Suspected Adverse Reactions to Veterinary Medicinal Products 2003

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National Pharmacovigilance Issues

The Irish Medicines Board (IMB) received 78 national reports of suspected adverse reactions (SARs) to veterinary medicinal products (VMP) for the period 1st January 2003 to 31st December 2003. Fifty-nine reports were received from marketing authorisation holders (MAH), 13 directly from veterinary surgeons in practice, three from veterinary surgeons in regional veterinary laboratories and three directly from animal owners.

Of the total number of SARs reported, 65 involved veterinary pharmaceutical products and 17 concerned vaccines. The majority of SAR reports (n=75) related to single VMPs, with two or more VMPs identified in three reports. Suspected adverse drug reactions were reported in the following species: human (three reports), cattle (23), horses (five), sheep (23), pigs (five), dogs (14) and cats (five).

Lack of expected efficacy was reported for 25 VMPs. These included 13 reports relating to the use of triclabendazole for the treatment of *Fasciola hepatica* in sheep (see below for further information).

Of the remaining reports (n=53), the product(s) used was considered to have been probably or possibly associated with the observed reaction in 29 cases. In a further 19 cases there was insufficient information on which to base a conclusion relating to causality and in the remaining 5 cases it was concluded that the VMP(s) was definitely not the cause of the observed reaction (for definitions see **Table 1**).

In 2003, there were three SARs in humans associated with the use of VMPs. All three of these reports related to inadvertent self-injection. In two cases, this resulted in transient local tissue reaction. In the third case, adverse effects (drowsiness, unsteady gait, slurred speech) were reported to have occurred in a farmer within a short period of time after inadvertent self-injection of detomidine. The volume of product administered is unclear, but the syringe contained a total volume of 5 ml of product (10 mg detomidine/ml). The man was admitted to hospital and symptomatic therapy initiated. Over a sixteen-hour period, he made a full recovery. It is noted that detomidine is classified as a VSO (Veterinary Surgeon Only) product and by definition should not have been available for use by the animal owner.

In relation to the SARs that were associated with veterinary pharmaceutical products, three reports were identified as probably/possibly related to the administration of anthelmintic boli to cattle. In all of these cases, the reactions reported were attributed to pharyngeal/oesophageal trauma. These figures represent a further reduction in the number of reported deaths associated with the administration of anthelmintic boli when compared to the figures for previous years (**Table 2**).

The individual SAR reports, originating from Ireland, that were considered probably/possibly related to product use are summarised on a species by species basis in **Table 3** (pharmaceutical products) and **Table 4** (immunological products).

Reports of lack of expected efficacy in sheep following the administration of triclabendazole

The Advisory Committee for Veterinary Medicines of the IMB discussed reports of lack of expected efficacy to triclabendazole in sheep in July 2003. Although not confirmed in all cases, it was considered that the reported inefficacy was likely to have been related to fluke resistance to triclabendazole. The Committee considered that the number of recent reports received were a cause for concern and advised that relevant authorisation holders should be required to re-evaluate the risk/benefit of relevant products and take action, as appropriate. The Committee, while recognising the benefit of products containing triclabendazole for the

treatment of triclabendazole-sensitive fluke infestation, considered that the principle corrective actions related to:

- Changes to the product labelling and any other promotional material,
- Dissemination of information on the potential for resistance development, and
- The monitoring of resistance development (both screening in cases of suspected resistance and 'proactive' resistance surveillance).

It was agreed with the relevant MAHs that the following warning statements (or similar) be included on the product labelling of relevant products:

> "*Anthelmintics are agents that destroy or result in the expulsion of susceptible parasitic worms. Parasite resistance to a particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class. To reduce this risk, dosing programmes should be discussed with a veterinary surgeon.*
> *<Product X> contains the anthelmintic Triclabendazole. Fluke (Fasciola hepatica) resistance to triclabendazole has been identified and losses associated with resistant strains of fluke in sheep flocks treated with triclabendazole can be significant. If signs of fascioliasis continue after treatment with <Product X>, DO NOT REPEAT THE DOSE and do not dose with other products containing triclabendazole. Seek veterinary advice. If resistance is suspected or confirmed, you should change active ingredient on veterinary advice.*"

Reports of suspected toxicity in sheep associated with the administration of nitroxynil

Four reports of SAR in sheep associated with the administration of a nitroxynil containing product were received over a two-month period in early 2003 (this compares to 1 report in 1998, none in 1999 or 2000, I report (cattle) in 2001 and 1 report (dog) in 2002); 3 of the reports involved sheep only, with sheep and a calf involved in the remaining case. A feature of all cases was an apparent underestimation of bodyweight resulting in overdose (extent of possible overdose estimated to range from 2.5 to 5.5 times the recommended treatment dose). In some of those cases where adverse effects were observed by the owner and/or veterinary surgeon, the clinical signs as reported were consistent with the known toxicity of the product (hyperthermia, recumbency, rapid respiration). In light of those reports, the relevant MAHs amended the product labelling to include additional warning statements relating to the following: advising against overdose; a recommendation to use properly calibrated dosing equipment; and, information on the clinical signs to be expected in the event of overdose.

Product recalls related to product defects

During 2003, thirty-three reports of product quality defects in veterinary medicinal products were investigated by the IMB. Eight of these investigations resulted in product recalls from the Irish market. One of these reports was classified as a critical quality defect and resulted in the recall, from farm level, of a specific batch of the product concerned. By way of a notice placed in a farming magazine, users were advised of the following:

- a quantity of the product was mislabelled with the potential for adverse effects in treated animals relating to levamisole toxicity;
- to check stocks of the product and, in the event that any unused containers of the relevant batch were detected, to quarantine relevant packs and contact the MAH concerned to have the product uplifted;
- to contact their veterinary surgeon for professional advice in the event that animals had been treated with this product.

European Pharmacovigilance Issues

During 2003, the Committee for Veterinary Medicinal Products, on the advice of the Pharmacovigilance Working Party, recommended that in view of available pharmacovigilance data the warning statements for **Zubrin** (authorisation number EU/2/00/028/001-008) should be amended in order to provide more information on the occurrence of adverse reactions.

Discussion and Conclusions

Pharmacovigilance is one of a range of post authorisation activities designed to ensure the ongoing production and use of safe, effective, high-quality veterinary medicines following their introduction to the marketplace. The primary input into the national pharmacovigilance system is reports of suspected adverse reactions, which are sent to either the IMB or the relevant marketing authorisation holder. More often than not, these reports relate to adverse effects experienced by an animal following the use of a particular product. However the scope of veterinary pharmacovigilance extends to other areas of post-authorisation surveillance, including: lack of expected efficacy of a veterinary medicinal product when used in accordance with label recommendations; adverse reactions associated with extra-label use; adverse environmental effects; violations of approved residue limits; and, harmful and unintended effects in humans exposed to VMPs. It should be noted that the scope of pharmacovigilance does not extend to quality defects or quality complaints as long as they are not accompanied by adverse effects. However, if a defective product is encountered, the user is advised not to use the product and to report the defect immediately to the MAH. The MAH is obliged to record and investigate all such reports.

Suspected adverse reaction reports are collated and evaluated by the MAH and the IMB. In the event that a safety issue is identified post-authorisation, appropriate steps can be taken to reduce the level of any associated risk. Specific benefits of an effective pharmacovigilance system include:

- Assurances on the continued safety of authorised VMPs;
- Increased knowledge of the safety profile of VMPs leading to better advice to the users of veterinary medicines;
- Updated and improved label warnings leading to safer use of medicines;
- Removal from the marketplace of product (or batches of product) that has an unacceptable safety profile.

As highlighted above, a number of significant safety issues were identified during 2003 that resulted in changes to product labeling. It is envisaged that the updated and improved label warnings will lead to safer use of the products concerned. Because of the potential for changes to the conditions of product authorisation during the life of a product, it is important that users of veterinary medicinal products continually monitor product labelling to ensure correct and safe use.

The IMB gratefully appreciates and acknowledges the efforts of reporters in completing reporting forms and responding to requests for clarification. While an individual's experience may be limited to one or two cases, when collated with data from other sources, it will contribute considerably to the assessment of a potential safety hazard. Readers are advised that specific SAR report forms may be downloaded from the IMB website (www.imb.ie) for off-line completion and submission. Alternatively, prepaid self-addressed forms can be requested from the veterinary department of the IMB.

Table 1 : Assessing Causality

The following factors will be taken into account: ⇒ Associative connection – in time or anatomic site ⇒ Pharmacological explanation, blood levels, previous knowledge of the drug ⇒ Presence of characteristic clinical or pathological phenomena ⇒ Exclusion of other causes ⇒ Completeness and reliability of the data in case reports	
Category 'A' ("Probable")	All of the following minimum criteria should be complied with: ⇒ There should be a reasonable association in time between the administration of the drug and the onset and duration of the reported event. ⇒ The description of the clinical signs should be consistent with the known pharmacology and toxicology of the drug. ⇒ There should be no other equally plausible explanation(s) of the reaction.
Category 'B' ("Possible")	When drug causality is one (of other) possible and plausible causes for the reported reaction, but where the available data do not fulfill the criteria for inclusion in Category 'A'
Category 'O' ("Unclassifiable/ unassessable")	When reliable data concerning an adverse reaction is unavailable or insufficient to make an assessment of causality.
Category 'N' ("Unlikely")	When sufficient information exists to establish beyond reasonable doubt that drug administration was not likely to be the cause of the event.

Table 2: Incidence of death associated with the use of anthelmintic boli

	1997	1998	1999	2000	2001	2002	2003
Units Sold	182,200	138,700	133,986	103,868	79,850	Not available	Not available
Deaths	50	30	32	18	9	6	3
Incidence (deaths/unit)	1/3,644	1/4,623	1/4,187	1/5,770	1/8,872	-	-

Table 3: Adverse reactions ('A' or 'B' causality) associated with the use of pharmaceutical products excluding anthelmintic boli

Active Substance	Route	No. treated	No. reacted	No. dead	Clinical signs	Speed of onset
Cattle						
Levamisole	topical	30	8	0	application site reaction	days
Flunixin	iv	1	1	1	collapse, death	immediate
Moxidectin	sc	60	6	2	depression, ataxia, ptyalism	<24 hours
Multivitamin	im	10	1	1	found dead	<24 hours
Levamisole	oral	12	6	1	neurological signs, dead	hours
Dog						
Amitraz	topical	1	1	0	lethargy and depression	minutes
Pentosan polysulfate sodium	sc	1	1	0	laboured breathing	12 hours
Meloxicam	oral	1	1	1	vomiting, inappetence, lethargy, death	14 days therapy
TMP/Sulphonamide	oral	1	1	0	reluctant to rise, swollen joints	4-5 days
Horse						
Flunixin	iv	1	1	1	ataxic, trembling, death	immediate
Penicillin/Streptomycin[1]	im	1	1	1	reared up, collapsed, died	minutes
Xylazine	iv	1	1	0	unusual response,	minutes
Xylazine	iv	1	1	0	unusual response,	minutes
Xylazine	iv	1	1	0	unusual response,	minutes
Sheep						
Nitroxynil[2]	sc	28		19	found dead, resp distress	<24 hours
Nitroxynil[3]	sc	33		7	found dead	<24 hours - days
Nitroxynil[4]	sc	22	19	19	hyperthermia, recumbency, death	<24 hours
Nitroxynil[5]	sc	26	7	7	found dead	<24 hours
Pigs						
Tilmicosin[6]	oral	700		20	trembling, death	<24 hours

im – intramuscular; iv – intravenous; sc - subcutaneous

[1] Off label use – product not authorised fro this species
[2] Product administered in overdose
[3] Product administered in overdose
[4] Product administered in overdose
[5] Product administered in overdose
[6] Product administered in overdose

Table 4: Adverse reactions ('A' or 'B' causality) associated with the use of immunological products

Antigenic components	Route	No. treated	No. reacted	No. dead	Clinical signs	Speed of onset
Dog						
Leptospirosis and parvovirus	sc	2	2	1	Pyrexia, forelimb lameness	1 week
Cat						
Feline leukaemia	sc	1	1	1	Fibrosarcoma at injection site	months
Pig						
M. hyopneumoniae[a]	unknown	150		3	Respiratory distress, death	minutes
M. hyopneumoniae[a]	im	225		4	Emesis, ataxia, vomiting, collapse	minutes

[a]The same veterinary medicinal product
im – intramuscular; iv – intravenous; sc - subcutaneous