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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use

Veterinary pharmacovigilance 2019

Annual bulletin

1. Executive Summary

This bulletin aims to inform veterinarians and the general public of the main outcome of pharmacovigilance[1] or post-marketing surveillance activities for veterinary medicinal products (VMPs) during 2019 at the European Medicines Agency (EMA or Agency). These investigations have led to several important new warnings and recommendations related to the use of the VMPs (detailed in section 3).

The bulletin also highlights ongoing monitoring of potential specific events in place for centrally authorised products (CAPs[2]). A summary of the pharmacovigilance discussions and recommendations at European Union (EU) level from the Committee for Medicinal Products for Veterinary Use (CVMP) Pharmacovigilance Working Party (PhVWP-V) regarding nationally authorised VMPs is also included.

The trend for a yearly increase of adverse event[3] reports since 2011 continued also in 2019 for reports having occurred in the EU/European Economic Area (EEA). Similar to 2018, the number of reports from outside the EU/EEA is significantly higher compared to previous years. Operationally, the Agency already continuously monitors adverse event data. This provides valuable experience as part of the groundwork for the future implementation of the new veterinary Regulation (EU) 2019/6. In particular there will be increased focus on improvements to communicate and exchange pharmacovigilance information with veterinarians in the field and the general public.

This bulletin will be followed with more frequent publications of the regulatory actions taken by the CVMP based on pharmacovigilance data to ensure safety related information for CAPs is available and accessible for product users in a timelier manner.

[1] Pharmacovigilance comprises all activities related to the reporting and investigation of any adverse event potentially associated with the use of a VMP, including possible lack of expected efficacy, environmental problems and investigations of the validity of withdrawal periods.
[2] These are VMPs that are authorised through the centralised marketing authorisation procedure operated by the European Medicines Agency.
[3] Adverse event reporting may include events already included on the package insert or events that are unexpected.

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Introduction

This is the 18th annual bulletin from the EMA on veterinary pharmacovigilance activities, providing an overview of the surveillance of adverse events and safety issues of veterinary medicines in the EU in 2019. This bulletin aims to promote public communication on veterinary pharmacovigilance.

All adverse events occurring in the EU, reported after the use of authorised VMPs, are collected and evaluated both by the marketing authorisation holder (MAH), who is responsible for the product, and by the national competent authorities and/or the EMA, the regulatory authorities authorising their use. Adverse events may be classified as "non-serious" or "serious", for those involving death, life-threatening reactions, permanent lesions and/or reactions resulting in significant disability or incapacity in the treated animal(s). Adverse events in humans exposed to veterinary medicinal products (VMPs) are also managed in expedite manner, in the same way as "serious" adverse events in animals. In addition to the reporting of all adverse events occurring in the EU, the MAH is obliged to report serious and unexpected adverse event reports occurring outside the EU, when the product concerned is also authorised in the EU.

Electronic reporting to the European veterinary pharmacovigilance database, EudraVigilance Veterinary (EVVet) became mandatory in November 2005 for serious reports only. EVVet now contains 382,858 adverse event[4] reports, approximately 50% of which occurred within the EU/EEA[5] and 50% outside the EU/EEA.

The overall surveillance of VMPs is predominantly based on two processes:

1) Periodic safety update reports (PSURs) - which are a review of all adverse events reported in a set timeframe on a specific product, compiled by MAHs and evaluated by regulatory authorities at defined time points.

2) Signal detection – which involves continuous monitoring of all adverse events reported electronically to EVVet by national competent authorities and the EMA.

Currently, the PhVWP-V is responsible for pharmacovigilance of CAPs, on behalf of the CVMP and has a dual mandate, advising Member States on the surveillance of not centrally authorised veterinary medicinal products (non-CAPs), which is undertaken by the competent authorities at national level.

[4] One report can contain more than one animal affected, especially in food producing animals. See Table 1 in the Annex for further detail on the number of reports/number of animals affected broken down by species (including humans).

[5] European Economic Area

2. Adverse events in animals and humans involving centrally authorised products

There are now 211 CAPs that have marketing authorisations valid across the entire EU. An overview of the products and detailed information on each product, including the summary of product characteristics, is accessible on the EMA website (http://www.ema.europa.eu/ema/).

A total of 33,656 adverse event reports following exposure to CAPs were received in 2019. Of these, 32,797 adverse event reports related to animals and 859 related to humans.

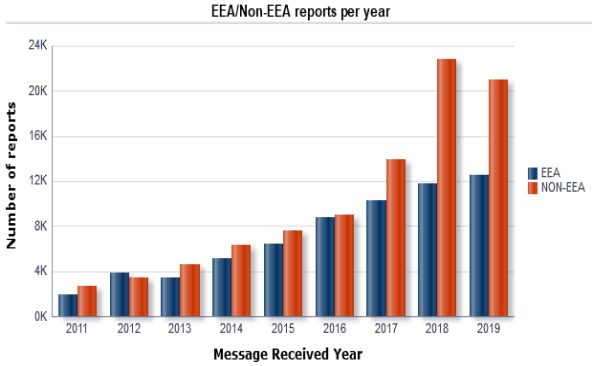


Figure 1. Total number of adverse events for centrally authorised products reported to EVVet from within and outside the EU/EEA between 2011 and 2019

A long-term, year-on-year increase in adverse event reporting (Figure 1) can be observed, which generally reflects the increasing number of CAPs authorised. In addition, in 2018 and 2019 we observe a significantly higher number of reports from non-EU/EEA countries, which is partly linked to the number of non-serious reports submitted to EVVet either on a voluntary basis by MAHs which have implemented the revised recommendation on basic surveillance that encourages reporting non-serious reports. Reports were received from a total number of 71 non-EU/EEA countries with the highest number of reports coming from the United States of America (11,811), Brazil (4,060), Canada (2,279), Australia (1,320), South Africa (345) and Japan (315).

The overall increase and volume of reports enhance the ability to investigate pharmacovigilance data and contribute to the robustness of the evaluation and help obtain valuable information on the use and safety of VMPs. The majority of the reports concern companion animals, with adverse event reports in dogs and cats accounting for 87% of the cases. Further descriptive statistics regarding the reports received in 2019 can be found in Annex 1.

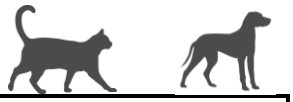
During 2019, the CVMP and its PhVWP-V evaluated 159 PSURs. Further, the continuous monitoring of centrally authorised VMPs through signal detection identified approximately 740 potential safety signals or lack of expected efficacy events for consideration/investigation. All signals detected were further analysed and, for some products, have led to the recommendation to add additional warnings to the product information (PI). However, for most signals the analysis concluded that the observed signs were either not likely to be associated with the use of the product, were expected following use of the product and/or were adequately addressed in the product information. For a small number of signals analysed a potential causal relationship with the product administered could not yet be excluded and these issues remain under investigation in 2020 (see tables under section 3).

Seventy-six pharmacovigilance requests for information were received, in addition to 43 requests for access to document (i.e. requests to release EVVet line listings & PSURs), the majority of the requests concerned potential safety issues related to anti-parasitic products in dogs and cats.

3. Findings and recommendations for centrally authorised veterinary medicinal products

During 2019, the continued monitoring of signals and evaluation of PSURs resulted in the following findings and recommendations.

3.1. Companion animals



Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[6]**
Activyl (indoxacarb)		Blindness in relation to the oral ingestion in cats, neurological signs in dogs (blindness and deafness), gastrointestinal reactions, allergic reactions, lethargy and anorexia in dogs and cats
Activyl Tick Plus (indoxacarb/ permethrin)		Hypersensitivity, convulsions, seizures, myoclonus, permethrin intoxication in cats (medication error), especially in the EU/EEA
Advocate (imidacloprid/ moxidectin)		Convulsions, ataxia and muscle tremor
Apoquel (oclaticinib)		Seizures and convulsions
Bravecto tablets (fluralaner)	Update section 4.6 of the SPC by adding the following adverse reactions: Lethargy, muscle tremor, ataxia and convulsion have been reported very rarely in spontaneous reports. Most reported adverse reactions were self-limiting and of short duration.	Neurological disorders, hepatopathy, death, congenital eye disorders, potential birth defects in dogs, ataxia in cats, haemorrhagic diarrhoea as cases with death outcome have been reported after haemorrhagic diarrhoea in dogs
Bravecto spot-on (fluralaner)		Behavioural disorders, dyspnoea and hepatopathy in cats, convulsions/seizures in cats and convulsions/seizures, tremors and ataxia in dogs
Bravecto Plus (fluralaner)	Update section 4.6 of the SPC by adding the following adverse reactions: Tremors and anorexia have been reported very rarely after the use of this product based on post marketing safety experience (pharmacovigilance).	Behavioural disorders, dyspnoea and hepatopathy in cats, convulsions/seizures in cats
Broadline (fipronil, S-methoprene, epinomectin, praziquantel)	Update section 4.6 of the SPC by adding the following adverse reactions: Transitory blindness or impaired vision have been observed in very rare cases based on post marketing safety experience.	Neurological signs, death, blindness, LEE and human cases
Canigen L4/Nobivac (for active immunisation of dogs against *Leptospira*)		Monitor the impact of age, weight, breed/genetic predisposition on anaphylactic reactions, sudden death and immune-mediated reactions (Immune mediated haemolytic anaemia and immune

[6] This section includes adverse events that are under investigation and for which the potential causal association has not yet been established.

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[6]**
		mediated thrombocytopenia and immune-mediated polyarthritis). Blindness considered to be potentially linked to immune mediated reactions. Monitor potential breed susceptibilities for developing immune-mediated reactions and/or blood and lymphatic disorders. Pancreatic enzymes, renal insufficiency, polydipsia, lymphadenopathy.
Credelio (lotilaner)	Update section 4.6 of the SPC by adding the following adverse reactions: (**additions to text in bold)** Mild, transient gastrointestinal signs (vomiting; diarrhoea) and **neurological signs (convulsion; muscle tremor; ataxia)** have been reported very rarely based on post-marketing safety experience. These signs typically resolve without treatment.	Convulsions, pruritus for both target species and cases of emesis cats
Cytopoint (lokivetmab)	Update section 4.6 of the SPC by adding the following adverse reactions: (**additions to text in bold)** Hypersensitivity reactions (anaphylaxis, facial oedema, and urticaria) **have been reported to** occur in rare cases **in field studies**. In such cases appropriate treatment should be administered immediately. Vomiting and/or diarrhoea have been reported **to occur** in rare cases **from spontaneous reports** and may occur in connection with hypersensitivity reactions. Treatment should be administered as needed. **Neurological signs (seizure, convulsion or ataxia) have been rarely observed in spontaneous reports following use of the veterinary medicinal product.**	Eye disorders including blindness, blood and lymphatic disorders, neurological disorders, respiratory tract disorders, immune system disorders, other types of hypersensitivity reactions (specifically immune-mediated haemolytic anaemia and immune-mediated thrombocytopenia)
Easotic (hydrocortisone aceponate, gentamicin sulfate, miconazole nitrate)		Deafness and loss of hearing
Galliprant (grapiprant)		Emesis, haematemesis, haemorrhagic diarrhoea, hepatopathy, renal insufficiency, 'abnormal test results' and death
Letifend (canine leishmaniasis vaccine (recombinant protein))	Update section 4.6 of the SPC by adding the following adverse reactions: Lethargy, vomiting, diarrhoea and hyperthermia following vaccination have each been reported to occur very rarely based on post-marketing safety	Lethargy, anorexia, emesis, and signs that could be related to hypersensitivity reactions

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[6]**
	experience. Treatment should be administered as needed.	
Leucogen (feline leukaemia vaccine (inactivated))		Local and systemic/immunological reactions
Metacam (meloxicam)	Updates were recommended for section 4.9 of the SPC. It is recommended that a small measuring syringe is prepacked with the product, along with the large measuring syringe. 4.9 Amounts to be administered and administration route Oral use […] Dosing procedure using the measuring syringes: The syringes fit onto the bottle and have a kg-body weight scale which corresponds to the maintenance dose (i.e. 0.1 mg meloxicam/kg body weight). For the first day, twice the maintenance volume will be required. The suspension could be administered using the small syringe for dogs less than 10 kg body weight (one graduation mark corresponding to 0.5 kg of body weight) or the large syringe for dogs over 10 kg body weight (one graduation mark corresponding to 2.5 kg of body weight).	Monitor overdosing in dogs, particularly small dogs
MiPet Easecto (sarolaner)	Amend section 4.6 of the SPC as follows: Neurological disorders such as tremor, ataxia or convulsion may occur in very rare cases. In most cases these signs are transient.	
Nexgard (afoxolaner)		Skin disorders, neurological signs, death, lack of expected efficacy
Nexgard Spectra (afoxolaner/ milbemycin oxim)	Amend section 4.6 of the SPC as follows: Neurological disorders such as tremor, ataxia or convulsion may occur in very rare cases. In most cases these signs are transient.	Erythema, neurological signs (convulsions, ataxia and muscle tremors)
Osurnia (terbinafine, florfenicol, betamethasone acetate)	Special precautions for use in animals. Amend section 4.5 of the SPC to inform the user of risks of neurological and systemic disorders when the product is used in the non-target species cats: The safety and efficacy of Osurnia in cats has not been evaluated. Post-marketing surveillance shows that the use of Osurnia in cats can be associated with neurological signs (including Horner's syndrome with protrusion of membrane nictitans, miosis, anisocoria, and internal ear disorders with ataxia and head tilt) and systemic signs	Central nervous system disorders in potential adverse events in cats

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[6]**
	(anorexia and lethargy). The use of Osurnia in cats should therefore be avoided.	
Posatex (orbifloxacin, mometasone furoate monohydrate and posaconazole)		Cranial nerve disorders, convulsions in dogs
Prac-Tic (Pyriprole)		Behavioural and neurological signs, lack of expected efficacy, medication errors, hyperactivity
Semintra (Telmisartan)		Death
Sileo (Dexmedetomidine hydrochloride)		Frequency of medication errors reporting
Simparica (sarolaner)	Amend section 4.6 of the SPC as follows: Neurological disorders such as tremor, ataxia or convulsion may occur in very rare cases. In most cases these signs are transient.	
Stronghold Plus (selamectin + sarolaner)		Neurological events, including ataxia in cats
Suprelorin (deslorelin acetate)	Amend section 4.6 adverse reactions of the SPC as follows (**additions to text in bold)** During the treatment period, rare clinical effects have been reported: hair coat disorders (e.g. hair loss, alopecia, hair modification), urinary incontinence, down-regulation associated signs (e.g. decrease in testicle size, reduced activity, **weight gain**). In very rare cases, a testicle may be able to ascend the inguinal ring. **In humans and animals, testosterone modulates seizure susceptibility. On very rare occasions (<0.01%) transient occurrence of seizure has been reported shortly after implantation, though the causal relationship with the application of the implant has not been established (see section 4.4). In some cases, the dog had displayed epileptic seizure prior to the implant administration or was diagnosed as suffering from epilepsy.**	Epileptic seizures and potential lack of efficacy
Vectra 3D (dinotefuran, pyriproxyfen and permethrin)		Convulsions, dyspnoea
Versican Plus DHPPi/L4, Versican Plus DHPPi L4R, Versican Plus		The potential of anaphylactic reactions related to foreign serum protein content is under investigation.

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[6]**
DHPPi, Versican Plus L4, Versican Plus Pi+L4, Versican Plus Pi+L4R and Versican Plus Pi		
Zycortal (desoxycortone)	Amends section 4.6 adverse reactions of the SPC as follows (**additions to text in bold)** **Injection site pain has been reported rarely in post-authorisation spontaneous reports following the administration of Zycortal.** Pancreas disorders have been reported very rarely **in post-authorisation spontaneous reports** following use of Zycortal. The concurrent administration of glucocorticoids may contribute to these signs.	Electrolyte imbalance, elevated protein/creatinine ratio, pancreas disorders and renal insufficiency, injection site pain

3.2. Food producing animals

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[7]**
Bovela (for active immunisation of cattle against bovine viral diarrhoea (BVD))	Amendment to the SPC for section 4.6: Hypersensitivity reactions, including anaphylactic-type reactions, have been reported very rarely (post-marketing safety experience).	abortion, anaphylactic/anaphylactic-type reactions
COXEVAC (*Coxiella burnetii* vaccine (inactivated))	Amendments to SPC as follows (additions to text in **bold)** 4.6 Adverse reactions (frequency and seriousness) Cattle: **Systemic signs as lethargy, hyperthermia and/or anorexia have been observed rarely in post marketing safety experience.** 4.7 Use during pregnancy, lactation or lay Lactation: Under field conditions, vaccination with COXEVAC has been followed by a decrease in milk production, **commonly** in goats **and rarely in cattle**. Since stress could contribute to this adverse reaction, appropriate precautions should be taken to reduce stress as much as possible during the administration of the product.	

[7] This section includes adverse events that are under investigation and for which the potential causal association has not yet been established.

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[7]**
Coliprotec F4/F18 (porcine post-weaning diarrhoea vaccine (live))		diarrhoea
Draxxin (tulathromycin)	Update section 4.5 of the SPC by adding the following special precaution: If a hypersensitivity reaction occurs appropriate treatment should be administered without delay.	
Eravac (for active immunisation against rabbit haemorrhagic disease type 2 virus)	Update section 4.6 of the SPC by adding the following adverse reactions: Lethargy and/or inappetence may be observed very rare in the first 48 hours after injection based on post-authorisation pharmacovigilance reporting.	
Exzolt (fluralaner)		Enteritis/gastrointestinal signs and pecking (nervous behaviour)
Galliprant (grapiprant)		Emesis, haematemesis, haemorrhagic diarrhoea, Hepatopathy, renal insufficiency, abnormal test results and death
Imrestor (pegbovigrastim)		Dystocia, hypocalcaemic condition, ketosis, premature parturition, retained placenta, ruminant stomach disorder, stillbirth, mastitis and metritis, anaphylactic reactions
Innovax ILT (live vaccine against avian infectious laryngotracheitis (ILT) virus and Marek's disease (MD) virus)		Lack of efficacy
Innovax-ND-IBD (cell associated live recombinant turkey herpesvirus (strain HVP 360) expressing the fusionprotein of Newcastle disease virus and the VPT protein of the infectious bursal disease virus)		Lack of efficacy
Kexxtone (monensin)		Death in dogs following accidental intake after regurgitation by treated cows
Naxcel (ceftiofur)		Blindness in cattle, bovine/cloudy eye
Panacur AquaSol (Fenbendazole)		Drop egg production, intoxication in doves after use of dosages that are recommended for chicken
Respiporc Flu3 (inactivated		Hyperthermia leading to abortion, abortion potentially linked to

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[7]**
influenza vaccine with 3 subtypes: H1N1, H3N2 and H1N2)		anaphylaxis, vomiting, erythema, anorexia and hyperventilation
Suvaxyn PCV (for immunisation of pigs against Porcine Circovirus type 2 (PCV2)) **Suvaxyn Circo + MH RTU** (for immunisation of pigs against Porcine Circovirus type 2 (PCV2)) and infections against *Mycoplasma hyopneumoniae)*	Update section 4.5 of the SPC by adding the following special precaution: In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.	Lack of efficacy, specifically on circulating field strains (PCV genotype)
Suvaxyn PRRS MLV (active immunisation against porcine respiratory and reproductive syndrome (PRRS))		Anaphylactic reactions
Vaxxitek HVT+IBD (recombinant vaccine intended for use against Infectious Bursal Disease (also known as Gumboro Disease) and Marek's Disease in chickens)		Lack of efficacy specifically against Gumboro and Marek disease
Varromed (Oxalic acid/formic acid)		Death
Vepured (*E. coli* verotoxoid vaccine (inactivated recombinant))	Update section 4.5 of the SPC as follows: In very rare cases within a few minutes after vaccination recumbency, convulsion, lethargy, and loss of consciousness, occur. The animals mostly start to recover within around 15 minutes. In case of severe anaphylactic-type reactions appropriate treatment is recommended.	Lack of efficacy (*recommendation for post-mortem examination to confirm oedema disease in piglets*), neurological disorders
Zactran (gamithromycin)		Localised pain NOS, lameness, injection site oedema
Zolvix (monepantel)		Lack of efficacy (due to resistance)

4.3. Humans

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[8]**
Activyl (indoxacarb)		Pruritus, eye irritation and erythema
Bravecto spot-on (fluralaner)	Update of section 4.5, special precautions, of the SPC to read as follows: Contact with the product should be avoided and disposable protective gloves obtained with this product at the point of sale must be worn when handling the product for the following reasons: Hypersensitivity reactions have been reported in a small number of people, which can potentially be serious. Persons with a hypersensitivity to fluralaner or to any of the excipients should avoid any exposure to the product. The product binds to skin and may also bind to surfaces after spillage of the product. Skin rashes, tingling or numbness have been reported in a small number of individuals after skin contact. If skin contact does occur, wash the affected area immediately with soap and water. In some cases, soap and water are not sufficient to remove the product spilled on the fingers. Contact with the product may also occur when handling the treated animal. Make sure that your animal's application site is no longer noticeable before resuming contact with the site of application. This includes cuddling the animal and sharing a bed with the animal. It takes up to 48 hours for the application site to become dry, but it will be noticeable for longer. If skin reactions occur, consult a physician and show them the product packaging. People with a sensitive skin or known allergy in general e.g. to other veterinary medicinal products of this type should handle the veterinary medicinal product as well as treated animals with caution. This product can cause eye irritation. In case of contact with the eyes, immediately rinse thoroughly with water. This product is harmful after ingestion. Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product. A used pipette should immediately be disposed of. In case of accidental ingestion, seek medical advice and show	Hepatopathy, hypersensitivity (especially generalised urticarial reaction/anaphylactic shock or anaphylaxis/oedema/dyspnoea/ taste), and dermatitis/eczema after contact with the treated animal, neurological signs, such as severe headache. Monitor the effect of glove distribution.

[8] This section includes adverse events that are under investigation and for which the potential causal association has not yet been established.

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[8]**
	the package leaflet or the label to the physician. The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition. In case of spillage onto, for example table or floor surfaces, remove excess product using paper tissue and clean the area with detergent. Section 4.6 (Bravecto spot on for dogs) will have the following amendments: Emesis, lethargy and anorexia have been reported very rarely in spontaneous reports after the use of this product.	
Bravecto Plus (fluralaner)	Update section 4.5, special precautions, of the SPC as follows: Contact with the product should be avoided and disposable protective gloves obtained with this product at the point of sale must be worn when handling the product for the following reasons: Hypersensitivity reactions have been reported in a small number of people, which can potentially be serious. Persons with a hypersensitivity to fluralaner or to any of the excipients should avoid any exposure to the product. The product binds to skin and may also bind to surfaces after spillage of the product. Skin rashes, tingling or numbness have been reported in a small number of individuals after skin contact. If skin contact does occur, wash the affected area immediately with soap and water. In some cases, soap and water are not sufficient to remove the product spilled on the fingers. Contact with the product may also occur when handling the treated animal. Make sure that your animal's application site is no longer noticeable before resuming contact with the site of application. This includes cuddling the animal and sharing a bed with the animal. It takes up to 48 hours for the application site to become dry, but it will be noticeable for longer. If skin reactions occur, consult a physician and show them the product packaging. People with a sensitive skin or known allergy in general e.g. to other veterinary medicinal products of this type should handle the veterinary medicinal product as well as treated animals with caution. This product can cause eye irritation. In case of contact with the eyes, immediately rinse thoroughly with water. This product is harmful after ingestion.	

Product name (active substance)	**Regulatory actions and recommendations for the MAH in 2019**	**Suspected adverse events that continue to be monitored in 2020[8]**
	Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product. A used pipette should immediately be disposed of. In case of accidental ingestion, seek medical advice and show the package leaflet or the label to the physician. The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition. In case of spillage onto, for example table or floor surfaces, remove excess product using paper tissue and clean the area with detergent. Section 4.6 (Bravecto spot on for dogs) will have the following amendments: Emesis, lethargy and anorexia have been reported very rarely in spontaneous reports after the use of this product.	
Canigen L4/Nobivac (for active immunisation of dogs against *Leptospira*)		Adverse reactions after accidental oral or skin exposure.
Cerenia (maropitant citrate)		Inhalation and ocular exposure in humans
Eravac (for active immunisation against rabbit haemorrhagic disease type 2 virus)		Accidental injection in humans
Nexgard (afoxolaner)		Hypersensitivity reactions
Osurnia (terbinafine, florfenicol,betamethasone acetate)	Implementation of a new wording in section 4.5 of the SPC, to minimize the risk of ocular exposure and subsequent disorders in humans	Ocular disorders
Poulvac E. coli (avian colibacillosis vaccine (live))		Monitor self-injection in humans
Simparica (sarolaner)		Dermal, ocular irritation
Suvaxyn PCV (Suvaxyn PCV MHyo)	Update section 4.5 of the SPC by adding the following special precaution: In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.	
Vectra 3D (dinotefuran, pyriproxyfen and permethrin)		Paraesthesia

4. Findings and recommendations related to non-centrally authorised veterinary medicinal products

While pharmacovigilance of non-CAPs falls under the responsibility of each Member State, regulatory tools are established within the EU that allow early communication of safety concerns and rapid exchange of pharmacovigilance information between national competent authorities and EMA, such as the rapid alert (RA) and non-urgent information (NUI) communication exchange systems. Since 2017, EVVet is also used as a tool for monitoring adverse events of vaccines that are not authorised in the EU/EEA, but which are used for control of emerging animal diseases, which are under the responsibility of the European Food Safety Authority (EFSA).

The following non-centrally authorised VMPs were discussed during 2019 at the PhVWP-V:

Sileo

The Dutch agency had received a report from an animal owner describing sedation and collapse after overdose of Sileo due to device failure. Unfortunately, the batch number was unknown. Because device failure was not reported in other Member States and no new reports were received in the Netherlands no further actions are required and the case is closed. These types of reports will be closely monitored in the future.

Febrivac

Adverse events were observed in minks when 8,750 were injected subcutaneously in their right hind legs. Anorexia was reported the day after vaccination and the minks became dull, anorexic, ataxic and some hyperventilated before dying. Five days after vaccination 80 out of 253 reacting minks had died, while the outcome for the remaining 173 minks was unknown. Causality B possible was assigned due to temporal association (within 24 hours); It was considered that these acute clinical signs were compatible with infection introduced at the time of vaccination. Post-mortem data on a few minks was reasonably compatible with infection. A link to the vaccine or the vaccination procedure was considered possible due to the close time-link, and the location in the herd was considered consistent with those minks vaccinated with a single vial of vaccine (minks in the same row of cages). The vaccine appeared to be solely used in Nordic countries. Only Sweden had reported similar adverse events to those described, which were considered to be due to contamination during the vaccination procedure.

Clenbuterol

The illicit use in humans (misuse/abuse) of Clenbuterol is being considered by the Pharmacovigilance Risk Assessment Committee (PRAC)[3]. Clenbuterol has the potential to induce muscle hypertrophy and possesses a strong lipolytic action without androgenic side effects. These properties led to its widespread illicit use as an image and performance enhancer drug (bodybuilders, athletes, etc.). It is classified as an anabolic agent and is prohibited by the World Anti-Doping Agency (WADA) and by the International Olympic Committee (IOC). In human medicine, clenbuterol has now very limited use; it has been banned in several countries due to concerns on misuse/abuse (USA, Australia).

Consideration has been given to the potential illicit use in humans of veterinary products containing clenbuterol. EVVET contains 6 cases from which 3 are related to illicit use in humans. However, there was no indication that veterinary medicinal products containing clenbuterol were specifically used illicitly in humans. The CVMP confirmed that the use of clenbuterol as veterinary medicine is considered essential for the treatment of

[3] The Pharmacovigilance Risk Assessment Committee (PRAC) is the European Medicines Agency's (EMA) committee responsible for assessing and monitoring the safety of human medicines.

respiratory disease in horses and as a uterus relaxant in cows.

Equine Influenza Vaccines

During 2019, the Swedish Medical Products Agency received several reports relating to suspected lack of expected efficacy (LEE) of equine influenza vaccines. LEE events had also been reported in France and the United Kingdom, in relation to disease outbreaks during 2019. Discussions concluded that it is important to raise awareness of the potential for LEE and highlight the annual recommendations from the OIE Expert Surveillance Panel on Equine Vaccine Composition regarding vaccine composition in relation to equine influenza viruses circulating nationally.

Needle stick injury with mineral oil containing vaccines

Two accidental needle stick injuries from vaccines containing mineral oil had been reported in the UK where, in both cases, the affected individuals had not received appropriate medical attention. In one case the lack of timely surgical intervention resulted in the amputation of a digit. From the NUI responses, similar events had not been reported in other Member States. The issue would be managed via communication to the appropriate [triage] healthcare professionals in the UK.

Florfenicol

Neurological signs and deaths in pigs have been observed after the administration of products containing Florfenicol for use in drinking water. A possible hypothesis to explain these cases is that impurities were found by adding chlorinated water. However, there is a need to identify and quantify these unknown impurities. Essays of qualification of the impurities and toxicological studies were requested.

Suvaxyn PRRS MLV + Unistrain PRRS live vaccines (NUI and RA)

The Danish NCA reported a suspected recombination event between two live vaccine viruses following the use of Suvaxyn PRRS MLV and Unistrain PRRS in the same animals. The recombinant virus appeared to have been transmitted to a boar station and subsequently to PRRS-naïve swine herds via semen. The clinical signs reported were comparable to manifestations following introduction of virulent PRRSV infection with respect to reproductive signs. PRRSV was confirmed on approximately 40 farms. Sequencing of the virus indicated homology to Porcilis PRRS MLV and the Unistrain PRRS vaccine. Following the circulation of the NUI, a RA was circulated to inform the network that the Danish Health and Veterinary Agency had taken the decision to suspend the use of Suvaxyn PRRS MLV in Denmark as a precautionary measure since the vaccine had very limited use (on a few individual holdings) compared with Unistrain PRRS. The majority of PhVWP-V members reported that they had not received similar reports associated with the products in their countries. Some Members reported that PRRS vaccines were not used routinely on their territories due to their national PRRSV disease control policies. As an update to the Latvian NUI response, it was reported that investigations were being conducted on several pig farms using boar semen imported from Denmark. There did not appear to be evidence reported from other Member States that Porcilis PRRS MLV was posing a problem in their countries and it was considered acceptable to continue using the vaccine with monitoring of adverse events.

Overall conclusions

Post-authorisation surveillance activities of veterinary medicinal products in the EU followed its normal course during 2019. The scheduling of signal detection for CAPs by the regulatory experts was further aligned to take place before the upcoming PSUR preparations by the MAH. This allowed, where necessary, to ask the MAH for a specific focus in the upcoming PSUR, which increased efficiency and earlier regulatory action.

The total yearly reported adverse events into EVVET showed again the steady yearly increase since 2011 for the reported events having occurred in the EU. Like in 2018, a significant higher number of adverse events from outside the EU were recorded and are to be attributed to requests for increased targeted analysis, which require supplementary electronic reporting, as well as increased compliance of reports originating from third countries.

In 2019 there was continued public interest, with requests for information related to the safety of antiparasitics used in dogs and cats. Adverse event reports related to antiparasitics used in dogs and cats continue to constitute the majority of reports available in EVVET, followed by reports related to the use of vaccines.

Most reports received in 2019 for CAPs related to the use in either dogs (71%) or cats (26%). Hence, it is no surprise to find most of the regulatory actions imposed related to antiparasitics in dogs and cats. Among the notable amendments to the product literature for these products are the known risks for neurological signs. In addition, there has been increased focus to the potential human user safety risks, in particular related to potential exposure following the use of spot-on formulations.

A relatively large number of potential adverse events have been identified for continued monitoring. Especially for rare events and events for which baseline population occurrence is unknown, it remains difficult to conclude on potential causality of the products involved in the reports. The nature of pharmacovigilance data from practice which is uncontrolled and often presented with limited detail increases this challenge. It remains important to emphasize the need for complete information and the future availability of real-world evidence data may also contribute to this quest in the field of pharmacovigilance.

In 2019 there were no activities related to increasing reporting in food producing animals due to business continuity measures related to the move of the Agency to Amsterdam. However, two dedicated focus group meetings are foreseen for 2020.

Preparations for the implementation of the new veterinary pharmaceutical legislation[9] are in full swing and will continue in the next years with the further development of signal detection taking a central role. Finally, it will also remain a priority to increase transparency and ease of access for the veterinarians and the general public to the knowledge generated by pharmacovigilance data on the VMPs authorised in the EU. In the short run, this bulletin will be complemented with more regular standard updates on the regulatory measures taken following pharmacovigilance activities in CAPs.

[9] Regulation (EU) 2019/6, published on 7 January 2019

Annex I
Descriptive analysis of adverse event reports received in EudraVigilance Veterinary

A total of 33,656 reports relating to exposure to centrally authorised VMPs were received in 2019. These include 33,656 adverse event reports relating to animals and 859 adverse event reports relating to humans exposed to VMPs.

The adverse event reports received concerned 181 products, which is approximately 86% of the total CAPs with a valid marketing authorisation granted by the end of 2019.

Of the 33,656 reports in animals, 29,474 reports concerned companion animals, most frequently dogs (24,044) and cats (5,430) and 3,228 reports concerned food-producing animals.

Of the reports received for CAPs in 2019, 12,575 occurred in EU/EEA countries. The 21,081 reports originating from outside the EU/EEA were from the United States (56%), Brazil (19%) and Canada (11%) with the remainder coming from 54 different countries. Table 1 and the figures in this Annex show the numbers of reports by target animal species (in addition to humans). A single report may relate to one or more animals or individuals (especially for treatment concerning livestock) and to one or more products, which may have been used concurrently.

The Figure 1 below gives raw figures of reports received, irrespective of whether or not the reaction can be attributed to administration of the product.

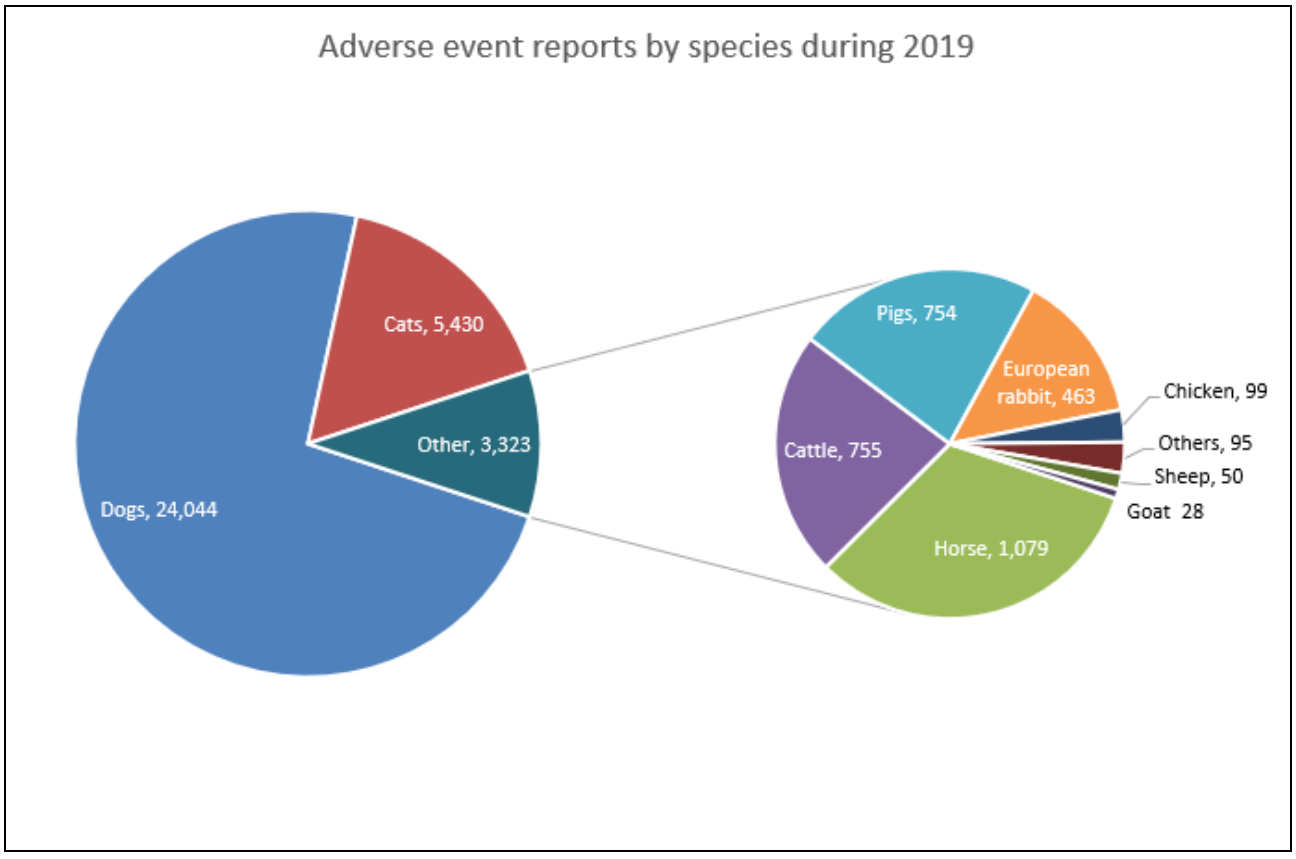


Figure 1. Adverse event reports by species received during 2019 following the use of centrally authorised products.

Summary statistics on reports for CAPs by target species and in humans received between 1 January 2019 and 31 December 2019 are presented in the table below.

Table 1. Reports received between 1 January 2019 and 31 December 2019 for CAPs by target species, including reports in humans.

Animal reports	**Species**	**Number of Safety Reports**	**Number of animals affected**
Animal	Dogs	24,044	26,081
	Cats	5,430	6,434
	Horse	1,079	1,698
	Cattle	755	52,455
	Pigs	754	185,000
	Rabbits	463	7,940
	Chicken	99	3,264,197
	Others*	95	362,443
	Sheep	50	7,533
	Goat	28	6,224
Total animals		**32,797**	**3,920,005**
Human reports		**Number of safety reports**	**Number of humans affected**
Human		859	859
Grand Total		**33,656**	**3,920,864**

* "Other" species include mainly donkey, ferrets and guinea pigs amongst others.

The total number of animals reacting and safety reports within EVVet by species until 2019 is presented in Figure 2 below. The logarithmic scale on the y-axis allows the inclusion of both the number of reports received and the total number of affected animals (which, in particular for food producing animals, can be a multiple of the actual number of reports).

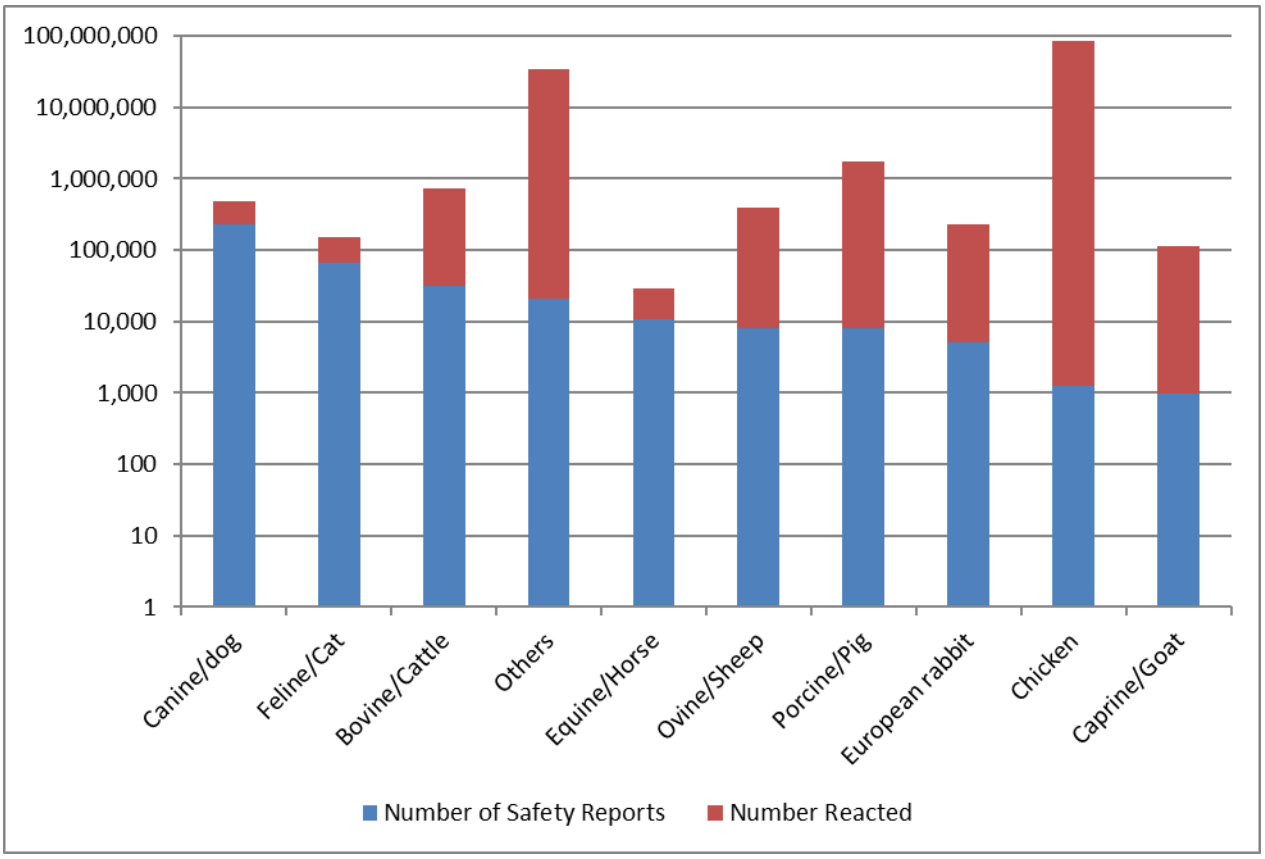


Figure 2. Total number of reports and animals affected by species in EVVet (1 January 2005-31 December 2019).

In the following Figure 3 the reports of adverse events in various animal species and in humans for all products have been grouped according to the anatomical therapeutical chemical (ATCVet) coding system (see http://www.whocc.no/atcvet/ for further explanations). The number of adverse event reports classified by ATC coded type of product until 2019 is presented in the figure below.

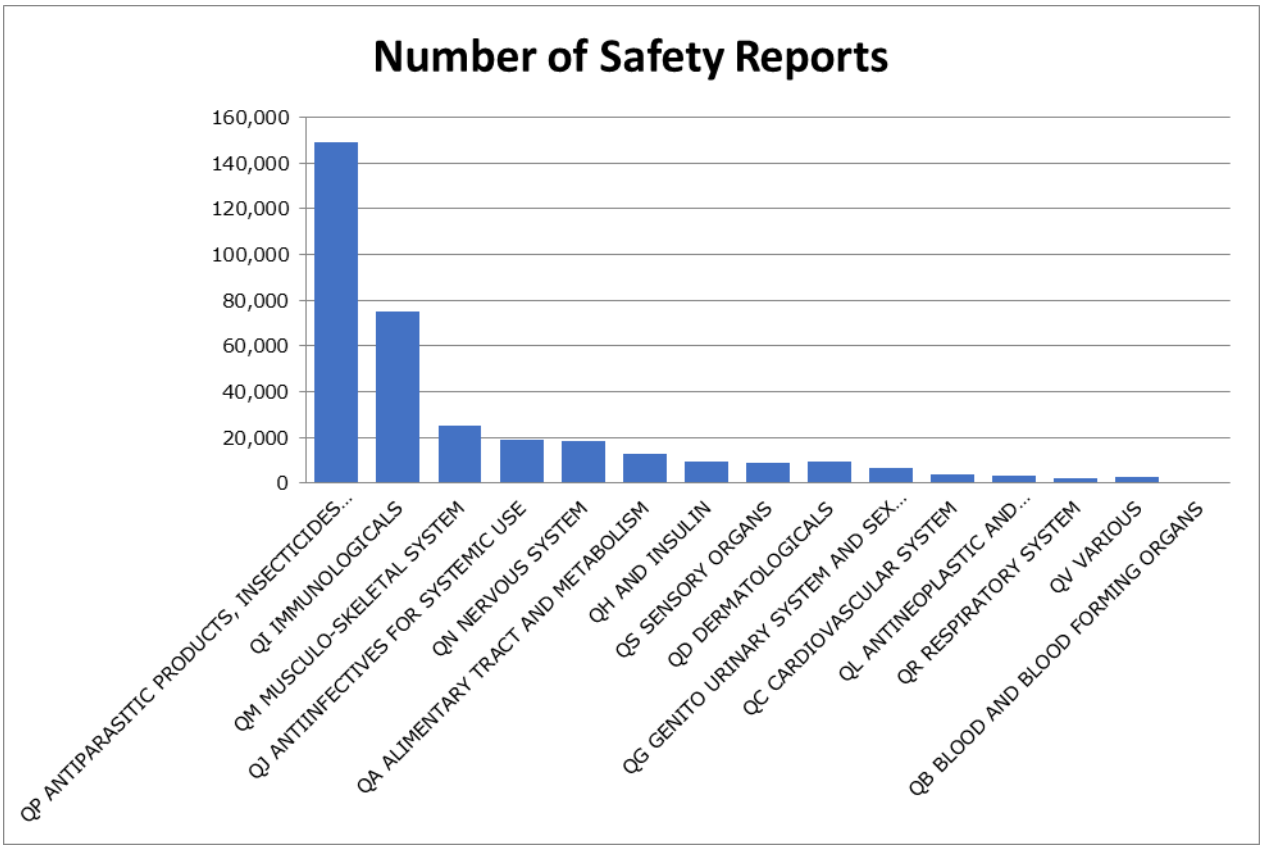


Figure 3. Total number of reports by ATCVet group in EVVet (1 January 2005-31 December 2019).