Suspected Adverse Reactions to Veterinary Medicinal Products 2006-2007

1. Introduction

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 (SARs), which are sent to either the Irish Medicines Board (IMB) or the relevant marketing authorisation holder (MAH). Suspected adverse reaction reports are collated and evaluated by the IMB and the MAH. In the event that a safety issue is identified post-authorisation, appropriate steps can be taken to reduce the level of any associated risk.

2. Pharmacovigilance Issues - 2006

2.1 National Issues

The IMB received 70 national reports of suspected adverse reactions to veterinary medicinal products (VMP) for the period 1st January 2006 to the 31st December 2006. Fifty nine reports were received from marketing authorisation holders and 11 directly from veterinary practitioners.

In the 70 reports received, a total of 41 veterinary pharmaceutical products and 33 immunological products were identified as possibly associated with adverse effects. While the majority of reports related to the use of a single VMP, two or more VMPs were identified in four reports.

Suspected adverse reactions were reported in the following species: Human (three reports), bovine (25), canine (24), ovine (eight), equine (six) and feline (four).

Of the 70 reports associated with the use of VMPs, 42 related to suspected adverse reactions in the treated animals, 25 related to suspected lack of expected efficacy and three cases involved suspected adverse reactions in individual users following exposure to a VMP.

2.1.1 Reports of suspected adverse effects

Three human reports associated with exposure to pharmaceutical products were received during the reporting period. In one of these reports accidental exposure to a VMP was suspected as the cause of a rash on the arm of a user. In a second report, a user complained of a taste in the mouth and nausea after applying a pour-on product to 200 cattle. The third report related to an animal owner that reported having sore eyes for six weeks after a cat had been treated with a topical ecto-parasiticide. In this latter case, it was considered unlikely that exposure to the product under the circumstances reported would result in persistent adverse effects.

Of the forty-two reports relating to suspected adverse reactions in the treated animal(s), the product was considered to have been probably or possibly associated with the observed reaction in 21 reports. In 18 reports, there was insufficient information available on which to assign causality. In three cases it was concluded that the VMP was definitely not responsible for the observed reaction. The criteria for assigning causality to a report are detailed in **Table 2**.

The individual SAR reports, originating from Ireland during 2006, that were considered probably (coded 'A') or possibly (coded 'B') related to product use are summarised on a species by species basis in **Table 3a** (pharmaceutical products) and **Table 4a** (immunological products).

2.1.2 Reports of suspected lack of expected efficacy

There were 25 reports of suspected lack of expected efficacy submitted to the IMB in 2006. Of these 25 reports, eight related to suspected lack of expected efficacy of pharmaceutical products. In one report it was suspected that triclabendazole was ineffective for the treatment of fascioliasis in sheep and a number of fatalities due to fascioliasis were recorded on the farm. The animals had previously received multiple doses of triclabendazole. Fluke resistance to triclabendazole was suspected. Subsequently, an alternative flukicide, containing a different active substance, was used and was found to be effective.

Eighteen suspected lack of expected efficacy reports related to apparent failure to establish immunity following vaccination, resulting in the development of the disease. In a number of these cases it was established that the vaccines had not been used in accordance with label recommendations. In some other cases, it was suspected that vaccinated animals were exposed to infection before immunity had properly developed.

2.2 European issues

During 2006 the Committee for Veterinary Medicinal Products (an expert scientific advisory committee of the European Medicines Agency) reviewed safety information, in the form of periodic safety update reports (PSUR), relating to a number of products. In respect of two products, Equilis StrepE (*Streptococcus equi* vaccine) and Profender Spot-On for Cats (topical endoparasiticide, emodepside/praziquantel combination), the Committee made recommendations for changes to the product literature.

- For Equilis StrepE, it was recommended that the product literature be updated to 1) reflect new information concerning potential adverse reactions, 2) add further instructions for appropriate administration and 3) provide advice to an attending physician in case of accidental exposure in man leading to reactions.
- For Profender, it was recommended that the product literature be updated to include information on the potential for the occurrence of application site reactions.

3. Pharmacovigilance Issues - 2007

3.1 National Issues

The IMB received 92 national reports of suspected adverse reactions to VMPs for the period 1st January 2007 to the 31st December 2007. There were 72 reports from marketing authorisation holders and 20 directly from veterinary practitioners.

One report was also received that could not be validated as there were no details provided on the reaction that occurred and the reporter could not be contacted. The minimum requirements for an adverse reaction report to be considered a valid report are outlined in **Table 1.**

Of the 92 valid reports received, a total of 62 veterinary pharmaceutical products and 40 immunological products were identified as possibly associated with adverse effects. While the majority of reports related to the use of a single VMP, two or more VMPs were identified in ten reports.

Suspected adverse reactions were reported in the following species: Human (four reports), canine (35), bovine (33), feline (seven), equine (six), ovine (five), porcine (one) and rabbit (one).

Of the 92 reports associated with the use of VMPs, 67 related to suspected adverse reactions in the treated animals, 20 related to suspected lack of expected efficacy, one related to a withdrawal period issue and four cases involved suspected adverse reactions in individual users following exposure to a veterinary medicinal product.

3.1.1 Reports of suspected adverse effects

Four human reports were received, three of these reports related to pharmaceutical products and one related to an immunological product. The report relating to the immunological product involved ocular exposure during administration of a canine vaccine by a veterinarian, resulting in soreness of the eye on the following day. Two of the reports relating to pharmaceutical products were associated with farmers accidentally self-injecting endectoparasiticides. The remaining report related to a pour-on product that accidentally splashed in a farmer's eyes; the farmer suffered no adverse effects.

Of the 67 reports relating to suspected adverse reactions in the treated animals, the product was considered to have been possibly or probably associated with the reaction in 30 reports. In 25 reports, there was insufficient information available on which to assign causality. In 12 cases it was concluded that the VMP was definitely not responsible for the observed reaction.

The individual SAR reports, originating from Ireland during 2007, that were considered probably (coded 'A') or possibly (coded 'B') related to product use are summarised on a

species by species basis in **Table 3b** (pharmaceutical products) and **Table 4b** (immunological products).

3.1.2 Reports of suspected lack of expected efficacy

There were 20 reports of suspected lack of expected efficacy submitted to the IMB in 2007. Of these 20 reports, eight related to suspected lack of expected efficacy with pharmaceutical products and 12 related to the apparent failure to establish immunity following vaccination. In a number of these cases it was established that the vaccines had not been used in accordance with label recommendations. In some other cases, it was suspected that vaccinated animals were exposed to infection before immunity had properly developed.

3.2 European issues

During 2007 the Committee for Medicinal Products for Veterinary use reviewed safety information, in the form of periodic safety update reports (PSURs), relating to a number of products. In respect of two pharmaceutical products and two immunological products, the Committee made recommendations for updates to the product literature in light of pharmacovigilance experience.

- For Metacam/Novem (meloxicam), it was recommended that the product literature be amended to 1) update information on adverse reactions for all formulations and 2) to add new special precautions for use in animals for the oral formulations intended for use in dogs.
- For Stronghold (selamectin), it was recommended that the product literature be updated to include information on the potential for the occurrence of neurological signs associated with use of the product. Typically, these effects are mild and transient.
- For Equilis Prequenza and Equilis Prequenza Te (equine influenza (+ tetanus toxoid) vaccine), it was recommended that the product literature be amended to update information on adverse reactions including detail on the frequency of occurrence of adverse reactions.

4. Conclusion

For VMPs authorised by the IMB, no regulatory actions were required to be taken in 2006 or 2007 as a result of the safety information received in the form of spontaneous adverse reaction reports.

The number of suspected adverse reaction reports received during 2007 (92) is increased compared to the number received during 2006 (70 reports) and 2005 (84 reports). However, it is suspected that there may be a significant level of under reporting of SAR's as evidenced by the low numbers of reactions reported directly to the IMB by veterinary practitioners and pharmacists. Persons licensed to sell or supply animal remedies are reminded that, in accordance with Regulation 12 of the Animal Remedies Regulations 2007 [S.I. 786 of 2007], they are obliged to notify the IMB or the relevant MAH of all

serious or unexpected SARs and all human adverse reactions associated with the use of VMPs that come to their attention within 15 days of receipt of such information.

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. If a safety risk is identified during the pharmacovigilance process appropriate steps can be taken to reduce this risk.

Further information on the topic of veterinary pharmacovigilance and information relating to the reporting of suspected adverse reactions can be obtained from the Safety & Quality section of the IMB website at www.imb.ie. Specific SAR report forms may be downloaded from the IMB website for off-line completion and submission. Alternatively, prepaid self-addressed forms can be requested from the veterinary medicines department of the IMB.

Table 1: Suspected adverse reaction reports – minimum information

A SAR report will be considered as valid provided that at least the following core data are available:

- An identifiable reporter (e.g. veterinary surgeon, pharmacist, animal owner).
- Animal/human details: species, age, sex
- Suspect product: name and product authorisation number
- Reaction details

It should be stressed that these are minimum requirements and the reporter should endeavour to be as comprehensive as possible in order to facilitate a full scientific evaluation. Where relevant, this may include laboratory findings and post mortem examination findings.

Table 2: 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'	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'	When drug causality is one (of other) possible and plausible causes for the reported reaction, but where the available data do not fulfil the criteria for inclusion in Category 'A'
Category 'O'	When reliable data concerning an adverse reaction is unavailable or insufficient to make an assessment of causality.
Category 'N'	When sufficient information exists to establish beyond reasonable doubt that drug administration was not likely to be the cause of the event.

Table 3a: 2006 adverse reactions (reports coded 'A' or 'B') associated with the use of pharmaceutical products.

Active Substance	Route	No Treated	No Reacted	No Dead	Clinical signs	Speed of onset
Bovine						
Oxytetracycline	im	1	1	0	periocular swelling, ataxia and recumbency	minutes
Amitraz**	Topical	20	20	0	varying degrees of sedation	8-12 hours
Oxfendazole bolus	Oral	17	1	1	Oesophageal damage, choking and death	1 week
Colecalciferol	im	1	1	0	anaphylaxis	Shortly after injection
Oxytetracycline	im	43	1	1	respiratory distress and death	Minutes
Flunixin Meglumine	iv	1	1	1	Collapse and death	minutes
Flunixin Meglumine	iv	1	1	1	Death	1½ hours
Carprofen	iv	3	3	3	Collapse and death	Immediately
Moxidectin **	sc	40	4	3	Sternal recumbency, dehydrated, bloating and death.	1 day
Equine						
Oxytetracycline	iv	1	1	0	Collapse	Minutes
Penicillin/ aminoglycoside	im	1	1	1	Ataxia, convulsions, death	10 min
Feline						
Milbemycin Oxime**	Oral	3	2	2	Fits, trembling and death	2 hours
Emodepside, Praziquantel	Topical	1	1	0	Application site reaction	1 day
Thiabendazole	Topical	2	2	0	Nystagus, disorientation and head tilt	30-40 min
Canine						
Selamectin**	Topical	3	1	1	Lethargy and death	hours
Fipronil	Topical	1	1	1	Hypersalivating, disorientated, wobbly on legs convulsions and death	
Cyclosporin	Oral	1	1	0	polyuria, polydipsia, diarrhoea, listless and lymphoma	

iv- intravenous: im-intramuscular: sc- subcutaneous
** Suspected overdose.

Table 3b: 2007 adverse reactions (reports coded 'A' or 'B') associated with the use of pharmaceutical products.

Active Substance	Route	No Treated	No Reacted	No Dead	Clinical signs	Speed of onset
Bovine						
cefalexin, kanamycin monosulphate*	intramammary	2	2	0	MRL violation	2-3 weeks
closantel	sc	8	8	0	panting, congested mucous membranes, oedema, salivation, bloat, tremors	1 hour
meloxicam marbofloxacin	iv	1	1	0	nasal secretions, panting, peri-orbital swelling, pulmonary oedema, ataxia	90 seconds
tilmicosin	sc	1	1	1	death	Hours
procaine penicillin G	unknown	6	6	1	restlessness, facial oedema, cyanosis, death	10 minutes
ivermectin	sc	23	8	0	coughing, staggering, difficulty breathing	immediate
moxidectin	sc	12	12	1	recumbency	1 day
oxytetracycline dihydrate	im	1	1	1	difficulty breathing, death	immediate
menbutone	iv	1	1	1	abdominal pain, ataxia, death	2 minutes
flunixin meglumine	iv	1	1	0	collapse, muscle spasms, nystagmus	Immediate
levamisole	topical	5	5	1	stiffness, head shaking, frothing at mouth, death	2-3 minutes
florfenicol	im	1	1	1	death	2 minutes
Ovine						
tilmicosin	sc	1	1	1	dyspnoea, collapse, increased respiratory & heart rate	45 minutes
closantel	oral	190	6	0	blindness	1 day
Equine						
sodium hyaluronate	ia	2	2	0	swelling, joint pain, lameness	hours
moxidectin†×	iv	1	1	1	shaking, death	3 minutes
electrolytes	iv	1	1	1	shaking, heavy breathing, collapse	immediate
Feline						

diazinon	topical	2	2	2	tremors, ataxia, convulsions, unconsciousness	6 hours
medetomidine hydrochloride	im/iv/sc	1	1	1	death	3 hours
cefovecin carprofen	sc	1	1	0	vomiting, restlessness, collapse, anorexia	hours
Canine						
ciclosporin	oral	1	1	0	diabetes, gum disease, gingival hypertrophy	6 months
benazepril	oral	1	1	1	fainted, vocalisation, possible abdominal pain, death	2 days
pentosan polysulphate sodium	sc	1	1	1	hypovolaemia, blood loss, shock	8 hours
fenbendazole	oral	1	1	0	discharging rectal blood	2 months
metoclopramide hydrochloride†	im	1	1	0	hypotension of skeletal muscles, involuntary jaw movements, diarrhoea	10 minutes
meloxicam	oral	1	1	0	duodenal ulceration	8 days
dimpylate	topical	1	1	0	ataxia, lack of consciousness, inability to stand	2 days
trilostane	oral	3	3	3	increased appetite, haematuria, lethargy, recumbency, death, euthanasia	4-8 weeks

iv- intravenous: im-intramuscular: ia- intra-articular: sc- subcutaneous: *overdose: †unauthorised species: ×unauthorised route of administration

Table 4a: 2006 adverse reactions (reports coded 'A' or 'B') associated with the use of immunological products

Antigenic Components	Route	No Treated	No Reacted	No Dead	Clinical signs	Speed of onset
Canine						
Leptospira interrogans	sc	2	2	1	death and collapse	30min
Leptospira interrogans /Distemper Virus	sc	8	1	0	periocular oedema and oedema of the injection site	2 hours
Equine						
Streptococcus equi	sub mucosal	1	1	0	Unease	5 hours
Feline						
Panleukopenia Virus, Rhinotracheitis Virus, Calicivirus, Leukaemia Virus, Chlamydia psittaci	sc	1	1	1	Vomiting, defecated, urinated and became dyspnoeic	minutes

sc-subcutaneous

Table 4b: 2007 adverse reactions (reports coded 'A' or 'B') associated with the use of immunological products

Antigenic Components	Route	No Treated	No Reacted	No Dead	Clinical signs	Speed of onset
Canine						
canine parvovirus	sc	1	1	1	collapse, torticollis, hyperextension of limbs	24 hours
canine distemper virus, canine adenovirus, canine parainfluenza virus, coronavirus, leptospira icterohaemorrhagiae, leptospira canicola interrogans	im/sc	1	1	1	pneumonia, enlarged heart and liver	3 days
canine distemper virus, canine adenovirus, canine parvovirus, canine parainfluenza virus & leptospira icterohaemorrhagiae, leptospira canicola	sc	2	2	0	collapse, generalised rash	3 minutes
Feline						
feline viral rhinotracheitis virus, feline calicivirus, feline panleucopenia virus	sc	1	1	0	vomiting, collapse, coma, hyperaesthesia	15 minutes

sc-subcutaneous: im-intramuscular