HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Suspected Adverse Event Reports to Veterinary Medicinal Products 2015 – 2016

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1. Introduction

The Health Products Regulatory Authority (HPRA) is responsible for the ongoing monitoring of the quality, safety and efficacy of authorised veterinary medicinal products (VMPs). In relation to safety and efficacy, this role is fulfilled through a nationwide reporting system (pharmacovigilance system), which is designed to monitor products under actual use conditions.

The scope of veterinary pharmacovigilance (as defined in Article 73 of Directive 2001/82/EC) involves the surveillance of:

- suspected adverse reactions in animals to VMPs used under authorised conditions,
- lack of expected efficacy (LEE) of VMPs;
- off-label use of VMPs in animals;
- reported violations of approved residue limits;
- adverse reactions in humans related to the use of VMPs; and
- potential environmental problems.

These reports are collectively known as suspected adverse events (SAEs) and they are received by the HPRA primarily from marketing authorisation holders (MAHs). The MAHs are required by legislation to report all serious SAEs to the HPRA within 15 days. Less frequently, reports are also received from veterinarians and animal owners directly. The minimum requirements for an SAE report to be considered valid are detailed in Table 1. Suspected adverse event reports are collated and evaluated by the HPRA and the MAHs. In the event that a safety issue is identified through this surveillance, appropriate steps can be taken to reduce the level of any associated risk.

Table 1: Suspected adverse event reports – minimum information

An SAE 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.

2. National Pharmacovigilance Issues

The HPRA received 429 and 337 valid national SAE reports involving VMPs in 2015 and 2016 respectively. The 766 valid SAE reports involved a range of food producing species and companion animals as presented in table 2 below. In addition, 18 of the reports concerned adverse reactions in humans following exposure to a VMP.

Table 2. Overview of reports received 2015-2016

Species	Total number reports	Total number reacting
Food producing animals		
bovine	335	5527
ovine	170	5758
equine	18	22
rabbit	6	9
bee	6	27 hives
avian (chicken & pheasant)	5	16579
porcine	4	16
caprine	1	5
Companion animals		
canine	162	311
feline	41	62
Other		
human	18	18
All	766	28334

Seven hundred and twenty reports were received from MAHs, 28 reports were received directly from veterinarians, 13 reports were received from animal owners, and five reports were received from licensed merchants and distributors of VMPs. Figure 1 shows the primary source of SAE reports received by the HPRA from 2011 to 2016.

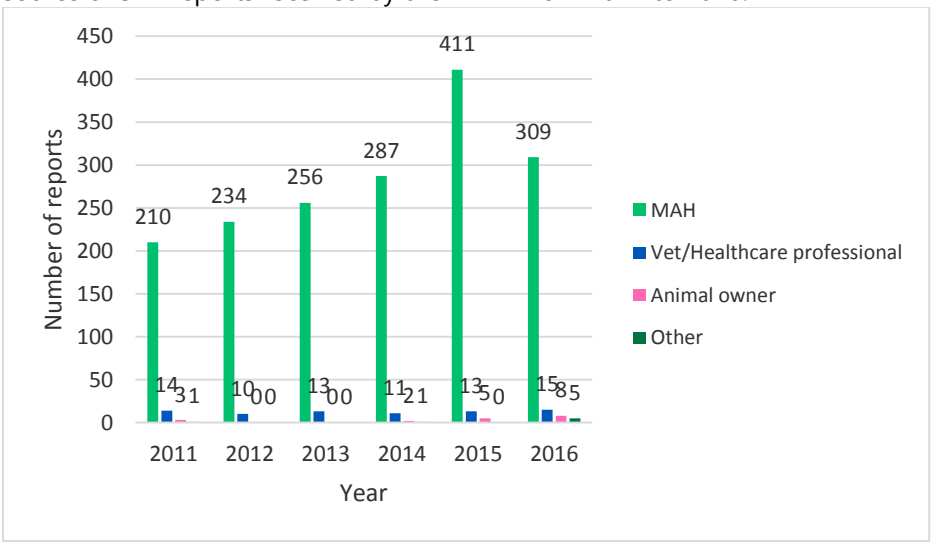

Figure 1: Source of SAE reports from 2011 to 2016

Of the total 766 SAE reports received, 286 involved pharmaceutical products, 442 involved immunological products and 38 reports related to the use of both pharmaceutical and immunological products concurrently.

Three hundred and one reports involved suspected adverse reactions in the treated animals, 442 involved LEE; 18 reports involved SAEs in individual users following exposure to a VMP and five reports related to violation of an approved residue limit. Figure 2 compares the types of reports received from 2014 to 2016.

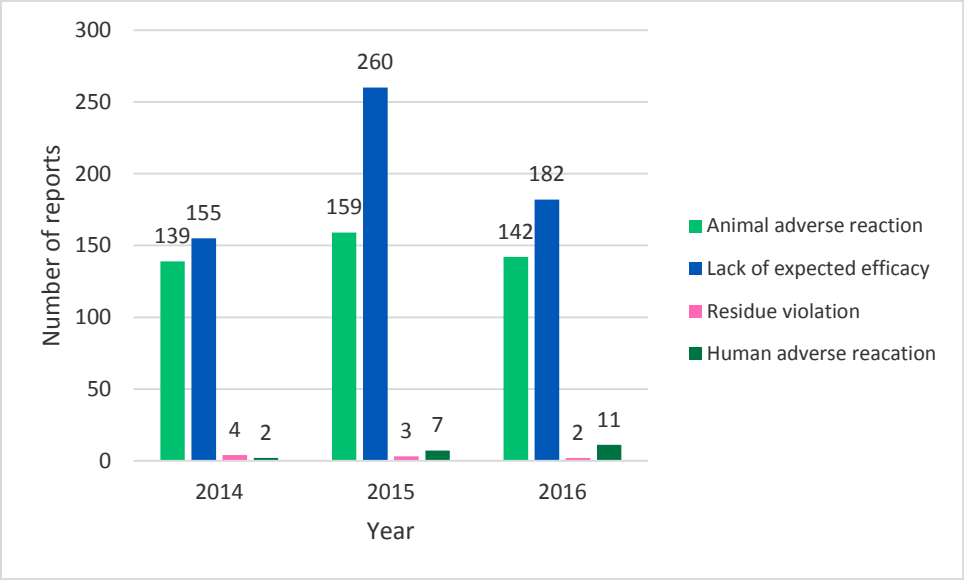

Figure 2: Number of SAE reports by category received from 2014 to 2016

2.1 Reports of adverse reactions

Eighteen reports of SAEs in humans associated with exposure to VMPs were received during the reporting period. Users are reminded to exercise due caution when handling VMPs, and pay particular attention to any special precautions for the use of individual products as detailed in the relevant product literature.

Of the 301 adverse reactions in the treated animal(s), the VMP was considered to have been 'probably' (causality 'A') or 'possibly' (causality 'B') associated with the observed reaction in 169 reports. In 136 reports, there was insufficient/inconclusive information (causality 'O'/'O1') available or it was considered unlikely (causality 'N') that the VMP was responsible for the observed reaction. Note that some reports involved multiple VMPs and as causality is assigned on a product basis rather than to the overall report, reports involving multiple products with different causality have been counted twice. The criteria for assigning causality to a report are detailed in Table 3.

The individual SAE reports, originating from Ireland during 2015 and 2016, that were assigned causality 'A' or causality 'B' are listed according to species in Table 4 (pharmaceutical products) and Table 5 (immunological products).

2.2 Reports of lack of expected efficacy

There were 260 LEE reports submitted to the HPRA in 2015 and 182 during 2016.

Of these reports, 79 involved pharmaceutical products and related to the following species; cattle (47 reports), sheep (17), dogs (10), cat (3), pheasant (1) and bees (1). Eighteen of the 79 reports were considered to be 'unlikely' related to the product.

Three hundred and forty five LEE reports involved immunological products that were suspected to have failed to induce protective immunity. The reports concerned cattle (170 reports), sheep (132), dogs (27), rabbits (5), chickens (4), cats (2), horses (2), pigs (2) and goat (1). Fifty five reports were assigned causality A (probable) or B (possible) and the remainder were assessed as 'unclassifiable/inconclusive' ('O' or O1') or 'unlikely' ('N') product related. One hundred and four reports involved off-label use of one or more vaccines.

In addition, 18 LEE reports involved both pharmaceutical and immunological products.

In May 2015 the HPRA published a safety advisory notice relating to lack of expected efficacy of Scabivax Contagious Pustular Dermatitis (Orf) Vaccine in sheep. No quality issue was identified, however a high number of reports of LEE or partial LEE relating to lack of vaccine take were reported during the spring of 2015 and, as a precautionary measure, the MAH of the product recalled one batch of product from the market. A total of 84 spontaneous reports of LEE or partial LEE was received by the HPRA relating to Scabivax during 2015.

3. European Pharmacovigilance Issues

During 2015-2016, the Committee for Medicinal Products for Veterinary Use (CVMP, an expert scientific advisory committee of the European Medicines Agency) reviewed safety information for centrally authorised VMPs by monitoring reports logged to a central EU SAE database and through the assessment of periodic safety update reports (PSURs) provided by MAHs. On the basis of these analyses, the CVMP made recommendations to update the product literature for 25 centrally authorised VMPs in line with new/emerging safety information. Further information concerning the changes made to individual product information for centrally authorised products is published in the Veterinary pharmacovigilance Public bulletins 2015 & 2016 on the EMA website (www.ema.europa.eu).

In June 2016, following consultations between the EMA, the national competent authorities (NCAs) and the relevant MAH, the HPRA published a safety advisory notice relating to the

centrally authorised product Velactis. Velactis, containing the prolactin inhibitor cabergoline, was authorised for use in the herd management programme of dairy cows as an aid in the abrupt drying-off by reducing milk production to reduce milk leakage at drying off, reduce the risk of new intramammary infections during the dry period, and reduce discomfort. However, following the receipt of multiple serious adverse event reports involving clinical signs including recumbency and death within four months of launching of the product on the market, the CVMP suspended the marketing authorisation for the product at its July 2016 meeting.
Although the exact cause of these adverse events was not determined, there was evidence to suggest that a number may have been linked to the use of Velactis. Given the number and severity of adverse events following use of this medicine in otherwise healthy dairy cows, the CVMP concluded that the risks outweigh the benefits of the product. The product authorisation was therefore suspended in the European Union (EU) until further information is available to show that the benefits outweigh the risks, possibly under new conditions of use. The product was also recalled from the market as a precautionary measure. It should be noted that Velactis had not been launched onto the market in Ireland prior to the decision to suspend its use throughout the EU.

4. Conclusion

On review of previous annual reports (which can be accessed on the HPRA website), it can be seen that there is a general trend towards increasing numbers of reports over the past nine years (429 in 2015, 300 in 2014, 272 in 2013, 244 in 2012, 228 in 2011, 209 in 2010; 148 in 2009; 104 in 2008 and 92 in 2007). While there was a decrease in the number of reports received in 2016 (337) compared to 2015, this is considered to be a stabilisation of normal reporting trends, following the sharp increase in reports in 2015 relating to the Scabivax issue (see section 2.2 above). This increasing trend over the past number of years is likely to reflect a greater awareness of the need to report SAEs, rather than an absolute increase in the number of reactions occurring. The HPRA is encouraged by this positive trend and 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 relating to the use of authorised VMPs is identified, appropriate steps can be taken to reduce this risk.

Although the overall trend with regard to reporting of SAEs is increasing, the number of cases reported directly to the HPRA by veterinary practitioners and pharmacists remains relatively low. Persons licensed to sell or supply animal remedies are obliged to notify the HPRA or the relevant MAH of all serious SAEs and all human adverse events associated with the use of VMPs, within 15 days of receipt of such information, (in accordance with Regulation 12 of the Animal Remedies Regulations 2007 [S.I. 786 of 2007]). The HPRA recognises that there may be a perception amongst the veterinary profession that contacting the HPRA will adversely impact on their workload, in that they may be asked to engage in discussion of the adverse event or case history. However, this is rarely the case. The reporting process itself is simple,

with the HPRA accepting reports by a variety of different methods. Provided that the mandatory information (as described in Table 1) is included in the report, the HPRA will not usually actively engage with the reporter. The HPRA will routinely acknowledge the report and use the information provided to contribute to the overall safety monitoring of the product.
Further information on the topic of veterinary pharmacovigilance and guidance on the reporting of SAEs can be obtained from the Veterinary section of the HPRA website at www.hpra.ie. Suspected adverse events can be reported using an online reporting form accessed from the homepage of the HPRA website. Alternatively SAE report forms may be downloaded from the HPRA website for off-line completion and can be sent by freepost to the HPRA, or prepaid self-addressed forms can be requested from the Veterinary Sciences Department of the HPRA.

Table 3: 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

Causality '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.
Causality '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'
Causality 'O'	When reliable data concerning an adverse reaction is unavailable or insufficient to make an assessment of causality.
Causality 'O1'	When a VMP association cannot be discounted but other factors prevent a conclusion being drawn.
Causality 'N'	When sufficient information exists to establish beyond reasonable doubt that drug administration was not likely to be the cause of the event.

Table 4: 2015-2016 adverse reactions assigned causality 'A' or 'B' associated with the use of pharmaceutical products

Table 4A: Bovine Reports

Active Substance	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
meloxicam marbofloxacin	unknown	1	1	0	fever, abortion	<= 24 hours
moxidectin	IV*	28	1	1	collapse, sudden death	<= 2 mins
deltamethrin	topical	45	1	0	pyrexia, hypothermia, behavioural disorder NOS, agitation, neuromuscular disorder NOS, muscle tremor, anorexia	<= 6 hours
moxidectin	IV*	30	2	1	unexplained death	<= 1 hour
moxidectin	SC	70	1	1	tachypnoea, tachycardia, ataxia, collapse, death	<= 30 mins
oxfendazole	oral	25	1	0	collapse, application site swelling	unknown

colecalciferol	IM	1	1	0	collapse, lateral recumbency, nystagmus, sternal recumbency, panting, foetal movement	<= 2 mins
ivermectin	topical	12	8	2	hyperexcitation, convulsion, coma, recumbency, death, neurological signs NOS	<= 24 hours
flunixin	IV	1	1	1	anaphylaxis, convulsion, loss of consciousness, nervous system disorder NOS, sudden death	<= 2 mins
moxidectin	SC	20	2	1	ataxia, collapse, death	<= 30 mins
moxidectin	IV*	20	1	1	collapse, ataxia, drowsiness, death	<= 2 mins
levamisole	topical	14	14	0	pruritus	<= 2 mins
moxidectin	SC	21	2	1	hypersalivation, ataxia, recumbency, drowsiness, scour, ataxia, dehydration, mouth ulcer, death	<= 24 hours

eprinomectin	topical	100	1	0	hyperaesthesia, application site erythema, application site alopecia, desquamation, skin oedema, application site skin change NOS	<= 24 hours
ivermectin	topical	35	5	3	hypersalivation, ataxia, recumbency, dull, staggering, death	<= 24 hours
moxidectin	SC	90	15	0	ataxia, hypersalivation, coma, staggering, lateral recumbency, recumbency, drowsiness	<= 24 hours
moxidectin	IV*	44	1	1	opisthotonus, hyperaesthesia, collapse, death	<= 30 mins
pentobarbital sodium	IV	8	8	8	involuntary defecation, aggression, shaking,	<= 30 mins
pentobarbital sodium	IV	4	4	4	laboured breathing, increased heart rate, fit, partial lack of efficacy	<= 30 mins
danofloxacin flunixin	IV	1	1	1	shock, death	<= 2 mins
xylazine	IV	1	1	1	death, laboured breathing, paddling, collapse	<= 30 mins
ivermectin & closantel	topical	37	2	1	dry nose, lethargy, death by euthanasia,	<= 14 days

					hyperhidrosis, recumbency, tachycardia, hyperpnoea, ataxia, congestion of mucous membrane, ruminal stasis, drooling, anorexia	
benzylpenicillin & dihydrostreptomycin	IM	2	1	1	sudden death	<= 2 mins
closantel & ivermectin	topical	100	1	1	recumbency, anorexia, lethargy, blindness, death by euthanasia	<= 7 days
closantel & ivermectin	SC	12	5	0	allergic reaction, hypersalivation, tachypnoea, hyperpnoea, recumbency, oedema NOS	15-20 mins.
oxytetracycline & flunixin	IM	17	17	0	allergic reaction, hyperexcitation, increased sweating, agitation	minutes
vitamin E & selenium	IM	40	30	0	allergic reaction, hyperpnoea, shivering, trembling, tachypnoea	<= 30 mins.
closantel	SC	60	1	0	lateral recumbency, swollen face, vulvar oedema, mammary gland oedema, laboured breathing, increased heart rate, hyperactivity	<= 30 mins.

halofuginone base	oral	2	2	2	collapse, death	<= 24 hrs.
moxidectin	SC	70	1	1	tonic seizure, collapse, death by euthanasia	<= 2 mins.
moxidectin	IV*	60	1	1	sudden death	<= 30 mins.
vitamin E & selenium	SC	220	176	1	abdominal pain, urticaria, death, bloated, vocalisation, recumbency, depression	<= 6 hrs.
moxidectin	SC	40	1	0	ataxia, recumbency, coma	<= 24 hrs.
meloxicam ceftiofur	SC SC	1	1	1	dyspnoea, recumbency, death	<= 30 mins.
moxidectin	SC	34	1	1	death, pyrexia, hyperpnoea, unconscious, recumbency	<= 30 mins.
levamisole	topical	20	10	0	application site lesion, application site crust, skin slough, peeling skin	<= 14 days

nicotinamide, dexpanthenol, vitamins A, D3, E, B1, B2, B6 & B12	IM	14	3	2	hypersalivation, recumbency, sudden death	<= 6 hrs.
moxidectin	SC	14	1	0	neurological pain NOS, neurological symptoms NOS	<= 30 mins.
amoxicillin	IM	1	1	1	death	<= 30 mins.
moxidectin	IV*	25	2	1	lethargy, death	unknown
moxidectin	IV*	20	1	1	death	<= 12 hrs.
levamisole	topical	32	32	1	hyperexcitation, hyperaesthesia, hypersalivation, recumbency, sudden death	<= 30 mins.
levamisole & oxyclozanide	oral	3	3	0	diarrhoea	<= 24 hrs.
amitraz	topical	7	7	0	fatigue, staggering	<= 12 hrs.
levamisole hydrochloride oxytetracycline hydrochloride oxytetracycline dihydrate	SC IM IM	110	7	3	hypersalivation, impaired consciousness, anorexia, loss of consciousness, convulsion, death	<= 1 hr.

ivermectin & closantel	topical	21	1	0	blindness	<= 7 days
closantel	SC	2	2	0	excitation, behavioural disorder NOS	<= 30 mins.
oxytetracycline & flunixin	IV*	2	2	0	blood in faeces, scour, melaena, LEE	<= 48 hrs.
levamisole	SC	22	1	1	hyperexcitation, hypersalivation, recumbency, sudden death, abnormal test result	<= 30 mins.
ivermectin & closantel	topical	78	2	0	impaired vision, blindness	<= 14 days
ivermectin & closantel	topical	22	1	0	recumbency, dullness, depression, anorexia	<= 24 hrs.

* denotes off-label route of administration
IM: intramuscular, IV: intravenous, SC: subcutaneous

Table 4B: Canine Reports

Active Substance	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
diethanolamine fusidate, framycetin sulphate, nystatin & prednisolone	auricular	1	1	0	deafness	<= 7 days
oxytetracycline	SC	51	51	0	cough, partial lack of efficacy, swelling around eye, skin swelling, allergic oedema, dyspnoea	<= 24 hours
ciclosporin	oral	1	1	0	muscle tremor, vomiting, seizure NOS, epileptic seizure, shaking	<= 7 days
selamectin	topical	2	1	0	collapse, respiratory distress, ataxia	<= 2 mins
meloxicam meloxicam cefquinome	SC	1	1	1	dullness, polydipsia, vomiting, ascites, depression, not eating, weakness, jaundice, acute renal failure, azotaemia, death	<= 14 days
oxytetracycline	IM	1	1	0	collapse, anaphylactic type reaction	<= 30 mins
carprofen	oral	1	1	1	hepatomegaly, hepatic disorder NOS, lymphocytosis, death by euthanasia, decreased	<= 7 days

					appetite, retching, vomiting, diarrhoea, polyuria, polydipsia, lethargy, respiratory sound, increased respiratory rate	
pyriprole	topical	1	1	0	seizure NOS, tachycardia, hyperthermia, muscular hypertonicity, panting, distress, behavioural disorder NOS	<= 24 hours
marbofloxacin, clotrimazole & dexamethasone	auricular	1	1	0	deafness	unknown
nitroscanate	oral	1	1	0	dull, ataxia, falling	<= 24 hours
buprenorphine	IV	3	3	0	crying, discomfort NOS, pain NOS	<= 2 mins
chlorhexidine gluconate & miconazole nitrate	oral*	1	1	0	diarrhoea, pale mucous membrane, lethargy, anorexia	<= 24 hours
insulin	SC	1	1	0	collapse, dehydration, hyperglycaemia	unknown
meloxicam	oral	1	1	0	digestive tract disorder NOS, renal disorder NOS	> 30 days
gentamicin sulfate, betamethasone valerate & clotrimazole	auricular	1	1	0	deafness	<= 24 hours

trilostane	oral	1	1	0	vomiting, diarrhoea, dullness, weakness, elevated ALT, elevated SAP, hyperkalemic condition, hyponatremia, inappetance, platelet disorder NOS	<= 7 days
fipronil	topical	1	1	0	pyoderma	4 days
selamectin	topical	1	1	1	haemorrhagic gastroenteritis, inappetance, seizure, death by euthanasia	24 hrs.
diethanolamine fusidate, framycetin sulfate, nystatin & prednisolone	auricular	1	1	0	deafness	<= 7 days
estriol	oral	1	1	0	syncope, elevated liver enzymes, elevated bile acids, abnormal test result	<= 6 hrs.
ciclosporin	oral	1	1	0	rash, colitis, haemorrhagic diarrhoea	<= 6 hrs.
trilostane	oral	1	1	0	elevated BUN, elevated creatinine, adipsia, anuria, inappetance, dehydration, increased packed cell volume (PCV), proteinuria, blood in urine, shivering, collapse, malaise, discoloured urine, hypoadrenocorticism, electrolyte disorder,	<= 7 days

					sudden death, urine abnormalities NOS, dull, vomiting, hyperkalemic condition, hypocalcaemic condition	
fluralaner	oral	2	1	1	pyrexia, lethargy, anorexia, erythematous rash, skin oedema, death, moist dermatitis, alopecia	<= 7 days
diethanolamine fusidate, framycetin sulfate, nystatin & prednisolone	auricular	1	1	0	deafness	<= 48 hrs.
meloxicam imepitoin	oral oral	1	1	0	seizure NOS, sedation, vomiting, ataxia, proprioception deficit, dull, restlessness	<= 24 hrs.
meloxicam	oral	1	1	0	sleepiness, melaena, vomiting, diarrhoea, elevated BUN, elevated creatinine, decreased red blood cell count, depression	<= 24 hrs.
milbemycin oxime & praziquantel	oral	1	1	0	lethargy, tremor, vocalisation	<= 1 hr.
praziquantel, pyrantel embonate & febantel	oral	2	2	0	vomiting, hypersalivation, twitching	<= 6 hrs.

amoxicillin & clavulanic acid	SC	3	3	0	injection site reaction NOS, injection site necrosis	unknown
oclacitinib	oral	1	1	0	lymphoma	> 30 days
milbemycin oxime & praziquantel	oral	1	1	0	lethargy, walking difficulty, distension of abdomen, shaking	<= 6 hrs.
desoxycortone pivalate	SC	1	1	0	inappetance, lethargy, hypokalaemia, electrolyte disorder, diarrhoea, decreased appetite, elevated BUN, elevated liver enzymes, inversion of albumin/globulin ratio, weight gain	<= 14 days
diethanolamine fusidate, framycetin sulfate, nystatin & prednisolone	auricular	1	1	0	deafness	<= 24 hrs
carprofen	SC	1	1	0	injection site reaction NOS, injection site necrosis	<= 7 days
carprofen propofol buprenorphine	SC SC SC	1	1	0	injection site reaction NOS	<= 14 days
firocoxib	oral	1	1	1	gastric ulceration NOS, death	> 30 days
metronidazole	oral	1	1	0	seizures, central vestibular syndrome (vertical nystagmus, severe ataxia)	<= 7 days

cimicoxib	oral	1	1	0	abdominal pain, vomiting, gastric perforation	> 30 days
cimicoxib amoxicillin & clavulanic acid	oral oral	1	1	1	vomiting, dull, lethargy, elevated renal parameters, emesis, death, gastric perforation	<= 30 days

* denotes off-label route of administration
IM: intramuscular, IV: intravenous, SC: subcutaneous

Table 4C: Ovine Reports

Active Substance	**Route**	**No Treated**	**No Reacted**	**No Dead**	**Clinical signs**	**Speed of onset**
oxytetracycline	IM	4	2	1	respiratory distress, recumbency, death, foaming at mouth, allergic reaction	<= 30 mins
ivermectin & closantel	IM	200	30	1	injection site reaction NOS, death, ataxia, staggering	<= 1 hour
cypermethrin	topical	84	14	2	staggering, death, pain NOS, recumbency	<= 1 hour
closantel sodium & mebendazole	oral	5	5	0	blindness	<= 14 days

tilmicosin	SC	1	1	1	recumbency, panting, death	<= 30 mins.
rafoxanide	oral	370	5	5	death	> 30 days
levamisole	oral	66	9	5	behavioural disorder NOS, neurological disorder NOS, hypersalivation, recumbency, death	<= 30 mins.

IM: intramuscular, SC: subcutaneous

Table 4D: Feline Reports

Active Substance	**Route**	**No Treated**	**No Reacted**	**No Died**	**Clinical signs**	**Speed of onset**
milbemycin oxime & praziquantel	oral	2	2	0	depression, neurological signs NOS, coma, unable to stand	<= 24 hours
buprenorphine	IV	1	1	0	crying, discomfort NOS, pain NOS	<= 2 mins
xylazine ketamine	IM	3	3	3	death	<= 1 hour
cefovecin fipronil, methoprene, eprinomectin & praziquantel	SC topical	1	1	1	melaena, dull, inappetance, apathy, ataxia, decreased body temperature, proprioception deficit, seizure NOS,	<= 24 hours

meloxicam	SC/IV				death, dehydration, dilated pupils	
pyrantel & praziquantel	oral	1	1	0	vomiting, disorientation	<= 30 mins.
fipronil, (S)-methoprene, eprinomectin & praziquantel	topical	1	1	0	vomiting, diarrhoea	<= 24 hrs.
thiamazole	oral	1	1	1	anaemia, death by euthanasia, leucopoenia	> 30 days
fipronil, (S)-methoprene, eprinomectin & praziquantel	topical	200	10	0	malaise, application site scab	<= 24 hrs.
cefovecin itraconazole	SC oral	1	1	0	off colour, hepatic jaundice, hepatic failure, not eating, lethargy	<= 30 days

IM: intramuscular, IV: intravenous, SC: subcutaneous

Table 4E: Equine Reports

Active Substance	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
trimethoprim & sulfadoxine	IV	1	1	1	staggering, collapse, laboured breathing, death	<= 2 mins

florfenicol	oral*	1	1	0	reddening of the skin, increased salivation, colic, application site swelling, medication error	<= 24 hours
butylscopolamine bromide & metamizole	IV	1	1	0	ataxia, collapse NOS, breathing difficulty, injection site swelling	<= 2 mins
ketamine	IV	1	1	1	death	<= 30 mins
oxytetracycline	IV	2	2	0	foam in nose, product problem, congestion of mucous membrane, tachypnoea	<= 30 mins
oxytetracycline	IV	1	1	0	foam in nose, congestion of mucous membrane, tachypnoea	<= 30 mins

oxytetracycline	IV	1	1	0	foam in nose, congestion of mucous membrane, tachypnoea	<= 30 mins
flunixin	IV	1	1	1	ataxia, mydriasis, lethargy, diarrhoea, death	<= 2 mins.
human chorionic gonadotrophin	IM	1	1	0	hives	<= 24 hrs.
trimethoprim & sulfadoxine	perivascular*	4	2	2	collapse, death, vocalisation, foetal death	<= 2 mins.
sodium hyaluronate	intraarticular	1	1	0	lameness	<= 24 hrs.
sodium hyaluronate	intraarticular	1	1	0	lameness	<= 24 hrs.

flunixin	IV	1	1	1	convulsion, twitching, death	<= 2 mins.

* denotes off-label route of administration
IM: intramuscular, IV: intravenous

Table 4F: Bee Reports

Active Substance	Route	No Treated	No Reacted	No Died	Clinical signs	Speed of onset
thymol	in-hive	8 (hives)	3 (queens)	0	uncoded sign: off-lay	<= 24 hrs.
formic acid	in-hive	2 (hives)	2 (hives)	unknown	increased mortality rate, death	<= 24 hrs.
formic acid	in-hive	10 (hives)	10 (hives)	3 (queens), hundreds of other bees	increased mortality rate, death	<= 48 hrs.
thymol	in-hive	7 (hives)	3 (queens)	0	uncoded sign: off-lay	<= 14 days

thymol	in-hive	2 (hives)	1 (queen)	0	uncoded sign: loss of queen, emergency cells built	<= 30 days

Table 5: 2015-2016 adverse reactions assigned causality 'A' or 'B' associated with the use of immunological products

Table 5A: Bovine Reports

Active Substance (antigen)	**Route**	**No Treated**	**No Reacted**	**No Died**	**Clinical signs**	**Speed of onset**
Inactivated Leptospira borgpetersenii serovar Hardjo	SC	57	6	0	stillbirth, partial LEE, weakness, death (offspring)	> 30 days
Inactivated antigen of cytopathogenic BVDV strain C-86	IM	30	1	0	swelling around eye, face and neck swelling, facial oedema, injection site reaction NOS	<= 24 hours
Bovine Herpes Virus type 1 (BHV-1)	IM	10	1	1	sudden death	<= 6 hours
BHV-1, strain GK/D (gE^-)	IM	50	1	1	injection site swelling, death	<= 48 hours
Salmonella Dublin & Salmonella typhimurium	SC	260	1	1	death	<= 24 hrs.

IM: intramuscular, SC: subcutaneous

Table 5B: Canine Reports

Active Substance (antigen)	**Route**	**No Treated**	**No Reacted**	**No Died**	**Clinical signs**	**Speed of onset**

Canine parvovirus (strain 154) *Inactivated Leptospira interrogans serogroup - Canicola; serovar portland-vere, strain Ca-12-000 Icterohaemorrhagiae; serovar copenhageni, strain 820K*	SC	4	4	2	anorexia, weight loss, recumbency, lateral recumbency, death, death by euthanasia, pyoderma	<= 24 hours
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans*	SC	1	1	0	seizure NOS	<= 24 hours

serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005)						
Canine parvovirus (strain 154)	SC	6	1	0	diarrhoea, lethargy	<= 30 mins
≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$ [2] of live canine parainfluenza virus strain Cornell.	intranasal	1	1	0	dyspnoea, collapse	<= 24 hours
Live attenuated canine Parvovirus, strain NL-35-D, low passage, Inactivated Leptospira canicola, and inactivated Leptospira icterohaemorrhagiae	SC	1	1	0	seizure NOS, lethargy, hypoglycaemia	<= 24 hours

Canine distemper virus, strain Onderstepoort, Canine adenovirus type 2, strain V197, Canine parvovirus, Strain SAH & Canine parainfluenza virus, strain FDL	IM	1	1	0	arched back, injection site complication NOS, injection site lump	<= 6 hours
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-*	SC	1	1	0	injection site abscess, lethargy	<= 7 days

073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005)						
≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$ [2] of live canine parainfluenza virus strain Cornell.	intranasal	1	1	0	collapse, tonic-clonic seizure	<= 6 hours
Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa	SC	7	1	0	injection site swelling, anorexia	<= 48 hours

serovar Dadas (strain Gr-01-005)						
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup*	SC	1	1	1	diarrhoea, death	<= 7 days

Grippotyphosa serovar Dadas (strain Gr-01-005) *Inactivated rabies virus strain Pasteur RIV*						
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri*	SC	1	1	0	injection site abscess	<= 14 days

serogroup Grippotyphosa serovar Dadas (strain Gr-01-005)						
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira interrogans serogroup - Canicola; serovar portland-vere, strain Ca-12-000 Icterohaemorrhagiae; serovar copenhageni, strain 820K*	SC	1	1	1	vomiting, lethargy, anaemia NOS, leucocytosis, pale mucous membrane, death by euthanasia	<= 24 hours
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira interrogans serogroup - Canicola;*	SC	1	1	1	lethargy, vomiting, circulatory collapse, death	<= 24 hours

serovar portland-vere, strain Ca-12-000 Icterohaemorrhagiae; serovar copenhageni, strain 820K						
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira interrogans serogroup - Canicola; serovar portland-vere, strain Ca-12-000 Icterohaemorrhagiae; serovar copenhageni, strain 820K*	SC	1	1	0	vomiting, dyspnoea, lethargy, panting	<= 6 hours
Canine parvovirus (strain 154) *Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L.*	SC	1	1	0	generalised weakness, ataxia	<= 12 hours

interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005)						
Inactivated rabies virus strain Pasteur RIV	SC	2	1	0	vomiting, drowsiness - neurological disorder, hind limb ataxia, impaired consciousness	<= 30 mins
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-*	SC	1	1	0	facial oedema, periorbital oedema	2 hrs.

000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005)						
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni*	SC	1	1	0	corneal oedema, corneal ulcer	<= 48 hrs.

(strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005)						
Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5, Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae	SC	1	1	0	anaphylactic shock, breathing difficulty, pale mucous membranes, fit	<= 24 hrs.
Canine distemper virus, strain N-CDV, Canine adenovirus Type 2, strain Manhattan, Canine parainfluenza virus, strain NL-CPI-5,	SC	1	1	0	emesis	10 mins.

Canine Parvovirus, strain NL-35-D, Leptospira canicola, Leptospira icterohaemorrhagiae *≥ $10^{8.0}$ and ≤ $10^{9.7}$cfu[1] of live Bordetella bronchiseptica bacteria strain B-C2 and ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$ [2] of live canine parainfluenza virus strain Cornell.*	intranasal					
Canine distemper virus, Canine adenovirus 2, Canine parvovirus & Canine parainfluenzavirus *Inactivated Leptospira strains: - L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) - L. interrogans serogroup Icterohaemorrhagiae serovar*	SC	1	1	0	vomiting, collapse	<= 6 hrs.

Copenhageni (strain Ic-02-001) - L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) - L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005)						

IM: intramuscular, SC: subcutaneous

Table 5C: Feline Reports

Active Substance (antigen)	**Route**	**No Treated**	**No Reacted**	**No Died**	**Clinical signs**	**Speed of onset**
Inactivated rabies virus strain Pasteur RIV	SC	1	1	1	circulatory collapse, death	<= 2 mins
live attenuated feline calicivirus, strain F9, live attenuated feline herpes virus type 1, strain G2620A, live attenuated feline panleucopenia virus, strain MW-1	SC	3	3	0	injection site abscess, pyrexia, lethargy	<= 7 days
live attenuated feline calicivirus, strain F9, live attenuated feline herpes virus type 1,	SC	1	1	1	sudden death, collapse	<= 30 mins

strain G2620A, live attenuated feline panleucopenia virus, strain MW-1						
live attenuated feline calicivirus, strain F9, live attenuated feline herpes virus type 1, strain G2620A, live attenuated feline panleucopenia virus, strain MW-1 *FeLV recombinant p45 antigen*	SC	1	1	0	hind limb ataxia, anorexia, general pain, lethargy	<= 24 hours
Live attenuated feline enteritis (panleucopenia) virus (FPV), Snow Leopard strain, Live attenuated feline rhinotracheitis virus (FVR), strain FVRm, Live attenuated Calicivirus, strain F9	SC	1	1	0	injection site pyoderma, injection site dermatitis	5 days
Inactivated feline panleucopenia virus, strain CU4 Inactivated feline calicivirus, strain 255 Inactivated	SC	2	2	0	hiding, aggression, reluctant to move, abnormal posture	3 hrs.

feline rhinotracheitis virus, strain 605 Inactivated Chlamydophila felis, strain Cello Inactivated feline leukaemia virus, strain 61E						
Inactivated feline panleucopenia virus, strain CU4 Inactivated feline calicivirus, strain 255 Inactivated feline rhinotracheitis virus, strain 605 Inactivated Chlamydophila felis, strain Cello Inactivated feline leukaemia virus, strain 61E	SC	1	1	0	anorexia, depression	<= 6 hrs.
Minimum quantity of purified p45 FeLV-envelope antigen	SC	2	1	0	emesis, anorexia	<= 6 hrs.

SC: subcutaneous

Table 5D: Ovine reports

Active Substance (antigen)	**Route**	**No Treated**	**No Reacted**	**No Died**	**Clinical signs**	**Speed of onset**
Clostridium perfringens beta toxoid, *Clostridium perfringens*	SC	200	200	4	injection site abscess, injection site swelling, bronchopneumonia, respiratory tract disorder NOS, death	<= 6 hrs.

epsilon toxoid, *Clostridium septicum* toxoid, *Clostridium tetani* toxoid, *Clostridium novyi* toxoid, *Clostridium chauvoei, Mannheimia haemolytica, Pasteurella trehalosi.*						
C. perfringens type A toxoid, *C. perfringens* type B & C toxoid, *C. perfringens* type D toxoid, *C. chauvoei, C. novyi, C. septicum, C. tetani, C. sordellii, C. haemolyticum.*	SC	2	2	0	injection site swelling, seizure NOS	<= 30 mins.

SC: subcutaneous

Table 5E: Rabbit report

Active Substance (antigen)	**Route**	**No Treated**	**No Reacted**	**No Died**	**Clinical signs**	**Speed of onset**
Live myxoma vectored RHD virus strain 009	SC	1	1	0	ataxia, nystagmus, head tilt	<= 6 hours

SC: subcutaneous

Abbreviations

HPRA: Health Products Regulatory Authority
IM: intramuscular
IN: intranasal
IV: intravenous
LEE: lack of expected efficacy
NOS: not otherwise specified
PSUR: periodic safety update report
SAE: suspected adverse event
SC: subcutaneous
VMP: veterinary medicinal product