (Pain *et al.*, 2008).

Population models developed for the Indian case have shown that less than 1% of cattle carcasses available to vultures would need to contain a lethal level of *diclofenac* to account for the observed rapid rates of decline in vultures (Green *et al.* 2004). Measurements of the concentration of *diclofenac* in large samples of cattle carcasses in India shows that the actual level of contamination of the vulture food supply was more than sufficient to account entirely for the decline (Green *et al.* 2007).



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Once *diclofenac* was established as the main cause of the dramatic vulture decline, BirdLife International, together with other conservation NGOs, worked together with the governments of India, Pakistan and Nepal towards banning the sale of veterinary formulations of *diclofenac* in the region. This was finally achieved in 2006, with stronger regulations being added in 2008. Bangladesh banned veterinary *diclofenac* in 2010.

Contamination by *diclofenac* of cattle carcasses in India declined by over two-thirds between the announcement of the ban and 2010. Vulture population declines have at least slowed and most populations assessed are either stable or increasing slowly, though surviving populations are very low. These changes are similar in India, Nepal and Pakistan (Prakash *et al.* 2012, Chaudhry *et al.* 2012).

Diclofenac continues to be used illegally for veterinary purposes in the Indian sub-continent, and dead vultures containing *diclofenac* residues are still found. The main source is now illegal use of human formulations of the drug for veterinary purposes and the packaging of human *diclofenac* in large vials, convenient for the treatment of large ungulates. This is something that the conservation community is currently lobbying to prevent with a ban as a highest priority.

A vulture-safe alternative drug, *meloxicam*, has been identified and tested on vultures and a range of other bird species (Swan *et al.* 2006b; Swarup *et al.* 2007). Another non-steroidal anti-inflammatory drug, *ketoprofen*, has been shown to be toxic to vultures and there are indications that other drugs, such as *aceclofenac* and *flunixin* are also likely to be toxic. Restrictions are desirable on the veterinary use of these drugs, and others whose safety to vultures has not been established, in countries where wild vultures occur.

Considerable efforts have also been made to prevent veterinary *diclofenac* being licensed in Africa, where large vulture populations still occur. These have been largely successful so far. It was mistakenly assumed that veterinary use of *diclofenac* was unlikely in Europe, except in very limited circumstances such as race-horses, where carcasses of treated animals were unlikely to be available to scavengers.



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Vultures in Europe – food, distribution, numbers and importance.

Out of the 16 species of old-world vultures, 4 occur regularly and breed in Europe: the globally Endangered Egyptian Vulture (*Neophron percnopterus*), the globally Near-Threatened Cinereous Vulture (*Aegypius monachus*), and the globally Least Concern Griffon Vulture (*Gyps fulvus*) and Bearded Vulture (*Gypaetus barbatus*).

Until recently a relatively discreet region for global vulture numbers, when compared with the vulture rich landscapes of southern Asia and Africa, Europe is now probably the continent in the old world with most vultures, in absolute numbers, as the vulture populations in South Asia have collapsed totally (see above), while Africa is now facing an unprecedented and large-scale vulture decline due to widespread poisoning (Botha *et al.*, 2012). On the contrary, in Europe three of the four species (only exception is the Egyptian vulture) have been increasing steadily (see Annex V), partly due to the intensive conservation effort funded by European Union budget lines – since 1996 the EU, and national governments, have invested significant financial resources for the conservation of vultures, and there has been at least 67 LIFE projects related with these species – only between 2008 and 2012 9 vulture conservation projects alone received 10.7 million Euro ([see here](#)).

The Iberian Peninsula, France and Italy include the bulk of the European vulture populations (BirdLife International 2004, see also Annex V).

Critical and key to vulture conservation in Europe is Spain – precisely one of the two counties now selling legally *diclofenac*. With more than 70,000 griffon vultures (90% of the European population), 5,000 cinereous vultures (97% of the European population), 3,000 Egyptian vultures (85% of the European population) and 300 bearded vultures (67% of the European population), Spain is the most important country on the continent for these species – and for some of them (e.g griffon and cinereous vulture) the most important country in the world. It is also the key country to secure a sustainable recovery of vulture populations across Europe – the healthy populations in Spain have been supporting, through normal dispersion, or through human-induced reintroduction and restocking projects with Spanish-origin birds, the recovery of griffon and cinereous vultures in France, Italy, and all the way to the Balkans (e.g. restocking of the griffon population in Bulgaria with Spanish birds, funded by the EU).



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Italy also plays a critical role in vulture conservation in Europe – for once, the reintroduced bearded vulture alpine population relies a lot on the Italian Alps, and Italy is key to restoring the migration flow and connect the increasing and healthy vulture populations in western Europe with the small and struggling eastern Europe/Balkan populations.

Vultures are mostly obligate carrion eaters. For centuries, particularly in Spain, vultures adapted to eat mostly the carcasses of free-ranging domestic livestock that were traditionally left in the fields, or in special places called *muladares*. The relevance of vultures for safe, cheap and natural disposal of livestock carcasses has been recognized in the most recent EU Animal byproducts regulation (CE 142/2011), which includes specific authorizations for managing “carrion-dumps” and leaving carcasses in nature, in areas frequented by vultures

This regulation, adopted in Spain since 2011 with a number of provisions, includes:

- The definition of Protection Areas for feeding scavenger species of Community interest. In these areas, where scavenger birds are already present, extensively grown animals could be placed (except if they die of infectious diseases).
- The establishment of carrion-dump sites (*muladares*) where animals produced intensively can be disposed, with certain conditions: if they die because of disease, specified risk materials (SRM) should be removed, and for certain death causes, the whole animal should be incinerated. The dump-sites are locked enclosures and the items disposed should also be controlled.

Vultures forage over very large areas, with birds often looking for food hundreds of kilometers from their breeding colonies. Immature vultures also disperse widely, with many griffon and black vultures from Spain going to France and the Alps, and vice versa.

Due to their food habits, vultures perform an important and unique ecological function: they prevent the spread of disease and outcompete stray dogs, reducing the costs associated with the collection and disposal of carcasses from the fields, thus also significantly reducing the emissions of greenhouse gases. The cost to Indian society of the collapse of vulture populations there was estimated at 34 billion US dollars (Markandya *et al.* 2008).



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Diclofenac in Europe

Veterinary *diclofenac* does not have a central marketing approval from the European Medicines Agency (EMA), but has received from the relevant national authorities legal permits for commercialization in at least two EU countries, Italy and Spain. It is also being exported from Italy to a number of other EU and non EU countries.

Italy

In Italy, veterinary *diclofenac* is commercialised by FATRO S.p.A. (Via Emilia, 285 Ozzano Emilia, Bologna), under the name Reuflogin, in 4 different vials, all with a concentration of *diclofenac* of 50 mg/ml:

- 20 ml - A.I.C (Codice di Autorizzazione all'Immissione in Commercio, or permit for commercialisation) n. 101597019;
- 50 ml - A.I.C. n. 101597021;
- 100 ml - A.I.C. n. 101597058;
- pedro250 ml - A.I.C. n. 101597060.

The authorisation to commercialise veterinary *diclofenac* in Italy dates, apparently, from the 1990s, but in February 2002 the Italian government banned its use following an opinion from the Committee for Veterinary Medicinal Products from the European Agency for the Evaluation of Medicinal Products on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMA/CVMP/187/00-FINAL) (note 187/00 FINAL adopted 10 January 2001) ([see here](#)). This ban was due to the new risk assessment guidelines, regarding consumers' safety ([see here](#)).

In July 2002 this ban was revoked to authorise the sale of *diclofenac* only for horses used in sports competitions ([see here](#))

In December 2009 the Italian authorities authorised further its use for bovine and porcine animals, and established the time periods before human consumption of treated animals is permitted ([see here](#)), but still banned it for bovine cattle producing milk for human consumption.

In September 2010, the authorities lifted the ban for bovine cattle producing milk for human consumption, and established minimum time periods before milk consumption can be resumed ([see here](#)). In summary, today Reuflogin is legally available for sale in Italy for horses, cattle and pigs, in 4 different packages/vial sizes.

Spain



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In Spain veterinary *diclofenac* is marketed under two brand names, Diclovet, and Dolofenac, both registered by FATRO Iberica SL, (Constitución 1, planta baja 3, 08960 Sant Just Desvern, Barcelona), and destined for use in bovines, pigs, and horses not destined for human consumption. Both formulations are produced in vials of 50, 100 and 250ml, with 50mg of *diclofenac* per ml. Recommended use is via intramuscular injection. Both drugs need veterinary prescriptions, and should be administered under the supervision of a veterinarian. Only Dolofenac is currently commercialised.

Dolofenac and Diclovet were first authorised for sale on the 20th March 2013 (permits 2759 ESP and 2760 ESP, respectively).

Nowhere, both in the summary of the characteristics of the veterinary drug (“Resumen de las características del producto, see Annex I and II), and on the risk assessment report (“Informe de evaluación públicamente disponible para un medicamento veterinario” – see Annexes III and IV), is mentioned the well-known impact on vultures. On the contrary, on page 4 of the risk assessments, it is written that “the drug is safe for the people administering it, for the consumers of animal products from treated animals, and for the environment, when recommendations are used”.

No pharmacological, toxicological or residues studies were done for these veterinary drugs as part of the risk assessment, because according to Spanish legislation (article 7 of the *Real Decreto* 1246/2008 of 18 July), this is not necessary when the drug is for a bioequivalent of a generic medicine with reference values established.

In relation to ecotoxicity, the manufacturer has only presented a phase I report, which dismissed the need for a phase II report, according to directive CVMP/VICH/592/98 ([see here](#)).

General conclusion of the risk assessments is that “the risk-benefit profile for the target species is favourable, and that the quality and biosecurity of the drug for humans and the environment is acceptable”. No mention of their well-known impact on vultures is made. The usual procedures involved in an environmental risk assessment do not involve scavenging, but since the effects of *diclofenac* on vultures are well known, this and other NSAIDs should always be evaluated against secondary poisoning by scavenger birds.

Follow interviews with several veterinarians in Spain, it is obvious that the risks are real and large. According to veterinarians, this drug will be particularly used to treat MMA (mastitis-metritis-agalactia syndrome) on lactating females, or respiratory diseases.



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In Spain, which has tens of thousands of intensive cattle and swine farms, carrion disposal is not always strictly enforced. Further, although vulture feeding stations are controlled strictly under the new EU sanitary regulations (CE 142/2011), carcasses are not tested for diclofenac, which would be prohibitively expensive. There are also some vulture dumps being operated illegally or in a semi-clandestine way, without strict controls. The probability that a *diclofenac*-treated carcass will be consumed by vultures is therefore important.

Wider EU, other countries

The EMA has not given any centralised marketing authorisation for veterinary *diclofenac* in Europe, nor are there any “mutual recognition” mechanisms in place for veterinary *diclofenac*. The EMA has only set Maximum Residue Limits in bovine and porcine species. Current national permits legalising the sale of veterinary *diclofenac* followed a decentralised (national) procedure.

Under Directive 2001/82/EC, an effective risk assessment has to be made for all veterinary drugs, including a proper evaluation of their effects on the environment.

It should also be noted that FATRO Italy has exported Reuflogin to other EU and non-EU countries. In particular, there is evidence that FATRO exported Reuflogin to Czech Republic (since 1997, only available for horses), Estonia (for horses, cattle and pigs) and to Latvia (since 2008, only for racing horses). Outside the EU, Reuflogin was also exported to Serbia, and also to Turkey (until 2013), where the drug was sold under the name Diklomet by Vestas ([see here](#))

Potential impact of *diclofenac* on vultures in Europe and elsewhere

Considering the proven impacts of *diclofenac* on vultures, the feeding habits of European vultures, the distribution and the status of vultures in Europe, and the legal sale of veterinary *diclofenac* in Italy and Spain, it is clear that what we have here is an immensely risky situation – key European vulture populations (mostly Spain, but also Italy) feeding on domestic carcasses that now have the potential to contain veterinary *diclofenac*. The consequences could be catastrophic, similar to what has happened in India.



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It is obvious that it is impossible to guarantee that *diclofenac*-treated cattle roaming the countryside in the extensive operations will not be available to vultures in case they die. Equally, it will be virtually impossible to identify and remove the possibility that *diclofenac*-treated carcasses are not included in the tons of meat given every week to vultures in the legal carrion dumps. *Diclofenac* treats a vast series of common inflammatory diseases and ailments that do not require special restrictions or quarantine. Also, *diclofenac* has a relatively long breakdown time in animals ([see EMA report](#)). Animals that were treated with *diclofenac* and die within the withdrawal period need to be discarded – and are quite likely to end up in carrion dumps in areas with vultures. Further, there is also in Spain an unknown number of uncontrolled carrion-dumps.

Considering the widespread contact between vultures and carcasses of domestic livestock in Spain (with benefits for public health through a quick removal of carcasses), it is likely that sooner or later vultures will contact with a *diclofenac*-treated dead animal. Even a small number of carcasses with *diclofenac* can have a significant impact on vulture populations, in wide area – given the nature and ecology of the species, threats do not have a local, rather a regional impact, as vultures travel and forage far and wide. A *diclofenac*-laced carcass can impact on vultures from a neighbouring region, or even country.

Further, if European countries license *diclofenac* for veterinary use, this may be seen as a precedent for countries in Asia and Africa to follow. Achieving the bans across South Asia and preventing the licensing in Africa has been a major achievement of the conservation movement, but the fact that it had never been allowed in Europe or North America was an important element in that process. In addition, the likelihood that neighbouring countries may purchase the drug from Europe and introduce them in veterinary practice is of major concern, and avoidable when safe alternatives are available.



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Our demands: Complete ban

Given the above, the VCF, BirdLife International, the Royal Society for the Protection of Birds, SEO/BirdLife and the IUCN Vulture Specialist Group are asking for a complete ban of the use of *diclofenac* and *aceclofenac* (the latter not yet marketed, but due to its high toxicity also a potential threat). Veterinary use of *diclofenac* in Europe will not only pose risks to the vulture populations here, but also set a dangerous precedent and encourage further use of the drug in Africa and Asia.

The case here is clear – it is really a question of learning from what happened in India, and also upholding and being coherent with the leading role of many EU policies, notably on nature conservation. Decades and millions of Euros have been spent protecting Europe's vultures. We should now not let all of them disappear.

In case of risks to the environment or human health, Member States and/or the Commission can launch a Referral procedure to eventually ban a certain drug. Under the Referral procedure, the Commission asks the European Medicines Agency in London for a scientific opinion, which is followed by a decision of the Commission.

We are therefore asking the EU and/or member states to start a Referral procedure to reevaluate the legal permits to sell and use veterinary *diclofenac* in Europe. We argue that the risk assessment legally required have not taken in consideration the well-proven effects on vultures, and that the risks of a vulture collapse in Europe far outweigh the benefits, particularly when there are alternatives drugs that can be used for the same treatments.

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