EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<08.10.2014>

Public consultation regarding the request to the European Medicines Agency from the European Commission for a scientific opinion regarding the risks to vultures and other necrophagous bird populations in the Union in connection with the use of veterinary medicinal products containing the substance diclofenac

Template for comments[1]

Comments to be provided by 10 October 2014

Comments from:

Name of organisation or individual
Vulture Conservation Foundation

VCF
VULTURE CONSERVATION FOUNDATION

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received. Supporting documentation which has been provided together with the comments will not be published.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

[1] For further information see the original request

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Comments on Topic 1

Procedure of feeding vultures and other necrophagous birds species with animal by-products in and outside feeding stations and measures put in place to mitigate risks related to the potential for the by-products to contain residues of veterinary medicines.

In replying to this request from the EC, the CVMP welcomes comments and information from concerned stakeholders.

Comment

Introduction

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* Bearded Vulture (*Gypaetus barbatus*), and the globally Least Concern Griffon Vulture (*Gyps fulvus*).

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, 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 , 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). Several vulture reintroduction projects have also been happening in Europe, notably the reintroduction of the bearded vulture in the Alps (successful, with 30 pairs now breeding in the wild, in one of the most celebrated wildlife comeback stories of our times), in Grands Causses (France) and in Andalusia (Spain). The estimated cost to "produce" a bearded vulture for reintroduction has been put at 70-80,000€ (Frey, 1998) Considering that in the last few years between 9 and 13 birds are released per year in the three on-going bearded vulture reintroduction projects, the yearly costs of bearded vulture reintroduction (not even considering the monitoring) is 650,000-900,000€. Further, black vultures are also being reintroduced in France (with already a very successful wild population established), and griffon vultures in several places in Europe (France, Italy, Bulgaria). All in all, hundreds of millions of Euros have been spent on vulture conservation in Europe in the last 3 decades.

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The Iberian Peninsula, France and Italy include the bulk of the European vulture populations (VCF data). **Vulture populations in Spain and Italy** Veterinary diclofenac has been made commercially available in two key Vulture countries. Spain: 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) (VCF data), 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 birds of Spanish-origin, several vulture conservation projects in Europe. Italy: Italy has a small and decreasing population of Egyptian vultures in the south (8 pairs in 2012), a small but increasing population of griffon vultures (92 breeding pairs in 2012 across the country, from Sardinia and Sicily to the Abruzzi and the Alps), and a successfully re-established bearded vulture population (9 territorial pairs, of which 5 started breeding in 2014, fledging 3 young). Italy is also key to restoring the migration flow and connecting the increasing and healthy vulture populations in Western Europe with the small and struggling Eastern Europe/Balkan populations. While Italy has important vulture populations and is a vital connecting country, Spain is no doubt the key in this issue of vultures and diclofenac. **Vulture population feeding and legislative framework (in Europe & in Spain)** In general, vultures in Europe benefited from traditional livestock practices that included abandoning dead animals in the fields. The first sanitation laws forbidding the abandonment of carcasses in the field were approved in Spain in the 1950s, but these were not enforced and implemented (Donázar et al. 2009a), and throughout the 20th century vultures in general could find lots of food in the fields, particularly in countries or regions with extensive livestock systems (southwest Iberia, mountains), and an ages old tradition of leaving carcasses of dead animals in “muladares”. Many of these *muladares* also started to receive carcasses from local intensive livestock farms. In 2000, the appearance of bovine spongiform encephalopathy (BSEs) brought about strict EU legislation (CE 1774/2002) aimed at the elimination of all animal by-products in the fields. As a consequence, state and regional administrations enforced measures requiring farmers to remove or destroy all the remains of dead livestock. This led to the closure of many vulture feeding station and *muladares* (in Spain in 2006/2007) (Donázar et al., 2010) This inevitably led to a sudden scarcity of once plentiful food, and triggered a change in the foraging behaviour and population of vultures. Faced with a

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reduced supply of carcasses, vultures moved to exploit garbage dumps for example (a lower-quality food source) (Donázar et al. 2010). The sudden closure of these feeding stations and *muladares*, in combination with other human-related threats, such as poisoning and wind-farms, caused a decline on the number of breeding pairs by c. 24%, adult survival by 30% and fecundity by 35% (data for *Gyps fulvus*), as well as an increase in the number of birds entering rehabilitation centers (Martínez-Abraín et al., 2011).

In 2009, following lobbying by conservation organisations, and recognising the value and role that vultures play in the ecosystem, the EU has introduced a new regulation (EC No 1069/2009) allowing for the reopening of the vulture feeding stations or *muladares*, listing a number of exceptions to the compulsory collection of carcasses, directed at supplementing food for scavenging birds in dedicated places. However, carcasses in the fields were still subject of enforced collection.

Later, 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)[2], which includes specific authorizations for leaving carcasses in nature, in areas frequented by vultures. This regulation has already been transposed to national law in Spain (Real Decreto 1632/2011), and adopted already in 10 Spanish autonomous regions. It includes a number if provisions:

- The definition of Protection Areas for birds of prey and/or feeding scavenger species of Community interest. In these areas, where scavenger birds are already present, some free-ranging animals don't need to be recovered when dead and therefore might be available for vultures (except if they die of infectious diseases). Exact definition of what can be left out in the fields varies in different autonomous region, depending mostly on endemic infectious diseases.
- The establishment of carrion-dump sites (*muladares*) for birds of prey and/or feeding scavengers where intensive indoor or free-ranging farmed animals can be disposed, with certain conditions. Some specified risk materials (SRM) are still forbidden, as it is the deposition of animals that died because of certain specified diseases (in this case the whole animal should still be incinerated). The dump-sites are locked enclosures and subject to a certain degree of control, and often receive lots of animal by-products and carcasses from intensive explorations. There are at least 199 official vulture feeding points in Spain, but it is also known that there exist a reasonable number of “illegal” (i.e. not approved) ones.
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Patterns of vulture foraging and feeding in nature

It is generally considered that domestic livestock constitute more than half of the biomass eaten by vultures in Europe. The exact figure varies from country to country, and from species to species, but it is generally accepted that domestic livestock are a significant proportion of what vultures eat in Europe.

[2] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:054:0001:0254:EN:PDF

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It is also relevant to note that vultures in general, and griffon vultures in particular, identify and start to feed on carcasses very soon after animals die in the fields or are deposited in vulture feeding stations – on average 31 minutes after death/deposition (Cortés-Avizanda et al. 2012, Duriez et al. 2012). So there is solid evidence that vultures prefer to feed mostly immediately after the death of an animal.

In Spain, and elsewhere in Europe, vultures feed mostly on two types of situations

1) Using carcasses and other animal products made available to them in registered and custom-built vulture feeding stations
2) Finding carcasses of dead animals in the field in a more natural foraging and feeding pattern (with more unpredictability, both temporal and spatial) (Monsarrat et al. 2013).

Vultures use more or less feeding stations depending on the location, the season and number of these in a specific area, and also the availability of "natural" (in the fields) carcasses. Patterns are extremely variable and cannot easily be characterised – in some regions with lots of feeding stations some vultures feed almost exclusively on feeding stations, in other places with no or few feeding stations they feed mostly on carcasses in the fields. Further, some vultures feed on feeding stations during some part of the year (e.g. in the Spanish pre-Pyrenees where they bred) and may migrate to areas with no or few feeding stations in another season (ex. Extremadura and southern Portugal, where they spend the winter, or Central Pyrenees in summer with extensive livestock farming), making the overall situation rather fluid and variable.

In Spain alone there are at least 199 authorized feeding stations, and these vary greatly in size and management. Some are run by local government, some by local NGOs, others by individuals (e.g. farmers and hunters) – some receive many hundreds of kilos of meat-animal by-products every week, others limited amounts more irregularly – again, the situation here is very diverse.

The format of meat disposal is also very diverse – in some cases whole carcasses are dumped, while in others only parts of carcasses (bones, organs, viscera, etc.) are given. Again, a very diverse and wide ranging situation.

In Spain, the Ministry of Agriculture and Environment (MAGRAMA) keeps a register of all carcasses (and in some cases parts of carcasses) transferred to official and recognized vulture feeding stations. According to their data, the following are sent to vulture feeding stations across the country in one year:
345 carcass-equivalents of cattle

38,413 carcass-equivalents of intensive-reared pork

259 carcass-equivalents of horses

(sheep and goats are not mentioned here because they are not susceptible to be treated with veterinary diclofenac – but please note that given the convenience of administration, veterinary diclofenac would appear to be a very convenient Non-steroid anti-inflammatory drug to be administered by shepherds without veterinary supervision!).

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(Data taken from the Spanish government report "Análisis del riesgo de uso de medicamentos veterinarios con diclofenaco sobre las populaciones de buitres en España – recomendaciones de actuación y escenarios potenciales de afección", July 2014, MAGRAMA (Direcciones Generales de Calidad y Evaluación Ambiental y Medio Natural (DGCEAMN), Sanidad de la Producción Agraria (DGSPP)) and the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)). These numbers are certainly underestimated, as our experience suggests that not all apportions are logged in. But even considering these as a good estimation of order of magnitude, **we can see that as an absolute minimum circa 40,000 cows/pigs/horses are deposited in vulture feeding stations across Spain per year**. Regarding carcasses left out in the fields, according to MAGRAMA´s own data, based on the official census of the livestock in the country, the average mortality rate, and the data from the companies that collect carcasses from the fields (from 2011), the estimation of number of carcasses left in the fields is the following: 7,365 free ranging cattle 18,881 free ranging pork (sheep and goats are not mentioned here because they are not susceptible to be treated with veterinary diclofenac) Data taken from the Spanish government report "Análisis del riesgo de uso de medicamentos veterinarios con diclofenaco sobre las populaciones de buitres en España – recomendaciones de actuación y escenarios potenciales de afección", July 2014, MAGRAMA (Direcciones Generales de Calidad y Evaluación Ambiental y Medio Natural (DGCEAMN), Sanidad de la Producción Agraria (DGSPP)) and the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)). This is likely to be a gross underestimates as this data is from 2011, when the sanitary regulation was not yet transposed and the collection of carcasses was supposedly enforced everywhere. Now that it is actually allowed, the number of carcasses left out in the fields is certainly considerably higher, but this estimate gives us an **order of magnitude for carcasses of free ranging cattle and pork available to vultures per year in Spain – circa 30,000**. There is solid scientific evidence that **almost all of the carcasses that are left out in the fields (i.e. not collected) are consumed by vultures where these occur**- Cortés-Avizanda et al. 2012 has suggested that 89,1% of carcasses observed registered vultures coming to feed. **We are therefore talking about an absolute minimum of 70,000 carcasses of cattle, pork and horses consumed by vultures in Spain, both in vulture feeding restaurants and in the fields**. This is certainly a lot of carcasses to control for presence of veterinary diclofenac!

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In Italy too many tens of thousands of animals are left to die in the fields every year. According to the Banca Dati Nazionale dell'Anagrafe Zootecnica (BDN), between October 2013 and September 2014 at least 19,000 heads of animals were lost/unaccounted for (see table 1 below). Interesting, the Italian database also points out to another potential problem with livestock that will make effective control extremely difficult – stealing! In the last year, more than 9,000 heads of livestock in Italy have been stolen, and thus eventually slaughtered without proper control . Italy does not have the vulture populations that live in Spain, and many of these lost heads would not be consumed by vultures, but these figures serve to show **that hundreds of thousands of livestock carcasses are left out in the fields across Europe every year** – this increases the risk that a few of them do include some toxic levels of diclofenac.

DATI AL 1/10/14 SUI 12 MESI PRECEDENTI	NUMERO ALLEVAMENTI BOVINI E BUFALINI IN CUI SONO AVVENUTI FURTI/SMARRIMENTI	NUMERO CAPI OGGETTO DI FURTO/SMARRIMENTO	- di cui oggetto di FURTO STOLEN	- di cui oggetto di FURTO/SMARRIMENTO Stolen/lost	- di cui oggetto di SMARRIMENTO LOST
PIEMONTE	175	382	207	1	174
VALLE D'AOSTA	33	42	3	38	1
LOMBARDIA	158	605	230	0	375
TRENTINO PROVINCIA TRENTO	9	9	0	1	8
VENETO	65	178	178	0	0
FRIULI	21	45	20	8	17
LIGURIA	78	175	74	3	98
EMILIA ROMAGNA	177	475	180	31	264
TOSCANA	171	505	249	10	246
UMBRIA	152	336	147	12	177
MARCHE	79	206	3	29	174
LAZIO	824	2972	801	78	2093
ABRUZZO	216	1001	584	0	417
MOLISE	127	304	206	0	98

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CAMPANIA	702	1784	485	63	1236
PUGLIA	622	2265	784	46	1435
BASILICATA	282	893	17	2	874
CALABRIA	1376	3789	1736	348	1705
SICILIA	2965	9442	2603	264	6575
SARDEGNA	676	4273	868	142	3263
TOTALE ITALIA	**8908**	**29681**	**9375**	**1076**	**19230**

Day to day operations of vulture feeding stations

Our practical experience in the field, coming from many years of observations and management of vulture feeding stations, suggests that currently there is no individual veterinary control over every single animal coming in to the vulture feeding stations. Crucially, veterinary control and monitoring, and decisions on what to send to the vulture feeding stations, are separate in time and done by different people, so the risk that a treated animal with veterinary diclofenac reaches the vulture feeding chain is real and exists.

While all industrial exploitations sending carcasses to vulture feeding stations need to be registered and are controlled by veterinarians, the day to day decisions to send animals or parts of animals to the local vulture feeding station is often done by farmhands and/or slaughterhouses. Theoretically, there are ways to prevent this (strict isolation of all animals treated with veterinary diclofenac), but this would certainly entail significant costs for the livestock farmer, that may be unrealistic (see below).

Below you can find a simple description of three typical vulture feeding stations, illustrating the scale of the issue

Case study 1

Feeding station in NE Italy run by local NGO. Feeding station used by 200+ griffon vultures, some black vultures that have started to summer in the Alps, and more irregularly by Egyptian vultures. Details are available on request.

On table 2 below you can see the total apportions of meat to that feeding stations last year. Pigs is from intensive pork farms, bovine mostly from intensive cattle farms, but includes some rests from slaughterhouses.

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2013	Roe Deer		Red Deer		Wild Boar		Pigs		Bovine	Other
	Kg	N°	Kg	N°	Kg	N°	Kg	N°	Kg	Kg
January	230	11	670	9	200	2	1470	21	250	20
February	620	30	1020	15	500	6	720	10		
March	660	37	1590	22	120	2	940	12		60
April	1690	89	2490	45	150	3	870	12		20
May	580	35	180	2	110	2	3660	55		
June	95	7	270	4	40	4	5370	86		
July	530	41	340	5	210	4	3682	43	245	5
August	295	22	280	2	175	5	3350	53		15
Septemeber	260	16	50	1	30	1	3520	58	760	15
October	270	18	550	5	250	4	1790	42	700	
November	290	17	460	5	530	8	1600	21		
December	1095	49	770	8	530	13	480	10		
TOT	**6615**	**372**	**8670**	**123**	**2845**	**54**	**27452**	**423**	**1955**	**135**

In Italy, all farmers must have a REGISTER where they have to write all the medicines used. In theory all dead animals treated with veterinary drugs must be destroyed after death. While carcasses of Category 1 animals (potentially subject to Bovine Spongiformis Encephalopathy) must be checked by a veterinarian first and only then destroyed, animals of category 2 (pigs, horses), that have died and were being treated, can be destroyed from the farmer but there is no direct veterinary control.

So in this case, if any of those pigs from industrial explorations that usually supply the feeding station had been treated with diclofenac, and died, the only

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way to prevent it from entering the vulture food chain would be for the farmer to identify treated animals, isolate them and destroy the carcasses without giving them to the feeding station. **Case study 2** Feeding station in Southwest Spain run by a regional government. Details available on request. Feeding station used by hundreds, sometimes 1000 griffon vultures that breed nearby, some black vultures in dispersion-winter, and a few of the reintroduced nearby bearded vultures. Data for 2013 – average of 1,600 kg of meat and animal byproducts deposited every month, mostly pigs from intensive farms. All carcasses and animal byproducts deposited come from slaughterhouses, and are thus animals that in principle are suitable for human consumption. However, there is no routine diclofenac analysis being done in Spain, so levels of diclofenac on those carcasses unknown. Decision on what goes to the vulture feeding station is often taken by slaughthouse staff. **Case study 3** Feeding station in the Pyrenees run by conservation foundation. Details available on request. Feeding station used by 250-300 griffon vultures that breed nearby, 10 Egyptian vultures, 20-25 red kites, 30 black kites and 2 pairs of bearded vultures. Data for 2013 – A total 104 depositions (approximately 2 every week) were made, totalling 15,600 kg, all parts of sheep, goats and cows (including viscera), from the local slaughterhouse. The animals there are subject to the normal veterinarian control for human consumption, but again diclofenac is not specifically tested for. Viscera and other animal parts are usually gathered in common pile and then given to the foundation staff that take it to the vulture feeding station. **Day to day operations of extensive systems** The recent report prepared by Spanish government agencies to evaluate the risk of veterinary diclofenac to vultures in Spain suggests that “in extensive systems it is expected that this type of veterinary agents usage is almost zero, because livestock suffers less from this type of diseases, and has much less management”. With an absence of detailed data on usage of veterinary diclofenac in Spain, it is impossible to assume that free ranging cattle are not treated with veterinary diclofenac in Spain – on the contrary, the precaution principle would recommend we do consider it may be used. In this case, and unless treated animals are permanently confined, it is virtually impossible to guarantee that a treated animal may not be available to vultures if it dies in the fields. Griffons usually eat 90% of dead carcasses, and they reach normally less than 1 hour after death, often well before the farmer. Our experience from the field suggests that often shepherds and farm hands administer anti-inflammatory medicines ad-hoc when they detect some of the

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ailments. Please note that in many extensive systems animals are still stabled during some periods (night/season). **Risk-assessments done** The general risk assessment for veterinary diclofenac in Spain were done by the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), that has concluded 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 (See Green et al. 2004; Green et al. 2006; Prakash et al. 2012 for well documented and dramatic impact on Indian vultures) is ever made in the risk assessments. 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". 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). The authority responsible for its control in Spain (AEMPS) has not carried any pharmacological, toxicological or residues studies for the drug's impact on scavenging species. This is so 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. There is, for the case of the Spanish products, a simple statement in its technical dossier stating "do not administer to animals susceptible to enter wild animals food chain". Given the known effects of *diclofenac* on vultures and the major depletion of their population caused by this drug in Asia, the eco-toxicity of this and other NSAIDs should always be strictly evaluated. **Potential Measures to mitigate risks from veterinary diclofenac** First, it must be noted that there are currently no measures in place to test the presence of diclofenac in tissues of dead animals. Neither the Spanish drug-alert system (VIGIAVET) nor its European equivalent (EUDRAVIGILANCE VETERINARIA) have ever registered an alert for intoxication of vultures by this drug. There is therefore no system in place to routinely detect veterinary diclofenac in tissues of animal by-products. Further, testing for diclofenac is very expensive, and can be done only in handful of laboratories – none in Spain. Given all the above, and in order to minimize the risks from veterinary diclofenac to vultures, this would require a complex set of additional controls and practices that are not only extremely expensive, but counterproductive, complex and not necessary – given that there is an alternative readily available, equally cheap, and with the same therapeutic properties (Meloxicam, Swan et al 2006). In order to minimise risk to vultures if veterinary diclofenac is

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allowed to continue to be marketed across Europe one would need, as an absolute minimum, to

- Establish a system to routinely test tissues of animals for this drug, within the EUDRAVIGILANCE VETERINARIA programme framework. Analysis for veterinary diclofenac are expensive.
- Establish additional control mechanisms in all livestock explorations. This would need to secure that all extensive livestock treated with diclofenac should be isolated and kept indoors for at least 7 days (and not 2 as the MAGRAMA report suggests – see below) after treatment; and that in the intensive operations cattle and pork treated with veterinary diclofenac should also be separated from the rest, controlled regularly by a veterinarian, and not sent to the vulture feeding stations in case of mortality
- In case any of the diclofenac treated animal dies, the carcass should be collected by a specialized company and destroyed, so as not to enter the vulture food chain, with all the corresponding costs.

These are also the measures identified in the Spanish government report published recently (page 7).

These measures entail considerable costs, regulation and red tape. Given the proven and dramatic impact on vultures (see also below), the status of vultures in Europe, the considerable investment done so far for their protection, and the existence of a generic, similar and readily available alternative, our opinion is that **these potential measures that would need to be set up and enforced to minimise risk are too costly, complicated and unnecessary**.

It should also be taken into account that in most counties in southern Europe, including Spain and in Italy, the current austerity policies have resulted in severe budgetary cuts that have significantly reduced the capacity of the regional governments, public veterinary agencies, and enforcement agents to monitor and enforce legislation and regulations across the country.

Further, there are lots of examples suggesting that even **the most strict veterinary controls are not 100% failsafe because somewhere, sometime, someone will fail the rules**. The recent spread of African Swine in Latvia has been linked to the illegal disposal of offal in the forest from an authorized slaughterhouse, even though a strict system was in place to prevent this situation happening (Vittorio Guberti, pers. comm.).

We thus need to choose between implementing more measures and regulations that are expensive, complicated, and add up to the red tape, and that are not 100% effective 100% of the time, to try to minimise proven risks to vultures, or to simply ban the drug, when an alternative that is equally cheap, readily available and with the same therapeutic properties exist (Meloxicam – see Swarup et al. 2007).

Precedent and possibility of expansion to other markets

Finally, one aspect often overlooked but very important. The EU is often regarded as the leader in civilization-setting procedures and principles, that often

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have a significant influence and impact elsewhere in the world as principles, laws and regulations are considered best practice and examples to follow. Legalising the use veterinary diclofenac would send the signal to others that it is ok to use it – also probably creating an export market from Europe to other regions. We all know that control systems and procedures elsewhere are substantially weaker than in Europe, so even if billions of Euros were spent in setting up the new mechanisms described above in the EU, these would not certainly be followed through in other places, where veterinary diclofenac could continue to kill/start to kill vultures. **Availability of diclofenac in Europe would mean worldwide availability, with significant impacts on vultures everywhere**.

Comments on Topic 2

Depletion of diclofenac residues in food-producing species.

In replying to this request from the EC, the CVMP welcomes comments and information from concerned stakeholders.

Comment

Depletion of diclofenac residues in food producing species

We have data on *diclofenac* depletion for Indian cattle (*Bos indicus*) and goat (*Capra hircus*) (Taggart et al. 2006). The EMA has data on *diclofenac* depletion for European cattle (*Bos taurus*) and pig (*Sus scrofa*) (EMAE 2004 *diclofenac* summary report). Both studies followed similar methods. A key difference, however, between the two is the dose of *diclofenac* given to the two species of cattle. Specifically, we used 1 mg/kg doses while the EMA used 2.5 mg/kg doses. The dose used by the EMA is the recommended dose per day for veterinary diclofenac.

Disposition of residues of Diclofenac in Indian cattle (*Bos indicus*) Cmax (1.0mg/kg i.m., (= recommended dose in India) 4.0 microgram/ml at tmax 0.5 hours post inj.. Tissue levels at 20h: 30 -1000 microgram/kg in muscle, liver, intestine and kidney, etc. time course of data similar to those published in EMEA documentation for 2.5 mg/kg in *Bos taurus* see below (Taggart et al. 2007). In *Bos taurus* EMEA Summary Report (2004) cattle dosed with 14C diclofenac, 2.5mg/kg i.m. daily for 3 days sacrificed at 3 days post appl. had 0.623, 0.324, and 0.04mg equivalents per kg in liver, kidney and fat, respectively. In non-radiometric depletion studies performed in European calves dosed with 6x 2.5mg/kg (=recommended dose in Europe) resulted in tissue concentrations 3h p.appl. of 3.7, 2.6 ,0.43 and 0.19 mg/kg of diclofenac (incl. 2 major hydroxymeta-bolites) in liver, kidney, skin &f at and muscle, respectively.

In both studies (Taggart & EMEA), *diclofenac* depleted from the cattle species slower than from the smaller-bodied animals (e.g. *diclofenac* was undetectable in goats after 26 hours). The Taggart study results show that *diclofenac* concentration was detectable after 167 hours (~7 days) in cattle viscera. The true concentration of *diclofenac* in this tissue was below our level of quantification at 10 µg/kg. The EMA results show that *diclofenac* was detectable after 144h

Comment
(6 days) in cattle liver 27 µg/kg and muscle 5 µg/kg. The experiment conducted by Oaks et al. (2004) shows that a dose as low as 7 µg/kg can kill an Oriental white backed vulture (*Gyps bengalensis*; there is no reason to think that Eurasian griffon (*Gyps fulvus*) would differ greatly from this response given it too is intolerable to low concentrations of diclofenac). In addition, among the carcasses of cattle that are being sampled in India, some that have been found that were treated with double the recommended dose (see Taggart et al. 2006). Larger doses would increase the time need for *diclofenac* depletion. It is possible that *diclofenac* will be misused in this way in Europe, just as it is in India. **Therefore, cattle tissue may be lethal to vultures for more than 1 week after *diclofenac* treatment – and not, like the recent report published by the Spanish governments suggests, only 48 hours**. This is why the SAVE programme in India uses cattle that have lived longer than 10 days in their care at Vulture Safe Feeding Sites in Nepal; to ensure that they have metabolise all *diclofenac* that they may have been treated with. In Europe, withdrawal periods of greater than 10 days for cattle should ensure *diclofenac* is sufficiently depleted for vulture consumption as well. But vultures can consume carcasses of animals not for human consumption, like horses (Spain). These animals can be slaughtered without prior withdrawal periods. Further, we do not know the time needed for *diclofenac* depletion in horses, but it is likely to be greater in these larger-bodied animals. There are two obvious problems associated with withdrawal periods in general: 1) it is up to the livestock owner to adhere to withdrawal periods; and 2) what happens to animal products that are found to be within the withdrawal period. Despite good regulation, Europe laws are not immune to human cheating. How is a livestock owner found to be breaching the withdrawal period? Either through checking veterinary logbooks, which can be fudged, or tissue sampling, which leads to tissues requiring disposal. Where do scraps from dodgy carcasses and tissue that fail maximum residue level tests end up? Are these supplied to feeding stations and dumped in *muladares*? Withdrawal periods are designed to protect humans, not vultures. We reiterate, only a very small proportion of carcasses contaminated with *diclofenac* can cause massive declines in vulture populations. In this way, a more precautionary approach is needed to protect Europe's vulture that simple relying on measures designed to protect humans. **Summary data on the toxicity of diclofenac in vultures** Studies performed in European Griffon Vultures & African White-backed Vultures (Swan et al. 2006) calculated LD50 values (the dose at which half of the vultures die) at 0.098 to 0.225 mg p.o.. **In other words, half of the average Griffon vultures will die after ingesting less than 1 mg diclofenac**. These data are consistent with results from similar studies in Indian *Gyps*-species: Oriental White-back-, Long-billed-, Slender-billed and also Himalayan Vultures (Oaks et al. 2004, Das et al. 2010). In mice, rats, dogs, rabbits and guinea pigs LD50s range between 95 and 1300 mg/kg about 3 log steps higher! (EMEA Summary Report 2004). Reasons for that unusual increase in toxicity to vultures are somewhat elusive. There is, however, evidence that diclofenac

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metabolism will result in reactive metabolites that can interfere with MRPs and urate transporters, thus causing irreversible damage of proximal tubular cells and irreversible toxicity of a single dose of diclofenac. The NOEL in those acute studies was as low as 30 micrograms/kg (References can be provided on request). So far no repeated dose data/study chronic toxicity data have been available! The EMEA data demonstrate tissue concentrations in liver of 623, 1040 and 150 microgram equivalents at 3, 7 and 14 days following 2.5mg/kg i.m /day for 3 days. Those data would indicate significant risk for a *Gyps*-vulture on days 3 and 7. An oriental White-backed Vulture, weighing about 4.75kg on an average (Del Hoyo et al. 1994) will eat some 1.02 kg every 3 days. If it ate the liver of one of the calves mentioned above, it would take up some 0.8mg/kg, which is 4 to 8 times the LD50 mentioned above. Though those figures would represent a worst case scenario, they clearly demonstrate the risk of diclofenac ingestion for vultures. European Griffon Vultures, that weigh 7,4 kg (Cramp 1998, Donázar 1993) can eat 1,2 kg of meat in a single meal (Donázar 1993). Given the unusually high toxicity to vultures, calculations published by Green et al. (2004) suggest that a prevalence of 0.13 to 0.75% of critically (i.e. containing an LD50 in one meal) contaminated cattle carcasses would suffice to fully explain the observed vulture declines in India. **In other words, the modelling done suggest that in India, 1 in 1000 carcasses containing a lethal concentration diclofenac is enough for a significant decline of >5% per year!** Needless to say that a chick fed with contaminated food by its parent will die as well. Due to the social feeding behavior of those gregarious vulture species, hundreds of individuals may be killed by ONE critically contaminated carcass. Though there have been no toxicology studies in Egyptian Vultures or Red Headed vultures, population dynamics resemble those of Indian *Gyps*-species, and thus it has been suggested that diclofenac is also toxic to them (Chaudry et al. 2012). This would be very relevant for the Egyptian vulture, a globally endangered species which has in Spain one of its global strongholds. Further, recent evidence surfaced that some steppe eagles (*Aquila rapax*) also died in India because of veterinary diclofenac (Sharma et al, 2014). The authors of this finding suggest that other closely related eagles such as the Spanish Imperial Eagle (*Aquila adalberti*) or the golden eagle (*Aquila chrysaetus*), both partial scavengers, could also be affected.

Comments on Topic 3

Use of veterinary medicinal products containing diclofenac in the field – which species are treated and how often? What measures are taken to ensure that necrophagous birds are not exposed to residues of diclofenac in treated animals either through feeding stations or inadvertent exposure (e.g. death of treated animals in regions where necrophagous birds are present)?

In replying to this request from the EC, the CVMP welcomes comments and information from concerned stakeholders.

Comment

VCF
Vulture Conservation Foundation

Which species are treated and how often

In Spain veterinary *diclofenac* is marketed under two brand names, Diclovet, and Dolofenac, (registered by FATRO Iberica SL). In Italy, Italy, veterinary *diclofenac* is commercialised under the name Reuflogi. (registered by FATRO S.p.A).

The drug is marketed to treat MMA (mastitis-metritis-agalactia syndrome) on lactating females, respiratory diseases (bronchopneumonia) and pathologies of the muscle-skeleton (tendinitis, myositis, arthritis), on cattle and pigs (destined for human consumption) and horses (not destined for human consumption).

It is administered by intramuscular injection, even though with horses it can also be administered by intravenous injection. It should be administered only with veterinary prescription, and by the veterinarian or under the supervision of the veterinarian.

Posology suggested requires inoculation of three doses in three consecutive days.

Both Diclovet and Dolofenac have already a warning in the technical fiche that “it should not be administered in animals that have the potential to enter wildlife food chains”.

While veterinary diclofenac is not indicated for sheep and goats, this does not necessarily mean that sheep or goats are not subject to diclofenac medication! Given the convenience of administration, veterinary diclofenac would appear to be a very convenient NSAID to be administered by shepherds, if they got the drug for other animals.

Comment

How much diclofenac has been sold in Spain & in Italy?

Unfortunately, neither the government nor FATRO have given us figures for the current usage of veterinary diclofenac in Spain (or Italy). However, we know that the **AEMPS has had access to the number of doses sold in Spain, from May 2013 to May 2014, and has thus calculated the scenarios used in the recent report published in July 2014 based on those figures**.

According to the AEMPS, and assuming a 5 times increase in the current number of animals treated (data from May 2013-May 2014), the total number of animals considered for the modelling in the report were (scenario 2, page 25):

11,000-28,000 cattle in intensive regime

1,000-2,000 cattle in extensive regime

35,000-58,000 pork in intensive regime

300-500 horses

This suggests that in the first year of the marketing of veterinary diclofenac in Spain the following animals were treated with diclofenac: 2,200-5,600 cattle in intensive explorations, 200-400 cattle in extensive regime, 7,000-11,600 pigs in intensive regime and 60-100 horses. So in total between 9460 and 27,700 animals were treated with diclofenac in Spain during the first year of marketing of this drug.

This figure has the potential to increase exponentially, if FATRO succeeds in implementing a good marketing strategy. New drugs exploding in a market are an intrinsic part of the dynamics of the veterinary drug sector.

How many carcasses of animals treated with diclofenac can reach the vulture food chain?

There is no reliable estimate or figure for the mortality rate of diclofenac-treated animals, as the diseases against which diclofenac is used are not liable to official registration. Hence the recent scenarios published by MAGRAMA are thus only estimates.

However, they **estimate that in the future, and assuming a 5 times increase in the sales of veterinary diclofenac in Spain from first year levels, ca. 0,1-0,2% of all the carcasses available to vultures in Spain may be laced with diclofenac (page 28). In other words, the estimate produced by the Spanish authorities suggests that there is a probability that 1 or 2 carcasses in every 1000 that are consumed by vultures in Spain may include diclofenac. These figures are within the percentages (0,13-0,75%) of cattle carcasses critically contaminated with diclofenac (i.e. containing an LD50 in one meal) and**

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available to vultures that explained the 99% decline in Indian vultures.

General conclusions

Even the report recently produced by the Spanish authorities ("Análisis del riesgo de uso de medicamentos veterinarios con diclofenaco sobre las poblaciones de buitres en España – recomendaciones de actuación y escenarios potenciales de afección", July 2014, MAGRAMA (Direcciones Generales de Calidad y Evaluación Ambiental y Medio Natural (DGCEAMN), Sanidad de la Producción Agraria (DGSPP)) and the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)) recognises that "there is a risk of mortality of vultures in Spain due to the use of anti-inflammatory products containing diclofenac", page 6).

Given that

- ✓ **Veterinary diclofenac is extremely toxic to vultures - half of the Griffon vultures will die after ingesting less than 1 mg**
- ✓ **In India, it caused a 99% decline of vultures – the decline observed could be explained if only 1 in 1000 carcasses available to vultures contained a lethal concentration of diclofenac**
- ✓ **Between 9,460 and 27,700 animals were treated with diclofenac in Spain during the first year of marketing of this drug alone**
- ✓ **Tens of thousands, probably hundreds of thousands, of carcasses of cattle, pork and horses are eaten by vultures alone in Spain**
- ✓ **Many of those come from intensive explorations where veterinary control is not individualised**
- ✓ **Animal carcasses treated with diclofenac can still kill vultures seven days after treatment (thus even more difficult to control)**
- ✓ **Vultures are gregarious eaters, with tens, often hundreds of animals eating from a single carcass. One animal carcass treated with diclofenac would be enough to kill dozens of vultures**
- ✓ **Day to day decision on what to send to vulture feeding stations remains in the hand of farm managers, not veterinarians**
- ✓ **There is risk that treated cattle in extensive systems can die in the fields and are then almost all eaten by vultures within 1 hour of death**
- ✓ **The practical measures suggested to minimise risk to diclofenac would be extremely expensive to set up, and would not be 100% safe 100% of the time, due to lack of enforcement, awareness, and veterinary oversight**
- ✓ **According to the Spanish government own estimate, between 0,11 and 0,22% of all carcasses available to vultures could include diclofenac in 5 years – close to the 0,13%-0,75% that caused the 99% decline in India!**
- ✓ **Legal availability of diclofenac in Europe causes a precedent and a conduit for a global boom in veterinary diclofenac worldwide**
- ✓ **THERE IS AN ALTERATIVE DRUG WITH THE SAME THERAPEUTIC PROPERTIES AND PRICE (Meloxicam)**

The VCF concludes that the risk to European vultures is unacceptable, and thus veterinary diclofenac should be banned in Europe

Comment

(This document was compiled by José Tavares, VCF Executive Director, with contributions from several people. It was also discussed with BirdLife International and the IUCN Vulture Specialist Group, with whom we have been working on this issue)

Vulture Conservation Foundation
Wuhrstrasse 12. CH-8003 Zurich, Switzerland
Tel. +90 532 461 3463 | **http://www.4vultures.org/**
j.tavares@4vultures.org

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