European Medicines Agency
Veterinary Medicines and Inspections

London, 13 December 2006
EMEA/CVMP/108858/2005-Rev.2

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

COX-2 INHIBITORS IN VETERINARY MEDICINE

Background

Following the developments in human medicine since the voluntary withdrawal of Vioxx (rofecoxib) by the Marketing Authorisation Holder and the subsequent review in the EU of selective cox-2-inhibitors by the Committee for Medicinal Products for Human Use (CHMP), the CVMP considered in 2005 the need for action in veterinary medicine in relation to cox-2 inhibitors, addressing selective cox-2-inhibitors of the coxib class as well as other non-steroidal anti-inflammatory drugs (NSAIDs) with cox-2-inhibitory activity.

Thereafter, the CHMP has further reviewed new thrombotic cardiovascular safety data and analyses on cardiovascular safety stemming from clinical and epidemiological studies which signal a potentially increased thrombotic risk (such as heart attack or stroke) for non-selective NSAIDs, especially when used at high doses and in long-term treatment. The European Medicines Agency then concluded that the benefit-risk balance for NSAIDs remains favourable for use in humans.

On basis of that recent review and the conclusions drawn, the need for action concerning veterinary medicinal products was considered by the CVMP.

Discussion

The information available for selective cox-2-inhibitors in human medicine indicate that the cardiovascular effects observed in human beings in relation to rofecoxib are most likely a class effect, which applies in varying degree to all substances of the coxib class.

1. Selective cox-2-inhibitors of the coxib class for food producing animals

Currently no substance belonging to the selective cox-2-inhibitors of the coxib class is included in Annex I or II of Council Regulation (EEC) No 2377/90. Firocoxib has been introduced in Annex III of Council Regulation (EEC) No 2377/90. At present, no products containing such substances are authorised in the EU for use in food producing animals.

The Committee notes that the cardiovascular effects including thrombotic events (e.g. myocardial infarction and cerebral vascular events) of selective cox-2-inhibitors observed in human medicine occur at therapeutic doses mainly after long-term use. In the EU, residue levels in food stuffs of animal origin after treatment of animals must be below maximum residues limits (MRLs) established in accordance with Council Regulation (EEC) No 2377/90. MRLs for any given substance are determined after a rigorous review in particular of its toxicological effects and usually on the basis of an acceptable daily intake (ADI), which in turn is based on a relevant toxicological no-observed-effect-level (NOEL) and applying an appropriate safety factor[1]. Any likely consumer exposure to coxib-residues would occur at negligible levels and be an infrequent event, not a long-term exposure.

[1] Detailed information on the establishment of MRLs is available in Volume 8 of the Rules governing medicinal products in the EU at http://pharmacos.eudra.org/F2/eudralex/vol-8/home.htm

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

No action is therefore considered necessary at present in respect of selective cox-2-inhibitors of the coxib class for food-producing animals. Any new MRL application for a substance of the coxib-class will be considered in the light of the experience gained with selective cox-2-inhibitors in human medicine to ensure that consumer safety remains protected.

2. Selective cox-2-inhibitors of the coxib class for companion animals

Currently one product containing a selective cox-2- inhibitor of the coxib class is authorised in the EU through the centralised procedure for use in dogs, Previcox, containing firocoxib. A possible concern in relation to this product would be the safety of the target animals.

Human beings and companion animals, such as dogs, differ, both in respect of the usage of selective cox-2-inhibitors of the coxib class and in susceptibility to the observed cardiovascular effects including thrombotic events (e.g. myocardial infarction and cerebral vascular events).

The Committee notes that during the assessment of the application for Previcox several studies in dogs of 3 to 6 months duration were provided, (see the European Public Assessment Report (EPAR) for the product published on the EMEA website at http://www.emea.eu.int/vetdocs/vets/Epar/previcox/previcox.htm). None of the studies indicated any cardiovascular effects of Previcox. It is however recommended that treatment with Previcox for more than 90 days should be considered carefully and regular monitoring be undertaken by the veterinarian.

No further action is therefore considered necessary. Any new application will be considered carefully in the light of the experience gained with selective cox-2-inhibitors in human medicine.

3. Substances of other classes with cox-2 inhibiting activity for food producing animals

Some other NSAIDs have been assessed in accordance with Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits for veterinary medicinal products in foodstuffs of animal origin, and were included in Annex I or II of said Regulation. These substances are carprofen, vedaprofen, flunixin, tolfenamic acid, meloxicam, metamizole, diclofenac, acetylsalicylic acid and salicylic acid plus certain derivatives thereof, ketoprofen and paracetamol. Meloxicam is considered to have cox-2-preferential activity, though it still inhibits the cox-1 isoenzyme. Similar preferential inhibition has also been postulated for tolfenamic acid and for diclofenac, however it was in comparison to the latter that the cardiovascular effects of selective cox-2-inhibitors were first noted. For paracetamol and metamizol the mode of action has been postulated as cox-3-inhibition rather than cox-1/cox-2-inhibition. For some of the remaining substances *in vitro* activity against the cox-2-isoenzyme has been reported (for instance carprofen) in varying degrees for different species, but overall all are considered not to be preferential cox-2-inhibitors.

As discussed under point 1, the Committee notes that the cardiovascular effects including thrombotic events (e.g. myocardial infarction and cerebral vascular events) of selective cox-2-inhibitors observed in human medicine occur at therapeutic doses after long-term use only. In the EU, residue levels in food stuffs of animal origin after treatment of animals must be below maximum residues limits (MRLs) established in accordance with Council Regulation (EEC) No 2377/90. MRLs for any given substance are determined after a rigorous review in particular of its toxicological effects and usually on the basis of an acceptable daily intake (ADI), which in turn is based on a relevant toxicological no-observed-effect-level (NOEL) and applying an appropriate safety factor. Any likely consumer exposure to residues of these NSAIDs would occur at negligible levels and be an infrequent event, not a long-term exposure.

No further action in relation of the above mentioned NSAIDs is considered necessary.

4. Substances of other classes with cox-2 inhibiting activity for companion animals

Other non-steroidal anti-inflammatory drugs (NSAIDs) are authorised nationally and centrally for companion animals, some of which are considered to have cox-2-preferential activity (see point 3 for substance names). As discussed under point 3, this applies in particular to meloxicam (names of the centrally authorised products: Metacam and Novem), tolfenamic acid and diclofenac (for the two latter substances there are national authorisations in EU Member States). For the centrally authorised NSAID tepoxalin (product name: Zubrin), it was shown *in vitro* that it inhibits the cox-1-isoenzyme with at least a thirty-fold higher potency than for cox-2 (see the EPAR published on the EMEA website at http://www.emea.eu.int/vetdocs/vets/Epar/zubrin/zubrin.htm). Thus tepoxalin should not be considered a preferential cox-2-inhibitor.

As discussed under point 2, human beings and companion animals differ in susceptibility to the observed cardiovascular effects including thrombotic events (e.g. myocardial infarction and cerebral vascular events).

Of the before mentioned substance, meloxicam and tolfenamic acid possess the strongest preferential cox-2-inhibitory action, followed by diclofenac. All three substances still inhibit the cox-1 isoenzyme, resulting in the well-known gastro-intestinal side effects of NSAIDs, which thus will remain the limiting factor of the use of products containing meloxicam, tolfenamic acid or diclofenac in companion animals.

Veterinary pharmacovigilance systems are established in all EU Member States. These systems record all reported adverse effects to veterinary medicines, and thus monitor and ensure the continued safety of veterinary medicines once they reach the market after authorisation and start being used in animal patients. For Metacam and Novem, the products containing meloxicam, the available pharmacovigilance data have not demonstrated any particular cardiovascular effects or thrombotic events associated with the substance. For Zubrin, the product containing tepoxalin, the available pharmacovigilance data also do not relate to cardiovascular effects or thrombotic events.

No cardiovascular effects or thrombotic events have been described in literature as adverse reactions in animals for the other NSAIDs mentioned above, so that there is no immediate cause for concern. However, specific pharmacovigilance data for the other NSAIDs authorised by national and mutual recognition procedures are available only to the Member States where the products are authorised, and therefore CVMP will request through its Pharmacovigilance Working Party (PhVWP-V) a review of relevant pharmacovigilance data in relation to potential cardiovascular effects including thrombotic events.

No further action is considered necessary.

Conclusion

In 2005, in respect to selective cox-2-inhibitors in veterinary medicine in the EU, the CVMP concluded that no action relating to consumer safety is necessary, since no products are authorised for use in food-producing species. Any potential consumer safety concerns will be considered in the course of respective MRL-procedures in accordance with Council Regulation 2377/90.

The CVMP also concluded that on the basis of the data available no action was required in relation to the only selective cox-2-inhibitor authorised for use in companion animals in the EU, considering the data provided with the application for a marketing authorisation, which did not show any cardiovascular effects in dogs, and the different susceptibility of companion animals as opposed to human beings to the specific cardiovascular effects of selective cox-2-inhibitors.

In relation to other NSAIDs with partial cox-2-inhibiting activity, the CVMP concluded that no action was required in respect of consumer safety. The increased risk of cardiovascular events in human beings related to selective cox-2-inhibitors occurred at therapeutic doses after long-term use. Any consumer exposure to residues of such substances would be an isolated event and residue levels from permitted use would be negligible and of no concern to human health.

In respect to target animal safety for such NSAIDs, the ongoing monitoring of the product safety has not revealed any of the cardiovascular effects in question in cats and dogs for centrally authorised products. Literature does not describe such effects for the nationally authorised products containing such substances. Therefore CVMP concluded in April 2005 that no immediate regulatory actions is required but will review through PhVWP-V the national pharmacovigilance data in respect to potential cardiovascular risks for NSAIDs with cox-2-inhibitory activity.

The PhVWP-V concluded at the meeting in November 2005 following a review of the national pharmacovigilance data that there were very few relevant cases associated with the incidence of cardiovascular disorders related to the use of NSAIDs. The incidence was no greater for Cox-2 inhibitors than for other NSAIDs.

Following the CHMP update in relation to cardiovascular and skin reactions observed in humans, the PhVWP-V also revisited the national databases for skin reactions reported after the use of NSAIDS. It was concluded that specific skin reactions, excluding general hypersensitivity symptoms, to Cox-2-inhibitors or other NSAIDs are very rarely reported in veterinary medicine.

Therefore CVMP confirmed that no immediate regulatory actions are required with respect to Cox-2 inhibitors and NSAIDs in relation to possible cardiovascular effects and skin reactions. Further to considerations in follow-up to the review made for medicinal products for human use, the CVMP reconfirms this conclusion in December 2006.