HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Annual Veterinary Pharmacovigilance Report 2021

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Suspected Adverse Event Reports to Veterinary Medicinal Products received by the HPRA during 2021

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ABBREVIATIONS

HPRA	**Health Products Regulatory Authority**
VMP	Veterinary medicinal product
SAR	Suspected adverse reaction
LEE	Lack of expected efficacy
SAE	Suspected adverse event
MAH	Marketing authorisation holder
VPA	Veterinary product authorisation
SPC	Summary of Product Characteristics
CVMP	Committee for Medicinal Products for Veterinary use
PSUR	Periodic Safety Update Report
CAP	Centrally authorised product
EMA	European Medicines Agency
NCA	National Competent Authority
PI	Product information
NVR	New Veterinary Regulation

1. Introduction

The Health Products Regulatory Authority (HPRA) is an independent public sector organisation responsible for the regulation of health products, including veterinary medicinal products (VMPs). Our mission is to regulate medicines and devices for the benefit of people and animals. Part of our remit is the ongoing monitoring of the quality, safety and efficacy of authorised VMPs (a process known as pharmacovigilance). This includes products that have been authorised nationally or centrally (following the opinion of the European Medicines Agency). In relation to safety and efficacy, this role is fulfilled through a nationwide reporting system for adverse events (pharmacovigilance system), which is designed to monitor products under actual use conditions. Veterinary pharmacovigilance is undergoing a huge change as the process of preparing for the introduction of the new veterinary regulation continued throughout 2021. Last year was the final year where pharmacovigilance was regulated under the Directive 2001/82/EC, as new legislation - Regulation 2019/6 – became applicable in the EU on 28 January 2022. That regulation brought about substantial change in how veterinary medicinal products are authorised, monitored and controlled in the European Union.

The scope of veterinary pharmacovigilance involves the surveillance of:

- Suspected adverse reactions (SAR) in animals to VMPs used under authorised conditions
- Off-label use of VMPs in animals (i.e. where a product is not used according to its authorised summary of product characteristics (SPC))
- Lack of expected efficacy (LEE) of VMPs
- Reported violations of approved residue limits
- Adverse reactions in humans related to the use of VMPs
- Potential environmental problems

These reports are collectively known as suspected adverse events (SAEs) and are received by the HPRA primarily from marketing authorisation holders (MAHs). MAHs are pharmaceutical companies that have been granted approval to market a VMP within the European Union (either by an EU Member State or the European Medicines Agency). MAHs are required under the current legislation to report all SAEs occurring in Ireland to the Union Pharmacovigilance Database within 30 days. Reports may also be received from veterinary health professionals and animal owners directly. SAE reports are collated and evaluated by the HPRA and relevant 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.

SPC: A document providing officially approved information on a VMP

The minimum requirements for an SAE report to be considered valid are detailed in Table 1.

Table 1: Suspected Adverse Events - minimum information required

An SAE report will be considered valid when at least the following core information is provided:
▪ **an identifiable reporter (e.g. Veterinary Surgeon/Veterinary Nurse, Pharmacist, animal owner)**
▪ **animal/human details: species, age, sex**
▪ **the name and veterinary product authorisation (VPA) number of the product in question**
▪ **details of the adverse event**
While the above outlines the minimum requirements for a valid SAE report, the reporter should endeavour to provide as comprehensive an account as possible in order to facilitate a full scientific evaluation. Where relevant, this may include the provision of laboratory test results and necropsy findings.

2. National Pharmacovigilance Surveillance

The HPRA received 426 valid national SAE reports in 2021. These reports involved a range of animals as presented in Table 2. Six reports concerned suspected adverse reactions in humans following exposure to a VMP.

Table 2. Overview of reports received in 2021

Species	Total number reports	Total number reacting
Food producing animals		
bovine	137	2497
ovine	50	1014
equine	9	21
porcine	3	1915
salmon	2	377,000
Companion animals		
canine	181	343
feline	31	34
rabbit	7	7
Other		
human	6	6
Total	**426**	**382,837**

Figure 1 outlines the primary sources of SAE reports received by the HPRA between 2016 and 2021 and Figure 2 shows a detailed look at the source of SAE reports received by the HPRA in 2021.

Figure 1: Source of SAE reports from 2016 to 2021

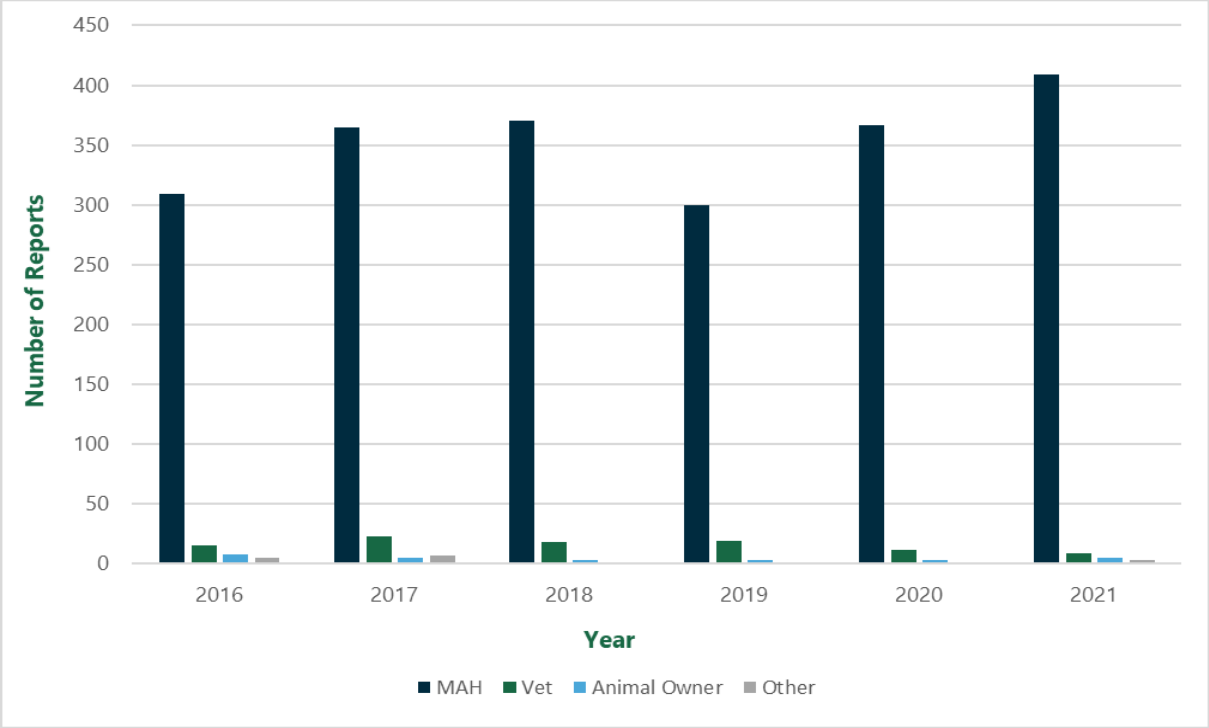
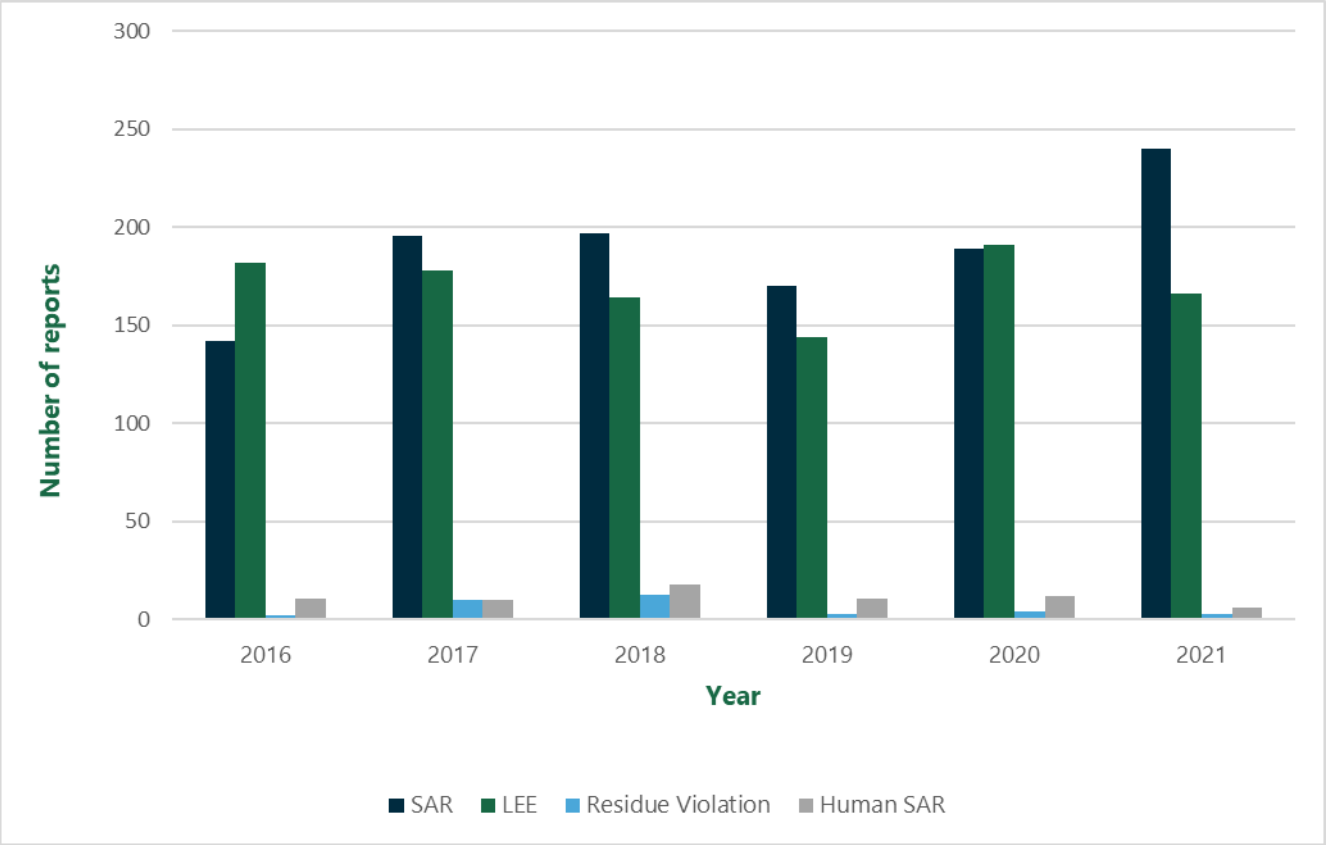


Figure 2: A detailed look at the number of SAE reports from sources in 2021

Of the 426 SAE reports received in 2021, 203 reports involved solely pharmaceutical products, 205 reports involved solely immunological products and 18 reports related to the use of both pharmaceutical and immunological products concurrently. There were 246 reports that involved SARs or serious SARs (SSAR) in animals, 166 reports involved suspected LEE, eleven reports involved combined SAR/LEE and three reports related to violation of an approved residue limit. Six reports related to SAEs in humans. A comparison of the types of reports received from 2016 to 2021 is shown in Figure 3 below.

Figure 3: Number of SAE reports by category received from 2016 to 2021


300
250
200
150
100
50
0
Number of reports
2016
2017
2018
2019
2020
2021
Year
SAR
LEE
Residue Violation
Human SAR

2.1 Reports of adverse reactions

Reports of SAEs are assessed by the relevant MAH and the HPRA for any association between the event and the product(s) administered to the animal(s), using an established causality assignment system as shown in Table 3 below.

Table 3: Assessing Causality

The following factors will be taken into account:
• **associative connection in time or anatomic site**
• **pharmacological explanation, previous experience 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 must be complied with: ◦ there must 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 must be consistent with the known pharmacology and toxicology of the drug ◦ there must 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 'O1'	When a VMP association cannot be discounted but other factors prevent a conclusion being drawn.
Causality 'O'	When reliable data concerning an adverse reaction is unavailable or insufficient to make an assessment of causality.
Causality 'N'	When sufficient information exists to establish beyond reasonable doubt that drug administration was not likely to be the cause of the event.

The European Commission (2011)

An adverse event report may contain details of more than one VMP administered. Where this occurs, causality is assigned on a product-specific basis rather than to the overall report. In the context of this article, reports involving multiple products with different causalities have been counted more than once. There were 246 SAR/serious SAR reports relating to animals received. For a report to be considered as a serious suspected adverse reaction (SSAR), it must fulfil certain criteria including:

- resulting in death
- is life-threatening
- results in a persistent or significant disability or incapacity or a congenital anomaly or birth defect

These reports related to a number of species including dogs (150 reports), cattle (42 reports), cats (22 reports), sheep (13 reports), rabbits (5 reports), horses (7 reports) and pigs (one report).

Of these reports, 140 related solely to pharmaceutical products. Twenty-nine reports were considered to be 'probably' (causality 'A') product related, forty-six reports were considered to be 'possibly' (causality 'B') product related. In fifty-one reports there was insufficient information (causality 'O1'/'O') to assign definitive causality. Four reports were considered 'unlikely' to be product related (causality 'N'). Ten reports contained multiple products which were assigned different causalities.

Eighty-seven reports related solely to immunological products. Product involvement was considered 'probable' (causality 'A') in fourteen reports, and possibly related (causality 'B') in thirty-two reports. In thirty-two reports there was insufficient information to assign a definitive product association (causality 'O1'/'O'). In three reports product involvement was considered 'unlikely' (causality N). Six reports included multiple products which were assigned different causalities.

Thirteen reports detailed concurrent pharmaceutical and immunological administration. None of these reports were assigned causality 'A'. Product involvement was considered 'possible' in one report (causality 'B'), and in three reports insufficient information was provided to assign a definitive association (causality 'O1'/'O'). Nine reports contained multiple products which were assigned different causalities.

2.1.1 Adverse reactions following human exposure

Six SAE reports of human exposure to VMPs were received during the reporting period. Four of these reports were received following exposure to immunological products and two reports arose from exposure to a pharmaceutical product. The most common clinical symptoms reported included injection site swelling/pain and injection site bleeding. Two reports involved ocular exposure to a product resulting in temporarily impaired vision and eye stinging. As per established pharmacovigilance practice for veterinary medicinal products, causality assessments of human adverse reactions have not been conducted by the HPRA for these reports.

Those administering VMPs are reminded to exercise due caution when handling veterinary medicinal products and to pay particular attention to any special precautions for the use of individual products as detailed in the relevant product information (SPC) published on the HPRA website or on the package labelling/leaflet accompanying the product.

Following implementation of the NVR on 28 January 2022, MAHs are reminded of their obligation to report any adverse events that occur following human exposure to a veterinary medicinal product to the Union Pharmacovigilance Database within the new timeframe of 30 days from receipt of the

report.

2.2 Reports of lack of expected efficacy

The HPRA received 166 reports relating solely to lack of expected efficacy (LEE) in 2021.

Of these reports, forty-nine related solely to pharmaceutical products and involved cattle (24 reports), sheep (11 reports), dogs (8 reports), horses (2 reports) and cats (4 reports). Three reports were considered 'probably' (causality 'A') related to product use and ten reports were considered to be 'possibly' (causality 'B') related to product use. In twenty-four reports insufficient information was provided to assign a definitive association (causality 'O1'/'O'), while in four reports product involvement was considered 'unlikely' (causality 'N'). In seven reports no assessment was performed as the reports involved off-label use of the products and efficacy can only be expected following recommended use of a product. One report contained multiple products which were assigned different causalities.

There were 112 LEE reports received that solely involved immunological products, where the product was suspected to have failed to induce protective immunity. The reports concerned cattle (62 reports), sheep (26 reports), dogs (18 reports), cats (1 report), salmon (1 report), rabbits (2 reports) and pigs (2 reports). No reports were classified as 'A' (probable), however, in eleven reports, product involvement was classified as 'B' (possible). Forty-two reports were assessed as 'unclassifiable/inconclusive' ('O' or O1') and twenty-three reports were classed as 'N' (unlikely). Twenty-one reports contained multiple products which were assigned different causalities. Fifteen reports involved off-label-use and as efficacy can only be expected following recommended use of a product, no assessment was performed for these reports.

In addition, five LEE reports involved both pharmaceutical and immunological products. Immunological product involvement was classified as 'O1' (inconclusive) in two reports and no assessment was performed for the immunological product in three reports as they involved off-label use.

Where it is not specified within an adverse event report whether product use was according to its authorised SPC or not, a worst case scenario is assumed – i.e. the report will be classified as though the product was used as recommended.

2.3 Causality assessment

An adverse event report may contain details of more than one VMP administered. Where this occurs, causality is assigned on a product-specific basis rather than to the overall report. In the context of this article, reports involving multiple products with different causalities have been counted more than once. Of the SAR, SSAR and combined SAR/LEE reports received by the HPRA in 2021 containing multiple products, the involvement of a reported VMP with the observed reaction was considered to have been 'probable' (causality 'A') in two reports and 'possible' (causality 'B') in fifty-five reports. In fifty-nine reports, there was insufficient/inconclusive information available to assign definitive causality (causality 'O'/'O1') and in twenty-four reports it was considered unlikely (causality 'N') that a reported VMP was responsible for the observed reaction. Where there is a difference in the causality assessment assigned to the report by the MAH and the HPRA, the causality assignment of the HPRA takes precedence and is the one uploaded to the central European database.

From 28 January 2022, in accordance with Regulation 2019/6, it is no longer a requirement for MAHs or NCAs to assign a causality to adverse event reports. However, they must continue to be categorised as either serious or non-serious. All serious and non-serious adverse event reports must be uploaded to the Union pharmacovigilance database within 30 days of their reporting.

A line listing of SAE reports originating from Ireland in 2021, organised by active substance, assigned causality 'A' or causality 'B' is included in Table 4 of the version of this report that is published on the HPRA website.

3. European Pharmacovigilance Issues: Regulatory action case study – Updated European Medicines Agency advice on the use of live attenuated PRRSV vaccines.

In April 2021, following a review of the use of live attenuated PRRSV vaccines in pigs, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the risk of recombination of a modified live PRRS vaccine strain with other PRRS viruses is low and, additionally, identified risk mitigation measures to further decrease the risk of these events occurring in the future. The HPRA published an updated safety notice to highlight the following conclusions of the CVMP:

- The benefit-risk balance of modified live PRRS vaccines remains positive.
- Modified live PRRSV vaccines continue to be an appropriate tool for the management of PRRSV infection/disease in Europe.
- In order to limit the potential risk of recombination between PRRS modified live virus (MLV) vaccine strains of the same genotype, veterinary practitioners should, where possible, avoid using live attenuated PRRSV vaccines from different manufacturers in animals in the same herd. Veterinary practitioners should monitor for clinical signs of PRRS in vaccinated pig farms. In case of switching from one PRRS MLV vaccine to another, a transition period between both MLV vaccines should be respected. This period should preferably last longer than the shedding period of the previous used MLV vaccine.

Further to this, the implementation of strict external and internal biosecurity measures is recommended to decrease the transmission of PRRS field viruses and PRRS MLV vaccine strains between and within farms. More information on the CVMP advice and outcomes of proceedings is available on the HPRA's website (here). As with all vaccines and veterinary medicinal products, any suspected adverse events should be reported to the HPRA or the marketing authorisation holder. The EMA continues to monitor the safety of all CAPs, taking regulatory action as appropriate.

3.1 Changes to Pharmacovigilance arising from the New Veterinary Regulation (EU) 2019/6

Throughout 2021, preparations continued for the implementation of Regulation 2019/6 which came into effect on 28 January 2022. The main areas of pharmacovigilance focus for progress during the year were the development of a Union Product Database system for all veterinary medicinal products that have been authorised within the EU/EEA and the launch of Eudravigilance Vet 3 (EVVet3). EVVet3 is a system that forms part of the Union Pharmacovigilance Database in respect of the reporting of adverse events and the requirements for signal management of adverse events in the European Union.

The main pharmacovigilance changes relating to the NVR are as follows:

- As and from 28 January 2022 MAHs must upload all suspected adverse event reports (this

includes both serious and non-serious) reported to them to the Union Pharmacovigilance Database within 30 days of receipt of the reports. Prior to this date, MAHs were required to report only serious adverse event reports to the HPRA within 15 days of receipt of the report.

- Periodic Safety Update Reports (PSURs) are no longer required. Instead, MAHs must to carry out a signal management process for their veterinary medicinal products. The signal management process will enable continuous monitoring of the benefit-risk balance of a product and forms a core element of the pharmacovigilance system. MAHs must record at least annually all results and outcomes of the signal management process in the Union Pharmacovigilance Database.
- MAHs must have in place a Pharmacovigilance System Master File that describes in detail the pharmacovigilance system for their product(s). The PSMF is to be located at the site location where the main pharmacovigilance activities of the MAH are performed, or where the QPPV operates (within the EU).

Throughout the year, the HPRA published updates on the implementation of Regulation 2019/6 which included updates in respect of pharmacovigilance matters and these are available on the HPRA website (link here). In October 2021, the HPRA held an Information Day webinar for stakeholders. This event included a dedicated session on pharmacovigilance changes, compliance and monitoring. Specific presentations on signal management, the QPPV and 'good pharmacovigilance practice' and ensuring compliance of the pharmacovigilance system were delivered. The material from these sessions, including recorded presentations and associated Questions and Answers are available on our website (link here).

'Signal' means information that arises from one or multiple sources, which suggests a potentially new causal association, or a new aspect of a known causal association between an intervention and an adverse event or a set of related adverse events, that is judged likely to justify further investigation of possible causality.

4. Conclusion

Figure 4: Total number of SAE Reports to the HPRA from 2009-2021

There remains a general trend of increasing numbers of reports since 2009, with 2021 figures representing receipt of the second highest number of adverse event reports to date. This trend for increased reporting of adverse events is very much welcomed by the HPRA and likely reflects a greater public awareness of the importance of reporting SAEs rather than an absolute increase in the number of adverse reactions occurring. The HPRA remains encouraged by this 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 and when a safety risk relating to the use of authorised VMPs is identified, appropriate regulatory steps can be taken by the HPRA in consultation with the MAH to reduce this risk.

Although the overall trend of reporting SAEs is increasing, the number of cases reported directly to the HPRA by Veterinary Surgeons and Pharmacists remains relatively low (nine SAE reports were submitted by veterinarians directly to the HPRA in 2021, equating to 2.1% of all reports received). Veterinary professionals as well as persons licensed to sell or supply animal remedies are reminded of their obligation to notify the HPRA or the relevant MAH of all suspected adverse reactions. In particular, serious SAEs, all unexpected adverse reactions and all symptomatic human adverse events associated with the use of VMPs should be reported.

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; reports may be submitted via a number of different methods and veterinary practitioners are encouraged to enlist their veterinary nurse colleagues' help in discharging their responsibilities to report adverse events. Provided that the mandatory information (as described in Table 1 above) is included in the report, there will normally be no need for the HPRA to consult 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 in question.

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. SAEs can be reported using an online reporting form accessed via 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.

Each of the Annual Pharmacovigilance reports from 2014 to present, are published on the HPRA website, available here.

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Table 4: 2021 adverse reaction reports involving pharmaceutical products in which product association was assigned causality 'A' or 'B' (listed by active substance)

Note: some of the following reports contain multiple products and different routes of administration. IM= Intramuscular, SC= Subcutaneous, IV= Intravenous, NOS= not otherwise specified.

Table 4a: Bovine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
enrofloxacin	IV	1	1	1	Abnormal posture NOS, collapse NOS, death	≤ 2 mins
bismuth subnitrate	Intramammary	90	8	0	Abortion, pyrexia, acute mastitis,	≤ 14 days

					shock, decreased appetite	
bismuth subnitrate **cephalonium**	Intramammary Intramammary	4	1	0	Hypersalivation, application site swelling, allergic oedema, allergic reaction, tachycardia, application site pain, pyrexia, anaphylaxis, skin swelling	≤ 30 mins
bismuth subnitrate **cloxacillin benzathine**	Intramammary Intramammary	56	18	3	Death, pyrexia, not eating, acute mastitis, shock, dehydration	≤ 48 hours
bismuth subnitrate, heavy **cefalonium**	Intramammary Intramammary	24	8	2	Death, mastitis	≤ 48 hr
calcium gluconate + boric acid + magnesium hypophosphite hexahydrate	IV	1	1	1	Abnormal breathing, death, anaphylaxis	≤ 30 mins
calcium gluconate + boric acid + magnesium hypophosphite hexahydrate	IV	1	1	1	Abnormal breathing, death, anaphylaxis	≤ 30 mins
copper + cobalt + selenium	Oral	10	1	1	Sternoabdominal recumbancy	≤ 24 hr
copper + cobalt + selenium	Oral	2	2	0		≤ 7 days

					Sternoabdominal recumbancy, lethargy	
eprinomectin **albendazole** **selinum + vitamin E + vitamin B12 + adenosine 5 monophosphoric acid**	Topical Oral SC	40	2	0	Increased respiratory rate, foaming at the mouth, ataxia, eyelid oedema, swollen vulva, stillbirth, anaphylaxis, abnormal breathing, drooling, hyperaemia	≤ 1 hr
ivermectin + closantel	Topical	70	70	0	Dull, dehydration, blindness	≤ 7 days
ivermectin + closantel	Topical	10	2	0	Scour	≤ 48 hr
ivermectin + closantel	Topical	20	1	0	Blindness	≤ 7 days
levamisole	Oral	70	2	1	Hypersalivation, recumbency, death	≤ 30 mins
levamisole hydrochloride + oxyclozanide	Oral	10	5	0	Scour	≤ 14 days
levamisole hydrochloride + oxyclozanide **calcium gluconate + boric acid + magnesium**	Oral IV	12	1	1	Lateral recumbancy, paddling, death	≤ 48 hr

hypophosphite hexahydrate **magnesium sulphate heptahydrate**	SC					
oxytetracycline	IM	8	1	1	Collapse, anaphylactic-type reaction, paddling, sudden death	≤ 2 mins
procaine hydrochloride + adrenaline	SC	1	1	0	Dull, cutaneous necrosis, surgical site disorder, devitalisation	≤ 48 hr
sulfamethoxazole + trimethoprim	IM	1	1	0	Falling, hind limb ataxia	≤ 2 mins
tilmicosin	SC	3	1	1	Ataxia, collapse, death	≤ 30 mins

Table 4b: Ovine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
closantel	Oral	140	3	3	Sudden death, Circling - neurological disorder, foaming at the mouth	≤ 24 hr
					Dullness, inappetence,	

flunixin	IM	46	12	4	diarrhoea, death, renal disorder NOS, necropsy performed, renal infarcts	≤ 7 days
levamisole hydrochloride + oxyclozanide	Oral	28	25	0	Ear flap oedema, facial swelling, dull	≤ 7 days
levamisole hydrochloride + oxyclozanide	Oral	30	3	0	Facial swelling, dull, generalised allergic reaction NOS	≤ 7 days
levamisole hydrochloride + oxyclozanide	Oral	36	4	0	Facial swelling, dull	≤ 7 days
triclabendazole	Oral	300	2	2	Death	≤ 48 hr

Table 4c: Equine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
acepromazine	Oral	1	1	0	Collapse NOS, anaphylaxis, hyperhidrosis, priapism	≤ 6 hr
deslorelin acetate	SC	23	8	0	Abnormal cycling	≤ 30 days

detomidine	IV	1	1	0	Tachypnoea	≤ 1 hr
gentamicin **procaine benzylpenicillin**	IV IM	1	1	0	Seizure NOS, ataxia, shaking	≤ 30 mins

Table 4d: Canine Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
aglepristone	SC	1	1	1	Off colour, collapse, unconscious, dilated pupils, death, and injection site oedema. Injection site	≤ 24 hr

					reaction NOS, skin reaction NOS	
aglepristone	SC	1	1	0	Lethargy, vaginal discharge, peritonitis, uterine rupture, pyometra	≤ 14 days
amoxicillin + clavulanic acid	Oral	1	1	1	Walking difficulty, laboured breathing, collapse NOS, pale mucous membrane , bradycardia, loss of consciousness, death	≤ 1 hr
buprenorphine	IV	1	1	0	Oedema of the extremities, abdominal pain, agitation, vomiting, injected sclera, increased heart rate, foam in the nose, distress, swollen lip, swollen tongue, stridor, pharyngeal oedema, laryngeal oedema, foam in the trachea, cyanosis, mucus in trachea, elevated	≤ 6 hr

					temperature, abnormal ultrasound finding, abnormal radiograph finding, anaphylactic-type reaction, panting	
desoxycortone pivalate	SC	1	1	0	Diarrhoea, lethargy, distress, anorexia, vomiting, hypokalaemia, weight loss, malaise, heavy breathing	> 30 days
diethanolamine fusidate + framycetin sulphate + prednisolone + nystatin	Topical	1	1	0	Deafness	≤ 24 hr
diethanolamine fusidate + framycetin sulphate + prednisolone + nystatin	Topical	1	1	0	Deafness	≤ 7 days
enrofloxacin	SC	1	1	0	Severe vomiting, bloody diarrhoea	≤ 30 min
eprinomectin	Oral	2	2	0	Neurological signs NOS, blindness, general illness	unknown

fenbendazole	Oral	1	1	0	Fit, foaming at the mouth, tiredness, loss of consciousness, shaking, twitching, urination related to convulsion	≤ 24 hr
fluralaner	Oral	1	1	0	Shaking, diarrhoea, neurological signs NOS, lethargy	≤ 6 hr
fluralaner	Oral	1	1	0	Diarrhoea, anorexia, staring, vacant	≤ 6 hr
fluralaner	Oral	1	1	0	Facial oedema	≤ 6 hr
imidacloprid + flumethrin	Topical	1	1	0	Application site erythema	≤ 7 days
insulin	SC	1	1	0	Hypoglycaemia, collapse NOS, spasm, emesis (multiple)	> 30 days
insulin	SC	1	1	0	Hypoglycaemia, elevated cholesterol (total), collapse NOS	> 30 days

insulin	SC	1	1	0	Hypoglycaemia, polyuria, polydipsia, peripheral neuropathy	> 30 days
ketoconazole	Oral	1	1	0	Head tremor, Head tilt - neurological disorder	≤ 24 hr
lokivetmab	SC	1	1	0	Vomiting, diarrhoea, anorexia, adipsia	≤ 48 hr
lokivetmab	SC	1	1	0	Vomiting, quiet, lethargy, elevated temperature, anorexia, adipsia, immune mediated haemolytic anaemia	≤ 24 hr
lokivetmab	SC	1	1	1	Vomiting, diarrhoea, inappetence, decreased drinking, death	≤ 24 hr
medetomidine hydrochloride	IM	1	1	0	Barking, vocalisation, behavioural disorder NOS	≤ 6 hr

meloxicam	. Oral	1	1	0	Elevated liver enzymes, elevated alanine aminotransferase (ALT)	≤ 7 days
meloxicam	Oral	1	1	0	Vomiting, shaking, pancytopenia, neutropenia, lymphopenia, thrombocytopenia	≤ 24 hr
methadone	SC	1	. 1	0	Panting, bradycardia, apnoea, rough recovery	≤ 1 hr
methadone	IM	1	1	0	Pale mucous membrane, panting, sedation	≤ 24 hr
methadone	IM	1	1	0	Hypersalivation, reduced responses, pale mucous membrane, panting	≤ 24 hr
metronidazole	Oral	1	. 1	0	Ataxia, nystagmus	≤ 24 hr

miconazole nitrate + prednisolone acetate + polymixin B sulfate	Topical	1	1	0	Deafness	≤ 24 hr
miconazole nitrate + prednisolone acetate + polymixin B sulfate	Topical	1	1	0	Impaired hearing	≤ 24 hr
pentosan polysulphate sodium	SC	1	1	1	Elevated cholesterol, low sodium-potassium ratio, leucopenia NOS, death by euthanasia, anorexia, shaking, nasal discharge, recumbancy, reduced responsiveness, bradycardia, bloodshot eye, eye disorder NOS	≤ 24 hr
permethrin (40/60)	Topical	1	1	0	Eye irritation, eye discharge, partial blindness	≤ 30 mins
phenylpropanolamine hydrochloride	Oral	1	1	0	Emesis, mydriasis, hyperactivity, panting	≤ 1 hr
pimobendan	Oral	1	1	0	Tachycardia, medication error	≤24 hr
	Oral	1	1	0		≤ 6 hr

praziquantel + pyrantel + febantel					Lethargy, itching, allergic oedema	
sarolaner	Oral	2	1	0	Hyposensitivity to pain, abdominal pain, lethargy, inappetence, not drinking, diarrhoea, vomiting, dehydration, proprioception deficit, hind limb paralysis, hind limb paresis	≤ 6 hr
trilostane	Oral	1	1	0	Weakness, vomiting, urinary incontinence, facecal incontinence, incoordination, lethargy	≤ 24 hr
trilostane	Oral	1	1	1	Pacing, retching, anorexia, shaking, high sodium-potassium ratio (Na:K ratio), haemorrhagic gastroenteritis, dull, sleepiness	> 30 days

					- systemic disorder, increased lung sounds, abnormal adrenocorticotropic hormone (ACTH) stimulation test, vomiting, hypercortisolaemia, death, flatulence, bloating and distension, weight loss, stiffness NOS, pain NOS, abdominal pain, malaise, elevated serum alkaline phosphatase (SAP)	
trilostane	Oral	1	1	0	Dull, quiet	≤ 14 days
trilostane	Oral	1	1	0	Not eating, diarrhoea, vomiting, malaise, azotaemia, hyperglycaemia, unsteady gait	> 30 days
trilostane	Oral	1	1	0	Anorexia, vomiting, weight loss, elevated renal parameters, hyperkalaemia condition	≤ 24 hr
trilostane	Oral	1	1	0	Vomiting, inappetence,	> 30 days

					haematemesis, abdominal mass, dehydration, enlarged liver	
trilostane	Oral	1	1	0	Vomiting, elevated creatinine, elevated BUN	≤ 24 hr
trilostane	Oral	1	1	1	Collapse, anorexia, dehydration, dull, oral erythema, head pressing, death	≤ 24 hr
trilostane	Oral	1	1	0	Lethargy, shivering, pyrexia	> 30 days
trilostane	Oral	1	1	0	Vomiting, dullness, depression, bloody diarrhoea	≤ 24 hr
trilostane	Oral	1	1	0	Polydipsia, urinary incontinence, hyposthenuria, lethargy, shivering, inappetence, crying, stiffness NOS, elevated cholesterol (total), polyuria	> 30 days

trilostane	Oral	1	1	0	Low sodium-potassium ratio (Na:K ratio), abnormal adrenocorticotropic hormone (ACTH) stimulation test, hypoadrenocorticism, malaise, unable to stand, lethargy, quiet, hyponatremia, weakness, vomiting, haemorrhagic diarrhoea, bradycardia	≤ 24 hr
trilostane	Oral	1	1	0	Alopecia NOS, ataxia, falling, knuckling, hypercortisolaemia, balance impaired, hyponatremia, proprioception deficit	> 30 days
trilostane	Oral	1	1	0	Limb weakness, falling, collapse (NOS)	≤ 24 hr
trilostane	Oral	1	1	1	Vomiting, diarrhoea, dyspnoea, death by euthanasia,	≤ 30 days

					renal failure, heart failure	
trilostane	Oral	1	1	1	Vomiting, diarrhoea, decreased appetite, lethargy, shaking, reluctant to move, not himself/herself, death	≤ 7 days

Table 4e: Feline Reports

Active substance(s)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
diethanolamine fusidate + framycetin sulphate + prednisolone + nystatin	Topical	1	1	0	Vocalisation, anisocoria, miosis, bradycardia, swollen lymph node,	≤ 7 days

					dehydration, dullness, ear pain, abnormal pupil light reflex	
diethanolamine fusidate + framycetin sulphate + prednisolone + nystatin	Topical	1	1	0	Partial deafness, medication error	≤ 24 hr
eprinomectin, fipronil, s-methoprene, praziquantel	Topical	1	1	0	Panting, distress, pain NOS, open mouth breathing, licking at application site, behavioural disorder NOS, Tachypnoea	≤ 1 hr
fluralaner + moxidectin	Topical	1	1	0	Discomfort NOS, pruritus, skin haemorrhage NOS, skin ulcer, application site pruritus, application site skin discolouration, application site alopecia, application site ulcer, application site pain, application site bleeding, application site itching, wound, pain NOS	≤ 24 hr
medetomidine hydrochloride **ketamine**	IM IM	1	1	0	Respiratory arrest	≤ 1 hr

meloxicam	SC	1	1	1	Vomiting, pain (NOS), shaking, death	≤ 30 mins
milbemycin oxime + praziquantel	Oral	5	4	0	Not eating, lethargy, breathing difficulty, vomiting, diarrhoea	≤ 24 hr
thiamazole	Oral	1	1	1	Proteinuria, urine abnormalities NOS, non-regenerative anaemia, elevated bile acids, jaundice, inappetence, death by euthanasia, lethargy, decreased appetite, elevated alanine aminotransferase (ALT), elevated serum alkaline phosphatase (SAP), elevated gamma-glutamyl transferase (GGT), elevated total bilirubin, anaemia NOS, bilirubinuria, haematuria	> 30 days
thiamazole	Oral	1	1	0	Dull, low platelet count, off colour	< 30 days

Table 5: 2021 adverse reaction reports involving immunological products, in which product association was assigned causality 'A' or 'B' (listed by active substance (antigen))

Note: some of the following reports contain multiple products and different routes of administration.

* IM= Intramuscular, SC= Subcutaneous, IV= Intravenous, IP= Intraperitoneal, NOS= not otherwise specified

Table 5a: Bovine reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Inactivated Leptospira interrogans serovar Hardjo 204 2 -3 x 10^9 Organisms.	SC	50	2	1	Photosensitisation, skin inflammation NOS, mammary gland oedema, vulvar oedema, death by euthanasia	≤ 6 hr
Live bovine herpesvirus type 1 (BHV-1), strain GK/D (gE^-): $10^{5.7}$ - $10^{7.3}$ $TCID_{50}$**.* **gE^-: glycoprotein E negative* ***$TCID_{50}$: tissue culture infective doses 50%.*	IM	20	4	1	Death, staggering	≤ 30 min
C. chauvoei whole culture Ph.Eur. *C. haemolyticum ≥ 10 U* *C. novyi type B toxoid ≥ 3.5 IU* *C. septicum toxoid ≥ 2.5 IU* *C. tetani toxoid ≥ 2.5 IU.*	SC					

Live bovine herpesvirus type 1 (BHV-1), strain GK/D (gE^-): 105.7 - 107.3 TCID50**. *gE^-: glycoprotein E negative **TCID50: tissue culture infective doses 50%.*	IM	150	11	0	Pyrexia, infertility NOS	≤ 7 days
Live bovine herpesvirus type 1 (BHV-1), strain GK/D (gE^-): $10^{5.7}$ - $10^{7.3}$ $TCID_{50}$**. *gE^-: glycoprotein E negative **$TCID_{50}$: tissue culture infective doses 50%.* *Live bovine respiratory syncytial virus (BRSV), strain Jencine-2013: 5.0– 7.0 log TCID50 * Live bovine parainfluenza virus type 3 (PI3), strain INT2-2013: 4.8– 6.5 log10 TCID50 * *50% tissue culture infective dose*	Intranasal Intranasal	30	30	0	Abdominal pain, peritonitis, dull, ocular discharge, decreased body temperature, elevated temperature, irregular breathing, diarrhoea, decreased appetite, ruminal bloat, ascites	≤ 48 hr

Mannheimia haemolytica Biotype A serotype A1, Inactivated cell free suspension containing leukoxid Ph. Eur. - ELISA > 2.8 (*)/dose. Inactivated Histophilus somni Bailie strain - MAT > 3.3 (**)/dose (*) A minimum of 80% of vaccinated rabbits show ELISA value of > 2.0; The mean ELISA is > 2.8. (**) A minimum of 80% of vaccinated rabbits show a log_2 MAT value of ≥ 3.0; The mean log2 MAT > 3.3.	SC	10	2	2	Found dead, respiratory disease, open mouth breathing, unable to stand, anaphylactic-type reaction	≤ 1hr
Modified live BVDV-1, non-cytopathic parent strain KE-9: $10^{4.0}$–$10^{6.0}$ TCID50**, Modified live BVDV*-2, non-cytopathic parent strain NY-93: $10^{4.0}$–$10^{6.0}$ TCID50**. * Bovine viral diarrhoea virus ** Tissue culture infectious dose 50%.*	IM	40	1	0	Injection site swelling, abortion spontaneous, hypersensitivity reaction, facial swelling, skin swelling, anaphylactic reaction	≤ 24 hr

Table 5b: Ovine Reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Clostridium perfringens beta toxoid inducing 10 IU *Clostridium perfringens epsilon toxoid inducing 5 IU* *Clostridium septicum toxoid inducing 2.5 IU* *Clostridium tetani toxoid inducing 2.5IU* *Clostridium novyi toxoid inducing 3.5 IU* *Clostridium chauvoei cells and equivalent toxoid of strains 655,656,657,658, 1048.* *inducing 0.5 guinea pig PD_{90}* *Formalin killed cells of Mannheimia haemolytica serotypes:* *A1 5 x 10^8 cells* *A2 5 x 10^8 cells* *A6 5 x 10^8 cells* *A7 5 x 10^8 cells* *A9 5 x 10^8 cells* *Formalin killed cells of Pasteurella trehalosi serotypes:* *T3 5 x 10^8 cells* *T4 5 x 10^8 cells* *T10 5 x 10^8 cells* *T15 5 x 10^8 cells*	SC	150	30	4	Injection site abscess, death,, dehydration, haematoma NOS, cellulitis, pyothorax, septicaemia, other abnormal test result NOS, cachexia	≤ 14 days

Clostridium perfringens beta toxoid inducing 10 IU *Clostridium perfringens epsilon toxoid inducing 5 IU* *Clostridium septicum toxoid inducing 2.5 IU* *Clostridium tetani toxoid inducing 2.5IU* *Clostridium novyi toxoid inducing 3.5 IU* *Clostridium chauvoei cells and equivalent toxoid of strains 655,656,657,658, 1048.* *inducing 0.5 guinea pig PD_{90}* *Formalin killed cells of Mannheimia haemolytica serotypes:* *A1 5 x 10^8 cells* *A2 5 x 10^8 cells* *A6 5 x 10^8 cells* *A7 5 x 10^8 cells* *A9 5 x 10^8 cells* *Formalin killed cells of Pasteurella trehalosi serotypes:* *T3 5 x 10^8 cells* *T4 5 x 10^8 cells* *T10 5 x 10^8 cells* *T15 5 x 10^8 cells*	SC	120	37	6	Injection site lump, injection site abscess, reduced growth rate, sudden death, pneumonia, diarrhoea, loss of condition score, infectious disease NOS	≤ 14 days

Table 5c: Equine Reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
*Inactivated EHV type 1, strain 438/77, inactivated: RP > 1** *Inactivated EHV type 4, strain 405/76, inactivated: RP > 1** **Relative Potency ELISA compared to a reference vaccine which has been shown to be efficacious in horses*	IM	1	1	0	Skin lump, stiffness NOS, febrile, lymph node abscess, general illness	≤ 7 days

Table 5d: Canine Reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Attenuated canine distemper virus, strain BA5 10^4 $CCID_{50}$ 10^6 $CCID_{50}$ Attenuated canine adenovirus type 2, strain DK13 $10^{2.5}$ $CCID_{50}$ - $10^{6.3}$ $CCID_{50}$ Attenuated canine parvovirus type 2, strain CAG2 $10^{4.9}$ $CCID_{50}$ - $10^{7.1}$ $CCID_{50}$ Attenuated canine parainfluenza virus type 2, strain CGF 2004/75 $10^{4.7}$ $CCID_{50}$ - $10^{7.1}$ $CCID_{50}$ *CCID50: 50% cell culture infective dose)* *Inactivated Leptospira interrogans serogroup and serovar Canicola strain 16070 Activity acc. to Ph. Eur.447* Inactivated Leptospira interrogans serogroup and serovar Icterohaemorrhagiae strain16069 Activity acc. to Ph. Eur.447* Inactivated Leptospira interrogans serogroup and serovar Grippotyphosa strain GrippoMal 1540 Activity acc. to Ph. Eur.447* *≥80 % protection in hamsters*	Unknown	1	1	0	Pale mucous membranes, collapse NOS, ataxia, anaphylaxis	≤ 2 mins

bedinvetmab	SC	1	1	1	Lethargy, crying, reluctant to move, monoparesis, localised pain, death by euthanasia	≤ 6 hr
Attenuated canine distemper virus, strain BA5 10^4 $CCID_{50}$ 10^6 $CCID_{50}$ Attenuated canine adenovirus type 2, strain DK13 $10^{2.5}$ $CCID_{50}$ - $10^{6.3}$ $CCID_{50}$ Attenuated canine parvovirus type 2, strain CAG2 $10^{4.9}$ $CCID_{50}$ - $10^{7.1}$ $CCID_{50}$ Attenuated canine parainfluenza virus type 2, strain CGF 2004/75 $10^{4.7}$ $CCID_{50}$ - $10^{7.1}$ $CCID_{50}$ *CCID50: 50% cell culture infective dose)*	SC	1	1	1	Death by euthanasia, multiple organ haemorrhage, thrombocytopenia	≤ 30 days
Bedinvetmab *Live Bordetella bronchiseptica bacteria strain B-C2: ≥$10^{8.0}$ and ≤$10^{9.7}$cfu[1], Live canine parainfluenza virus strain Cornell ≥$10^{3.0}$ and ≤$10^{5.8}$ $TCID_{50}$[2]* *[1]colony forming units* *[2]Tissue Culture Infective Dose 50%* *Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not*	SC Intranasal SC	1	1	0	Otitis externa, pruritus, pyoderma, crust, pemphigus foliaceus	≤ 30 days

less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, *$^{*}TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC					
*Canine distemper virus, strain Onderstepoort not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2, strain Manhattan LPV3 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus, strain 154 not less than $10^{7.0}$ $TCID_{50}$**	SC	1	1	0	Swollen face, swelling NOS	≤ 30 mins

Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units* *Live Bordetella bronchiseptica bacteria strain B-C2: ≥$10^{8.0}$ and ≤$10^{9.7}$cfu[1], Live canine parainfluenza virus strain Cornell ≥$10^{3.0}$ and ≤$10^{5.8}$ $TCID_{50}$[2]* *[1]colony forming units* *[2]Tissue Culture Infective Dose 50%*	SC Intranasal					
*Canine distemper virus, strain Onderstepoort not less than $10^{4.0}$ $TCID_{50}$** *Canine adenovirus 2, strain Manhattan LPV3 not less than $10^{4.0}$ $TCID_{50}$** *Canine parvovirus, strain 154 not less than $10^{7.0}$ $TCID_{50}$**	SC	1	1	0	Seizure NOS, foaming at the mouth, diarrhoea, hind limb paralysis, lethargy	≤ 30 mins

Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC					
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$,, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$,, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000)*	SC	1	1	0	Foaming at the mouth, twitching, seizure NOS	≤ 30 mins

3550–7100 U[1] *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC					
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira interrogans serogroups: Canicola; serovar Portland-vere, strain Ca-12-000 >957-1,676 Units/ml*, Icterohaemorrhagiae; serovar Copenhageni, strain 820K > 625-1,335 Units/ml*	SC SC	1	1	0	Sleepiness, anorexia, not drinking, staggering, nystagmus, weak pulse, anaphylaxis	≤ 12 hr

Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$,, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$,, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%*	SC					
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC	1	1	0	Subdued, urination, bloody diarrhoea, unresponsive to stimuli, laboured breathing, emesis (multiple), anaphylaxis	≤ 2 mins

Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC SC	1	1	0	Swollen lip, swollen eyelid	≤ 6 hr
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza	SC					

virus not less than $10^{5.5}$ $TCID_{50}$,* **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC	1	1	0	Vomiting, unresponsive to stimuli, pale mucous membrane, increased respiratory rate, diarrhoea, anaphylaxis	≤ 2 mins

Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC	1	1	0	Anorexia, dull, jaundice, vomiting, increased percentage reticulocytes, elevated total bilirubin, anemolytic anaemia, decreased PCV, pale mucous membrane	≤ 48 hr
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000)*	SC					

3550–7100 U[1] *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC	1	1	0	Lethargy, weakness, jaundice, pale mucous membrane, decreased PCV, saline slide agglutination test, positive	> 30 days
Live Bordetella bronchiseptica bacteria strain B-C2: ≥ $10^{8.0}$ and ≤ $10^{9.7}$ cfu[1], Live canine parainfluenza virus strain Cornell ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$[2] *[1]colony forming units* *[2]Tissue Culture Infective Dose 50%*	Intranasal					
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$,, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$,, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%*	SC	1	1	0	Injection site reaction NOS, pyrexia, anorexia, vomiting, injection site swelling, injection site oedema	≤ 7 days

Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC					
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$,, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$,, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans*	SC SC	1	1	0	Inappetence, pain NOS, pyrexia, injection site swelling, panting, congested mucous membrane, injection site abscess, localised skin reaction, reluctant to move	≤ 7 days

serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1] *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*						
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%*	SC					
Inactivated Leptospira interrogans serogroups: Canicola; serovar Portland-vere, strain Ca-12-000 >957-1,676 Units/ml, Icterohaemorrhagiae; serovar Copenhageni, strain 820K > 625-1,335 Units/ml*	SC	1	1	0	Facial oedema	≤ 6 hr
Bordetella bronchiseptica fimbriae[1] 88 - 399 U[2] *[1] Purified from strain Bb7 92932*	Intranasal					

[2] Antigenic mass ELISA units						
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira interrogans serogroups: Canicola; serovar Portland-vere, strain Ca-12-000 >957-1,676 Units/ml*, Icterohaemorrhagiae; serovar Copenhageni, strain 820K > 625-1,335 Units/ml*	SC SC	1	1	0	Saline slide agglutination test, abnormal red blood cell, immune mediated haemolytic anaemia, decreased PCV, lethargy, not himself/herself, dull, sleepiness - systemic disorder, not eating, pale mucous membrane, elevated temperature, abdominal pain, non-regenerative anaemia	≤ 7 days
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira interrogans serogroups: Canicola; serovar Portland-vere, strain*	SC 1	1	0	Swollen face	≤ 1 hr	

Ca-12-000 >957-1,676 Units/ml, Icterohaemorrhagiae; serovar Copenhageni, strain 820K > 625-1,335 Units/ml* *Live Bordetella bronchiseptica bacteria strain B-C2: ≥ $10^{8.0}$ and ≤ $10^{9.7}$ cfu[1], Live canine parainfluenza virus strain Cornell ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$[2]* *[1]colony forming units* *[2]Tissue Culture Infective Dose 50%*	SC Intranasal					
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–*	SC SC	1	1	0	Medication error, cough, injection site lump, thrombocytopenia, elevated serum alkaline phosphatase	≤ 48 hr

1000 U[1] *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units* *Live Bordetella bronchiseptica bacteria strain B-C2: ≥ $10^{8.0}$ and ≤ $10^{9.7}$ cfu[1], Live canine parainfluenza virus strain Cornell ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$[2]* *[1]colony forming units* *[2]Tissue Culture Infective Dose 50%*	Intranasal					
Live Bordetella bronchiseptica bacteria strain B-C2: ≥ $10^{8.0}$ and ≤ $10^{9.7}$ cfu[1], Live canine parainfluenza virus strain Cornell ≥ $10^{3.0}$ and ≤ $10^{5.8}$ $TCID_{50}$[2] *[1]colony forming units* *[2]Tissue Culture Infective Dose 50%* *Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$,, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$,, Canine parainfluenza*	Intranasal SC	1	1	0	Swollen face	≤ 1 hr

virus not less than $10^{5.5}$ $TCID_{50}$,* **$TCID_{50}$ = Tissue culture effective dose 50%* *Inactivated Leptospira strains:* *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC					
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]*	SC	1	1	0	Unsteady gait, increased salivation, elevated temperature, petit mal epilepsy, head tremor, cyanosis, anaphylaxis, leucocytosis NOS	≤ 30 mins

- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1] *[1] Antigenic mass ELISA units*						
Inactivated Leptospira strains: *- L. interrogans serogroup Canicola serovar Portland-vere (strain Ca-12-000) 3550–7100 U[1]* *- L. interrogans serogroup Icterohaemorrhagiae serovar Copenhageni (strain Ic-02-001) 290–1000 U[1]* *- L. interrogans serogroup Australis serovar Bratislava (strain As-05-073) 500–1700 U[1]* *- L. kirschneri serogroup Grippotyphosa serovar Dadas (strain Gr-01-005) 650–1300 U[1]* *[1] Antigenic mass ELISA units*	SC	1	1	0	Facial oedema, swollen eyelid, allergic skin reaction	≤ 6 hr
Canine distemper virus strain not less than $10^{4.0}$ $TCID_{50*}$, Canine adenovirus 2 not less than $10^{4.0}$ $TCID_{50*}$, Canine parvovirus not less than $10^{7.0}$ $TCID_{50*}$, Canine parainfluenza virus not less than $10^{5.5}$ $TCID_{50*}$, **$TCID_{50}$ = Tissue culture effective dose 50%*	SC					

Canine parvovirus (strain 154) not less than 10^7 $TCID_{50}$ *Tissue culture infective dose 50%*	SC	1	1	1	Sudden death	≤ 6 hr
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Vomiting, diarrhoea, swollen face, oedematous erythema, erythema, anaphylaxis	≤ 30 mins
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Regurgitation, vomiting, weakness, unable to stand, pale mucous membrane, blood in faeces, anaphylaxis	≤ 2 mins
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Vomiting, drowsiness	≤ 1 hr
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Face and neck swelling, swollen eyelid	≤ 1 hr
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Dullness, depression, weakness, unable to stand, urinary incontinence, lymphocytosis,	≤24 hr

					monocytosis, leucocytosis NOS	
Bordetella Bronchiseptica Fimbriae *Attenuated canine distemper virus, strain ba5* *Attenuated canine adenovirus type 2, strain dk13* *Attenuated canine parvovirus, strain cag2* *Attenuated canine parainfluenza virus type 2, strain cgf 2004/7* *Inactivated leptospira interrogans serogroup canicola strain 16070* *Inactivated leptospira interrogans serogroup icterohaemorrhagiae strain 16069* *Inactivated leptospira interrogans serogroup grippotyphosa strain mal 1540*	SC SC SC	1	1	0	Diarrhoea, shaking, panting	≤ 6 hr
*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$**						

*Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction: Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50* *Leptospira canicola inactivated* *Leptospira icterohaemorrhagiae inactivated*	SC SC	1	1	0	Facial oedema, lip oedema, bloodshot eye	≤ 6 hr
*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction: Canine Parvovirus, strain NL-35-D, low*	SC					

*passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50* *Leptospira canicola inactivated* *Leptospira icterohaemorrhagiae inactivated*	SC	1	1	0	Vomiting, facial oedema, lip oedema, hyperaesthesia	≤ 6 hr
*Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction: Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira*	SC	1	1	0	Facial oedema	≤ 6 hr

icterohaemorrhagiae (inactivated) at least 40 hamster protective doses. **Cell culture infectious dose-50* *Leptospira canicola inactivated* *Leptospira icterohaemorrhagiae inactivated*	SC					
Freeze dried fraction: *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction:* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50*	SC	1	1	0	Periorbital Oedema	≤ 6 hr

Leptospira canicola inactivated *Leptospira icterohaemorrhagiae inactivated*	SC					
Freeze dried fraction: *Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$** *Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$** *Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$** *Liquid fraction:* *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50* *Leptospira canicola inactivated* *Leptospira icterohaemorrhagiae inactivated*	SC SC	1	1	0	Collapse NOS, inappropriate urination, harsh lung sounds, pale mucous membranes, weak pulse, lethargy	≤ 2 mins

Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$ Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$* Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$* Liquid fraction: Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$* Leptospira canicola (inactivated) at least 40 hamster protective doses Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses. *Cell culture infectious dose-50*	SC	1	1	0	Lethargy, anorexia, vomiting, diarrhoea, anaemia NOS, azotaemia, enlarged kidney(s), peritoneal fluid abnormal NOS, omentum inflammation	≤ 48 hr
Freeze dried fraction: Canine distemper virus, strain N-CDV (live attenuated) minimum titre: $10^{3.0}$ $CCID_{50}$ Canine adenovirus Type 2, strain Manhattan (live attenuated) minimum titre: $10^{3.2}$ $CCID_{50}$* Canine parainfluenza virus, strain NL-CPI-5 (live attenuated) minimum titre: $10^{6.0}$ $CCID_{50}$**						

Liquid fraction: *Canine Parvovirus, strain NL-35-D, low passage (live attenuated) minimum titre : $10^{7.0}$ $CCID_{50}$** *Leptospira canicola (inactivated) at least 40 hamster protective doses* *Leptospira icterohaemorrhagiae (inactivated) at least 40 hamster protective doses.* **Cell culture infectious dose-50* *Leptospira canicola inactivated* *Leptospira icterohaemorrhagiae inactivated*	SC SC	1	1	0	Syncope, lethargy, weak pulse, vomiting	≤ 2 mins
Lyophilisate (live attenuated): Minimum Maximum *Canine distemper virus, strain CDV Bio 11/A $10^{3.1}$ $TCID_{50}$* $10^{5.1}$ $TCID_{50}$* *Canine adenovirus Type 2, strain CAV-2 Bio 13 $10^{3.6}$ $TCID_{50}$* $10^{5.3}$ $TCID_{50}$* *Canine parvovirus Type 2b, strain CPV-2b Bio 12/B $10^{4.3}$ $TCID_{50}$* $10^{6.6}$ $TCID_{50}$* *Canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 $10^{3.1}$ $TCID_{50}$* $10^{5.1}$ $TCID_{50}$* *Suspension (inactivated): Leptospira interrogans*	SC	1	1	0	Circulatory collapse, pale mucous	≤ 30 mins

*serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae strain MSLB 1089 ALR** titre ≥ 1:51* *Leptospira interrogans serogroup Canicola serovar Canicola, strain MSLB 1090 ALR** titre ≥ 1:51* *Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091 ALR** titre ≥ 1:40* *Leptospira interrogans serogroup Australis serovar Bratislava, strain MSLB 1088 ALR** titre ≥ 1:51 * Tissue culture infectious dose 50%.* *** Antibody micro agglutination-lytic reaction.*	SC				membrane, bradycardia	
Live Bordetella bronchiseptica bacteria strain B-C2: ≥$10^{8.0}$ and ≤$10^{9.7}$cfu[1], Live canine parainfluenza virus strain Cornell ≥$10^{3.0}$ and ≤$10^{5.8}$ $TCID_{50}$[2] *[1]colony forming units* *[2]Tissue Culture Infective Dose 50%*	Intranasal					

Table 5e: Feline reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Inactivated rabies virus strain Pasteur RIV inducing at least 2 IU as measured in the potency test.	SC	1	1	0	Diarrhoea, vomiting, lethargy, not eating, not drinking, dehydration	≤ 6 hr
Inactivated feline panleucopenia virus, strain CU4 ≥ 8.50, Inactivated feline calicivirus, strain 255 ≥ 1.26, Inactivated feline rhinotracheitis virus, strain 605 ≥ 1.39, Inactivated Chlamydophila felis, strain Cello ≥ 1.69, Inactivated feline leukaemia virus, strain 61E ≥ 1.45	SC	1	1	0	Injection site pain, reluctant to move, hissing, vocalisation, anorexia, not drinking, lethargy, depression	≤ 12 hr
Inactivated feline panleucopenia virus, strain CU4 ≥ 8.50, Inactivated feline calicivirus, strain 255 ≥ 1.26, Inactivated feline rhinotracheitis virus, strain 605 ≥ 1.39, Inactivated Chlamydophila felis, strain Cello ≥ 1.69, Inactivated feline leukaemia virus, strain 61E ≥ 1.45	SC	1	1	1	Hind limb ataxia, halitosis, vomiting, diarrhoea, pallor, anaemia NOS, partial anorexia, staring, recumbancy, listless, death	≤ 14 days
Minimum quantity of purified p45 FeLV-envelope antigen 102 µg	SC	1	1	0	Lethargy, third eyelid protrusion, hyperthermia, decreased appetite, eye redness,	≤ 6 hr

					anterior uveitis, tremor, hind limb paresis, urinary incontinence, faecal incontinence, blindness, neurological signs NOS	
Live attenuated feline calicivirus, strain F9: ≥4.6 log_{10} PFU[1]; live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 log_{10} PFU[1]; live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 log_{10} $CCID_{50}$[2] *[1]PFU: Plaque-Forming Units,* *[2]$CCID_{50}$: Cell Culture Infective Dose 50%*	SC	5	4	0	Not eating, lethargy, breathing difficulty, vomiting, diarrhoea	≤ 24 hr
Live attenuated feline calicivirus, strain F9: ≥4.6 log_{10} PFU[1]; live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 log_{10} PFU[1]; live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 log_{10} $CCID_{50}$[2] *[1]PFU: Plaque-Forming Units,* *[2]$CCID_{50}$: Cell Culture Infective Dose 50%*	SC	1	1	0	Injection site panniculitis, off colour, abnormal serum protein NOS, elevated globulins	> 30 days
Attenuated feline rhinotracheitis herpesvirus (FHV F2 strain) ≥$10^{4.9}$ CID50[1], Inactivated feline calicivirus (FCV 431 and G1 strains) antigens ≥ 2.0 ELISA U, Attenuated feline	SC					

panleucopenia virus (PLI IV) ≥$10^{3.5}$CCID$_{50}$[1] *FeLV recombinant Canarypox virus (vCP97) ≥$10^{7.2}$* CCID50[1]	SC	1	1	0	Facial oedema, polydipsia	≤ 6 hr
Live attenuated feline calicivirus, strain F9: ≥4.6 log$_{10}$ PFU[1]*; live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 log$_{10}$ PFU*[1]*; live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 log$_{10}$ CCID$_{50}$*[2] [1]*PFU: Plaque-Forming Units,* [2]*CCID$_{50}$: Cell Culture Infective Dose 50%*	SC	1	1	1	Dyspnoea, fluid from nose, fluid in thorax, death, anaphylactic shock	≤ 1 hr

Table 5f: Rabbit reports

Active substance(s) (Antigen)	Route(s) of administration	No. treated	No. reacted	No. died	Clinical Signs	Speed of onset
Inactivated rabbit haemorrhagic disease type 2 virus (RHDV2), strainV-1037≥70% cELISA40 (*) ≥70 % of vaccinated rabbits shall give cELISA antibody titres equal to or higher than 40.*	SC	1	1	0	Lameness	≤ 6 hr
Live myxoma vectored RHD virus strain 009: ≥$10^{3.0}$ and ≤$10^{6.1}$ FFU, Live myxoma vectored RHD virus strain MK1899: $10^{3.0}$ - $10^{5.8}$ FFU** ***Focus Forming Units***	SC	1	1	0	Lethargy, increased skin temperature, pinnal ulcer, skin ulcer, droopy ear, ear pruritus	≤ 7 days
Live myxoma vectored RHD virus strain 009: ≥$10^{3.0}$ and ≤$10^{6.1}$ FFU, Live myxoma vectored RHD virus strain MK1899: $10^{3.0}$ - $10^{5.8}$ FFU** ***Focus Forming Units***	SC	1	1	1	Swollen vulva, eyelid oedema, ear flap oedema, death by euthanasia	≤ 7 days