EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 February 2019
EMA/CVMP/809750/2018
Committee for Medicinal Products for Veterinary Use

Veterinary pharmacovigilance 2018

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 2018 at the European Medicines Agency (EMA or Agency). These investigations have led to a number of important new specific warnings and recommendations related to the use of the VMPs (detailed in section 4).

The bulletin also highlights ongoing monitoring of potential specific events in place for several 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.

Another significant growth in the total number of adverse event[3] reports in the central veterinary pharmacovigilance database Eudravigilance veterinary (EVVet) was observed in 2018, due to large number of data becoming available from outside the EU and also in part as a consequence of increased requests for targeted investigations.

However, the initiatives undertaken in the EU to promote reporting in food producing animals remain largely ineffective with continued low reporting levels pointing to significant underreporting. Operationally, the Agency is already moving towards continuous monitoring of adverse event data in line with the new requirements of Regulation 2019/6. In particular there will be increased focus on improvements to communicate and exchange information with veterinarians in the field and the general public, in preparation of the full implementation of Regulation 2019/6.

[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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

2. Introduction

This is the 16th bulletin from the EMA on veterinary pharmacovigilance activities, covering the year 2018. This is the only publication that provides an annual overview of the surveillance of adverse events and safety issues of veterinary medicines in the EU. This bulletin also 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 EMA as agencies that authorised 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 classed as "serious". In addition to the reporting of all suspected 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 EVVet became mandatory in November 2005 for serious reports only. EVVet now contains 315,805 reports of adverse events[4], approximately 52% of which occurred within the EU/EEA[5] and 48% 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 time-frame on a specific product, are compiled by MAHs and submitted to the regulatory authority for evaluation 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.

Under the current EU legislation, the CVMP and its Pharmacovigilance Working Party (PhVWP-V) are responsible for pharmacovigilance of centrally authorised VMPs, i.e. the products that have been granted an EU-wide marketing authorisation, whereas the surveillance of non-centrally authorised VMPs is undertaken by the competent authorities at Member State 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

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

There are now 194 VMPs that have been authorised via the centralised procedure since 1995 and which 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 35,835 adverse event reports following exposure to centrally authorised products were received in 2018. Of these, 34,733 adverse event reports related to animals and 1,102 adverse event reports related to humans exposed to a VMP.

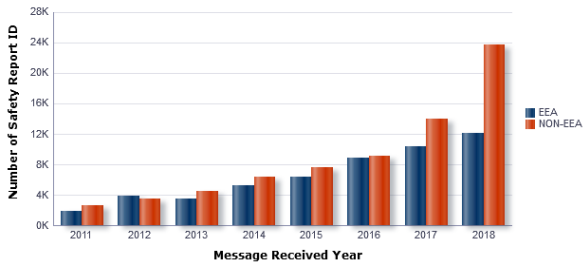


Figure 1. Total number of adverse events for centrally authorised products reported to EVVet from within and outside the EU/EEA between 2011 and 2018

A long-term, year-on-year increase in reporting (Figure 1) can be observed which reflects the increasing number of CAPs authorised. In addition, in 2018 we observe a significant increase of reports from non-EEA countries, which is also partially linked to a number of targeted investigations for which non-serious reports have also been imported in EVVet. Reports were received from a total number of 45 non-EEA countries with noticeable increases in the number of reports from Argentina (42), Australia (1284), Brazil (5198), Chile (31), Colombia (52), New Zealand (226), South Africa (280), and the United States of America (14317).

The overall increase and volume of reports improves the ability to investigate and deduct useful information on the use and safety of VMPs. The majority of reports concern companion animals, with adverse event reports in dogs and cats accounting for 81% of the cases. Further descriptive statistics regarding the reports received in 2018 can be found in Annex 1.

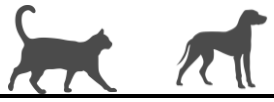
During 2018, the CVMP and its PhVWP-V evaluated 158 PSURs provided by the MAHs. Further, the continued monitoring of the safety and efficacy of centrally authorised VMPs through signal detection resulted in approximately 600 outcomes of potential safety signals or lack of expected efficacy concerns. All signals detected were further analysed and, for some products, have led to the recommendation to add additional warnings to the product information (PI). For most signals the analysis concluded that the observed signs were either not likely to be associated with the use of the product or the observed signs fell within those adverse events 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 2019 (see tables under section 4).

Also in 2018, the Agency observed a significant increase in requests for information (173), including 87 access to documents requests (i.e. requests to release EVVet line listings & PSURs), the majority of which concerned potential safety issues related to anti-parasitic products in dogs and cats.

4. Findings and recommendations for centrally authorised veterinary medicinal products

During 2018, the continued monitoring of signals and evaluation of PSURs resulted in the following findings and recommendations.

4.1. Companion animals



	Regulatory actions and recommendations for the MAH in 2018	**Suspected adverse events that continue to be monitored in 2019[6]**
Activyl (indoxacarb)		Neurological disorders (including deafness and blindness), gastrointestinal reactions, allergic reactions, lethargy and anorexia in dogs and cats
Activyl Tick Plus (indoxacarb/ permethrin)		Hypersensitivity, convulsions, seizures, myoclonus
Advocate (imidacloprid/ moxidectin)		Convulsions
Apoquel (oclaticinib)	New adverse reactions for inclusion in the PI: *Anaemia and lymphoma have been reported very rarely in spontaneous reports.*	Seizures, convulsions
Bravecto tablets (fluralaner)		Neurological disorders, hepatopathy, death, congenital eye disorders, potential birth defects
Bravecto spot-on (fluralaner)		Behavioural disorders, dyspnoea and hepatopathy in cats
Broadline (fipronil, S-methoprene, epinomectin, praziquantel)	Amendments to precautionary measures in the PI: *The veterinary medicinal product is not intended for use in dogs. Some dog breeds may present increased susceptibility to macrocyclic lactones, potentially leading to signs of neurotoxicity. Oral uptake by dogs, specifically by Collies, Old English Sheepdogs and related breeds or crossbreeds should thus be avoided.*	Neurological signs, death, blindness
Canigen L4/Nobivac (for active immunisation of dogs against *Leptospira*)		Blindness An additional analysis on cases with death since authorisation until 31/12/2017 has been submitted and is under investigation. In this analysis the role of potential risk factors (e.g. age, breed, size, underlying conditions, history of previous vaccines exposure) and batch-related effects are considered.

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

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[6]
Canigen L4, Nobivac L4 & Versican Plus DHPPi/L4, Plus DHPPi/L4R, Plus L4, Plus Pi/L4, Plus Pi L4R (for active immunisation of dogs against *Leptospira*)		Painful local and systemic reactions A high number of reports of painful local reactions and systemic reactions were reported with different multivalent Leptospira vaccines. Further investigations on the underlying cause e.g. potential role of the additional antigenic load, are ongoing.
Cardalis (benazepril hydrochloride/ spironolactone)		Gastrointestinal and dermatological signs Dry cough
Credelio (lotilaner)	New adverse reactions for inclusion in the PI: *Mild and transient gastrointestinal effects such as vomiting and diarrhoea have been reported to occur very rarely based on post-marketing safety experience. These signs typically resolve without treatment.*	Convulsions and pruritis
Cytopoint (lokivetmab)	New adverse reactions for inclusion in the PI: *Vomiting and/or diarrhoea have also been reported in rare cases and may occur in connection with hypersensitivity reactions. Treatment should be administered as needed.*	Eye disorders including blindness, blood and lymphatic disorders, neurological disorders, respiratory tract disorders, immune system disorders
Easotic (Hydrocortisone Aceponate, Gentamicin Sulfate, Miconazole Nitrate)	Amendments to adverse reaction section of the PI: *In very rare cases, the use of the veterinary medicinal product has been associated with hearing impairment (partial hearing loss or deafness), ~~usually temporary, and~~ primarily in geriatric dogs. If ~~this~~ deafness or partial hearing loss occurs, treatment should be stopped. See section 4.5 of the SPC.* *In very rare cases, type-I hypersensitivity reactions (facial swelling, allergic pruritus) have been observed. If this occurs, treatment should be stopped.*	Deafness and loss of hearing
Galliprant (Grapiprant)		Emesis, haematemesis, haemorrhagic diarrhoea, hepatopathy, renal insufficiency, 'abnormal test results' and death
MiPet Easecto (sarolaner)	New adverse reactions for inclusion in the PI: *Mild and transient gastrointestinal signs such as vomiting and diarrhoea, transient neurological disorders such as tremor, ataxia or convulsion and systemic disorders such as lethargy, anorexia/inappetence may occur in very*	

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[6]
	rare cases. These signs typically resolve without treatment.	
Nexgard (afoxolaner)		Skin disorders, neurological signs, death
Nexgard Spectra (afoxolaner/ milbemycin oxim)		Erythema, neurological signs (convulsions, ataxia and muscle tremors)
Osurnia (terbinafine, florfenicol, betamethasone acetate)	New special precautions for use for inclusion in the PI: *OSURNIA may be irritating to eyes. Avoid accidental contact to the dog's eyes. If accidental ocular exposure does occur, the eyes should be flushed thoroughly with water for 10 to 15 minutes. If symptoms develop, seek veterinarian advice.* *In very rare cases, eye disorders such as keratoconjunctivitis sicca and corneal ulcers have been reported in treated dogs, in absence of eye contact with the product. Although a causal relationship with OSURNIA was not definitively established, owners should be recommended to monitor ocular signs (such as squinting, redness and discharge) in the hours and days following OSURNIA application, and to promptly consult a veterinarian in case such signs appear.* A press release was published on 20 April 2018: https://www.ema.europa.eu/en/news/eye-injuries-people-dogs-when-using-osurnia-ear-gel-dogs. The MAH also agreed to disseminate communication for veterinarians to raise awareness of these risks.	Central nervous system disorders in potential adverse events in cats
Posatex (orbifloxacin, mometasone furoate monohydrate and posaconazole)		Cranial nerve disorders
Prac-Tic (Pyriprole)		Behavioural and neurological signs
Sileo (Dexmedetomidine hydrochloride)		It was noted that the US Food and Drug Administration (FDA) published a safety communication (https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm559954.htm) on accidental overdose in dogs. No similar reports had been identified in EVVet for the previous 6-month period. In 2017 the MAH performed tests on the locking device and it was concluded that medication errors were not related to defects in the function of the medication device. Nevertheless, the

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[6]
		MAH has been requested to review all medication errors reporting.
Simparica (sarolaner)	New adverse reactions for inclusion in the PI: *Mild and transient gastrointestinal signs such as vomiting and diarrhoea, transient neurological disorders such as tremor, ataxia or convulsion and systemic disorders such as lethargy, anorexia/inappetence may occur in very rare cases. These signs typically resolve without treatment.*	
Stronghold Plus (selamectin + sarolaner)		Neurological events, including ataxia in cats
Suprelorin (deslorelin acetate)	Investigations recommended on the mechanism(s) underlying testosterone modulation of seizure susceptibility in dogs.	Epileptic seizures and potential lack of efficacy
Upcard (torasemide)		Visual disorders and pancreatitis
Vectra Felis (pyriproxyfen / dinotefuran)	New adverse reactions for inclusion in the PI: *Other application site disorders such as erythema, pruritus, lesions and inflammation may occur very rarely. Hyperactivity and tachypnoea may occur very rarely.*	
Vectra 3D (dinotefuran, pyriproxyfen and permethrin)	New adverse reactions for inclusion in the PI: *Signs of ataxia such as unsteady movement have been reported in very rare cases.*	Application site reactions, anxiety, behavioral disorders NOS, hyperactivity, vocalisation, lethargy, convulsions and/or epileptic seizure and anorexia
Veraflox (pradofloxacin)		Eye disorders including blindness in cats
Versican Plus DHPPi/L4,Versican Plus DHPPi L4R, Versican Plus DHPPi, Versican Plus L4, Versican Plus Pi+L4, Versican Plus Pi+L4R and Versican Plus Pi		Anaphylactic reactions
Zycortal (desoxycortone)	New adverse reactions for inclusion in the PI: *Pancreas disorders have been reported very rarely 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

4.2. Food producing animals

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[7]
Bovela (for active immunisation of cattle against bovine viral diarrhoea (BVD))		Anaphylactic type reactions, reproductive disorders including abortion (malformations), return to oestrus The MAH was requested to continue to investigate reports with suspicion of vaccine positive calves and provide information on the characteristics of "iatrogenic" persistently infected calves (e.g. whether the vaccine strain is found only in the skin, confirmation of the persistency of the infection including data on the investigation at a second time-point, the frequency of these events, details of the dam's vaccination schedule and specifically whether it was primo-vaccinated with Bovela) and on the epidemiological impact of these calves on the BVD control programmes undertaken throughout Europe. Since the passage of a vaccine strain has been documented (Wernicke 2017 & 2018), the MAH was requested to monitor and critically discuss reproductive disorders including abortion, return to oestrus, or similar clinical signs in relation to the overall benefit-risk balance of the product.
Eravac (for active immunisation against rabbit haemorrhagic disease type 2 virus)		Lack of efficacy
Eryseng (vaccine with inactivated *Erysipelothrix rhusiopathiae* bacteria, strain R32E11)	New adverse reactions for inclusion in the PI: *Anaphylactic-type reactions have been reported in spontaneous reports and appropriate symptomatic treatment is recommended.*	
Eryseng Parvo (Inactivated vaccine against porcine parvovirus and swine erysipelas)	New adverse reactions for inclusion in the PI: *Anaphylactic-type reactions have been reported in spontaneous reports and appropriate symptomatic treatment is recommended.*	

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

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[7]
Kexxtone (monensin)		Adverse events including death in Dogs following accidental intake after regurgitation by treated cows
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
Panacur AquaSol (fenbendazole)		Egg drop Concerns were raised of potential intoxication in pigeons being treated out of label at the same dosage as recommended for chickens.
Respiporc Flu3 (Inactivated influenza vaccine with 3 subtypes: H1N1, H3N2 and H1N2)		Hyperthermia leading to abortion, abortion potentially linked to 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)*		Lack of efficacy, potentially due to new 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)		Lack of efficacy (specifically against Gumboro)

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[7]
and Marek's Disease in chickens)		
Vepured (E. coli verotoxoid vaccine (inactivated recombinant))		Lack of efficacy (recommendation for post-mortem examination to confirm oedema disease in piglets)
Zactran (gamithromycin)		Localised pain NOS, lameness, injection site oedema
Zolvix (monepantel)		Lack of efficacy (due to resistance)

4.3. Humans

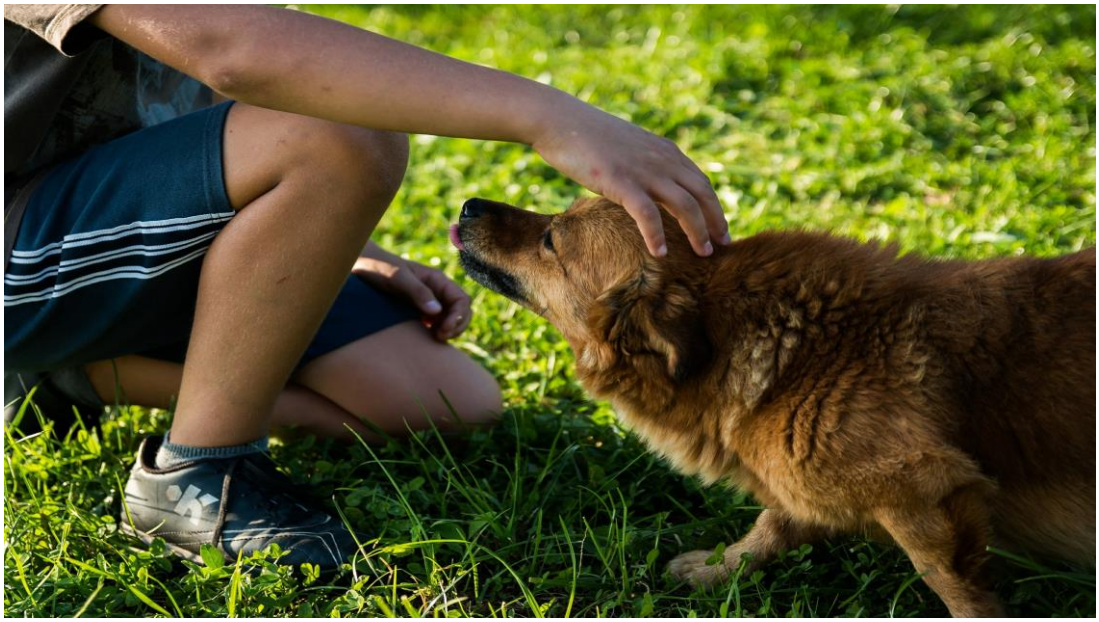
	Regulatory actions and recommendations for the MAH in 2018	**Suspected adverse events that continue to be monitored in 2019[8]**
Activyl (indoxacarb)		Pruritus, eye irritation and erythema
Bravecto chewable tablets (fluralaner)	New user safety warning for inclusion in the PI: *Hypersensitivity reactions in humans have been reported.*	
Bravecto spot-on (fluralaner)	Improved user safety warnings for inclusion in the PI: *A relatively high number of reports were received that included local skin reactions that occurred due to spillage during administration and/or close contact with the animal following administration. Users are strongly advised to use gloves during the administration as outlined in the product information.* ***Special precautions to be taken by the person administering the veterinary medicinal product to animals*** *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 the package leaflet or the label to the physician.* *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. Contact may occur either directly, when handling the product, or when handling the treated animal. In order to avoid contact, disposable protective gloves provided with this product must be worn when handling and administering the product.* *If skin contact does occur, wash the affected area immediately with soap and water. In some cases, soap and water is not sufficient to remove the product spilled on the fingers, therefore gloves must be used.* *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.*	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

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

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[8]
	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.* *This product can cause eye irritation. In case of contact with the eyes, immediately rinse thoroughly with water.* *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.* *Hypersensitive reactions to the product have been reported in a small number of people. The product should not be used by persons with a hypersensitivity to the active substance or to any of the excipients (see contraindications, section 4.3). 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.*	
Canigen L4/Nobivac (for active immunisation of dogs against *Leptospira*)		Adverse reactions after accidental oral or skin exposure. The clinical impact of accidental oral/ skin exposure in humans should be followed-up.
Cerenia (maropitant citrate)	New user safety warning for inclusion in the PI: *People with known hypersensitivity to maropitant should administer the veterinary medicinal product with caution.*	
Eravac (for active immunisation against rabbit haemorrhagic disease type 2 virus)		Accidental injection in humans
Improvac (induction of antibodies against gonadotropin-releasing factor (GnRF) conjugated to dipthheria toxoid)	New user safety warning for inclusion in the PI: *Advice to the user in the event of accidental self-injection:* *Accidental injection/self-injection may result in severe pain and swelling, particularly if injected into a joint or finger, and in rare cases could result in the loss of the affected finger if prompt medical attention is not given.* *In the event of accidental self-injection, wash the injury thoroughly with clean running water. Seek prompt medical advice even if only a very small amount is*	

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[8]
	injected and take the package leaflet with you. If pain persists for more than 12 hours after medical examination, seek medical advice again. Do not administer the veterinary medicinal product in the future. *Advice to the physician:* *Even if small amounts have been injected, accidental injection with this product can cause intense swelling, which may, for example, result in ischaemic necrosis and even the loss of a digit. Expert, PROMPT, surgical attention is required and may necessitate early incision and irrigation of the injected area, especially where there is involvement of finger pulp or tendon.*	
Nexgard (afoxolaner)		Hypersensitivity reactions
Osurnia (terbinafine, florfenicol, betamethasone acetate)	New precautionary measures/user safety warnings for inclusion in the PI: *OSURNIA may be irritating to eyes. Eye exposure may occur when the dog shakes its head during or just after administration. To avoid this risk for the owners, it is recommended that the product is administered only by a veterinarian or under their close supervision. Appropriate measures (e.g. wearing safety glasses during administration) are needed to avoid exposure to the eyes. If accidental ocular exposure does occur, the eyes should be flushed thoroughly with water for 10 to 15 minutes. If symptoms develop, seek medical advice.* *Consult a physician in case of accidental ingestion by humans and show the package leaflet or the label to the physician. In case of accidental skin contact, wash exposed skin thoroughly with water.* A press release was published on 20 April 2018: https://www.ema.europa.eu/en/news/eye-injuries-people-dogs-when-using-osurnia-ear-gel-dogs. The MAH also agreed to disseminate communication for veterinarians to raise awareness of these risks.	
Simparica (sarolaner)		Dermal, ocular irritation
Suvaxyn Circo+MH RTU (for active immunisation of pigs against porcine circovirus type 2 and *Mycoplasma*	New user safety warning for inclusion in the PI: *In the case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.*	

	Regulatory actions and recommendations for the MAH in 2018	Suspected adverse events that continue to be monitored in 2019[8]
hyopneumoniae)		
Vectra Felis (pyriproxyfen / dinotefuran)	New user safety warning for inclusion in the PI: *If the veterinary medicinal product accidentally gets into the eyes, they should be rinsed with water immediately, with the eyelids open, and for a sufficient length of time.*	
Vectra 3D (dinotefuran, pyriproxyfen and permethrin)		Eye disorders after accidental exposure



5. 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 2018 at the PhVWP-V:

Overvac EC (Ovine parapoxvirus attenuated) (Spanish national authorisation)

A quality defect rapid alert was issued in April 2018 following adverse events (death and abortion) in sheep flocks in Spain. Pestivirus contamination of the batches has been confirmed by polymerase chain reaction (PCR) and the marketing authorisation has been temporarily suspended in Spain.

Gentamicin containing products – use in horses

Discussions in 2017 continued on the rapid alerts initiated in 2016 relating to gentamicin containing products. The RAs were originally circulated following receipt of adverse event reports concerning horses presenting with signs of anaphylactoid reactions such as urticaria, increased breathing frequency, colic-like signs, trembling and sweating (154 reports in total). All adverse events were reported shortly after a new batch of the finished product produced with a new batch of the active pharmaceutical ingredient (API) gentamicin was placed on the market. Regulatory actions, including batch recalls and caution in-use communications, were taken in some Member States.

Early in 2017, the marketing authorisation holder for Genta 100 identified that the batches causing adverse events contained much more histamine than those for which no adverse events were reported. A correlation between the concentration of histamine and the occurrence of adverse events was found. The clinical signs reported were considered consistent with the pharmacological profile of histamine and there was also a correlation in time. It was noted that the manufacturer of the active pharmaceutical ingredient had taken measures to reduce the histamine content in the active substance in October 2017.

On 18th April 2018 an EU procedure was started regarding the need for inclusion of a maximum limit of histamine in API specifications for gentamicine containing VMPs for parenteral administration in horses. This procedure concluded in November 2018 and recommends that the interim limit of 16 ppm for histamine in API batches should be reduced further. A limit of 8 ppm is recommended and considered within the current manufacturing capability of the API manufacturer/supplier. Further measures were recommended to lower the risk for inclusion on histamine residues and the MAHs were recommended to continue monitoring any new adverse event reports while detailing the levels of the histamine content in the relevant API and finished product batches.

Rabdomun, Enduracel T and Versifel CVR-T (Monovalent rabies vaccines)

Hypersensitivity reactions including anaphylaxis (allergic Type I reactions), potentially due to high total protein content were discussed. While the sale of several of the products had been stopped voluntarily by the MAH in several Member States, it was advised to continue monitoring and requesting submission of adverse event reports for batches that were still marketed and had not yet expired.

Nobivac Rabies

An increase of reports on pinna vasculitis was observed in Finland which appeared 17-26 days after vaccination of either Nobivac Rabies vaccine alone or in combination with Nobivac DHPPI. The findings are under investigation and Member States have been alerted to monitor for similar findings.

6. Overall conclusions

The year 2018 was another year where the pharmacovigilance activities have further underlined their essential role in safeguarding animal and public health. Regular signal management has become routine for CAPs with increased targeted investigations by regulators and the MAHs on specific areas of potential safety concern. These investigations have led to a number of important new specific warnings and recommendations related to the use of the VMPs (detailed in section 4). Recommendations ranged from warnings for potentially rare adverse events to recommendations to reinforce the correct use of VMPs, supported by publications to raise awareness by users and specific warnings aimed at increasing user safety. A number of actions related to safeguarding non-target animals accidentally exposed to VMPs e.g. cats and permethrin containing products, and dogs accidentally eating regurgitated cow boluses.

Notwithstanding the significant growth in the total number of adverse event reports in EVVet, a number of issues hinder the full realisation of the potential of the database. In particular, on average, the quality of the data in an individual adverse event report remains low and the data is often incomplete. This presents challenges for concluding on the potential association between an adverse event and the VMP. It is therefore important to continue investing in and finding ways to increase awareness of the importance of detailed and complete data for pharmacovigilance reports, in particular for veterinarians. Further work is also needed to get better insights in the pharmacovigilance profiles of VMPs used in food producing animals for which there is considerable underreporting of potential adverse events. Unfortunately the activities planned in 2018 to hold pharmacovigilance focus-group meetings with veterinarians specialised in food producing animals were postponed due to the reduction of Agency activities related to its relocation to Amsterdam.

The finalisation of the discussions on the new veterinary legislation[9] in the past year already resulted in a gradual shift in focus from periodic reporting (in periodic safety update reports (PSURs)) to a more continuous surveillance involving signal management of all electronically-available data. A number of MAHs voluntarily implemented revised guidance[10] providing all their pharmacovigilance data electronically. This allows regulators to use their limited resources more effectively and further streamline surveillance based on a complete electronic dataset. This provides a foundation for exploring and strengthening approaches to surveillance which will also provide valuable experience for future development of guidance for implementation of Regulation 2019/6. Activities in 2019 will continue the preparations for the implementation of Regulation 2019/6. One important aspect, also based on the experience from 2018, will be to further agree on ways for harmonising and improving methods for pharmacovigilance communication across the EU.

The rising number of requests from the general public for information or documents shows an increased awareness and interest in veterinary pharmacovigilance and corresponds to the commitment from the Agency to ensure transparency. While this public bulletin delivers an annual overview of the main findings and actions taken in relation to VMPs there is scope in future for improved and continuous access to VMP information in such a way that these routes become recognised as the authoritative reference source for independent and up-to-date pharmacovigilance information on the safe and effective use of VMPs in the EU. The Agency remains committed to progress this area further in the coming years.

[9] Regulation (EU) 2019/6, published on 7 January 2019
[10] Revised recommendation for the basic surveillance of EVVet data (EMA/CVMP/PhVWP/171122/2016)

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

A total of 35,835 reports relating to exposure to centrally authorised VMPs were received in 2017. These include 34,733 adverse event reports relating to animals and 1,102 adverse event reports relating to humans exposed to VMPs.

The adverse event reports received concerned 165 products, which is approximately 85% of the total CAPs with a valid marketing authorisation granted by the end of 2018.

Of the 34,733 reports in animals, 31,214 reports concerned companion animals, most frequently dogs (26,439) and cats (4,775) and 3,519 reports concerned food-producing animals.

Of the reports received for CAPs in 2018, 12,120 occurred in EU/EEA countries. The 23,715 reports originating from outside the EU/EEA were from the United States (60%), Brazil (21%) and Canada (7%) with the remainder coming from 45 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 table gives raw figures of reports received, irrespective of whether or not the reaction can be attributed to administration of the product.

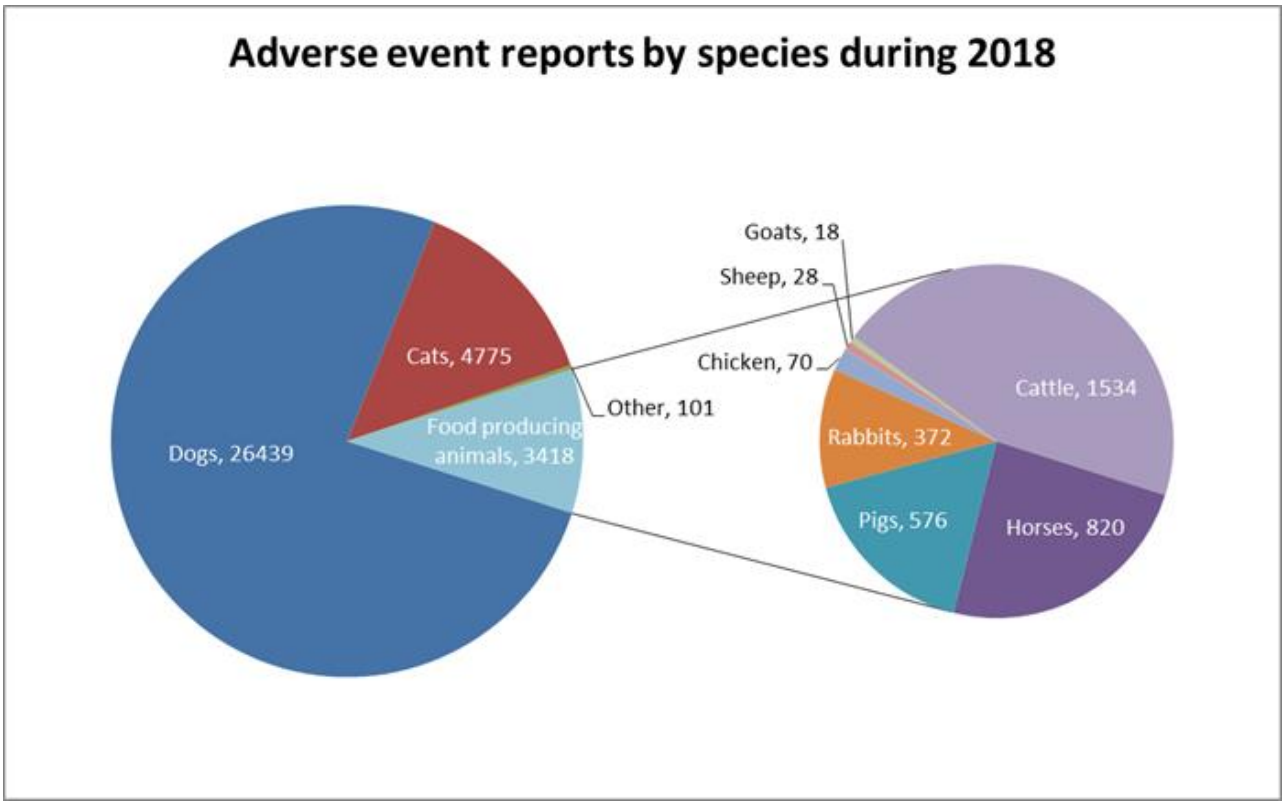


Figure 1. Adverse event reports by species received during 2018 following the use of centrally authorised products.

Summary statistics on reports for CAPs by target species and in humans received between 1 January 2018 and 31 December 2018 are presented in the table below.

Table 1. Reports received between 1 January 2018 and 31 December 2018 for CAPs by target species, including reports in humans.

Animal reports	Species	Number of Safety Reports	Number of animals affected
Animal	Dogs	26,439	28,678
	Cats	4,775	5,906
	Cattle	1534	28,230
	Horses	820	1,530
	Pigs	576	130,318
	Rabbits	372	3111
	Other*	101	41,195
	Chicken	70	1,157,656
	Sheep	28	875
	Goats	18	664
Total animals		**34,733**	**1,398,163**
Human reports		**Number of safety reports**	**Number of humans affected**
Humans		1,102	1,102
Grand total		**35,835**	**1,399,265**

* "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 2018 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).

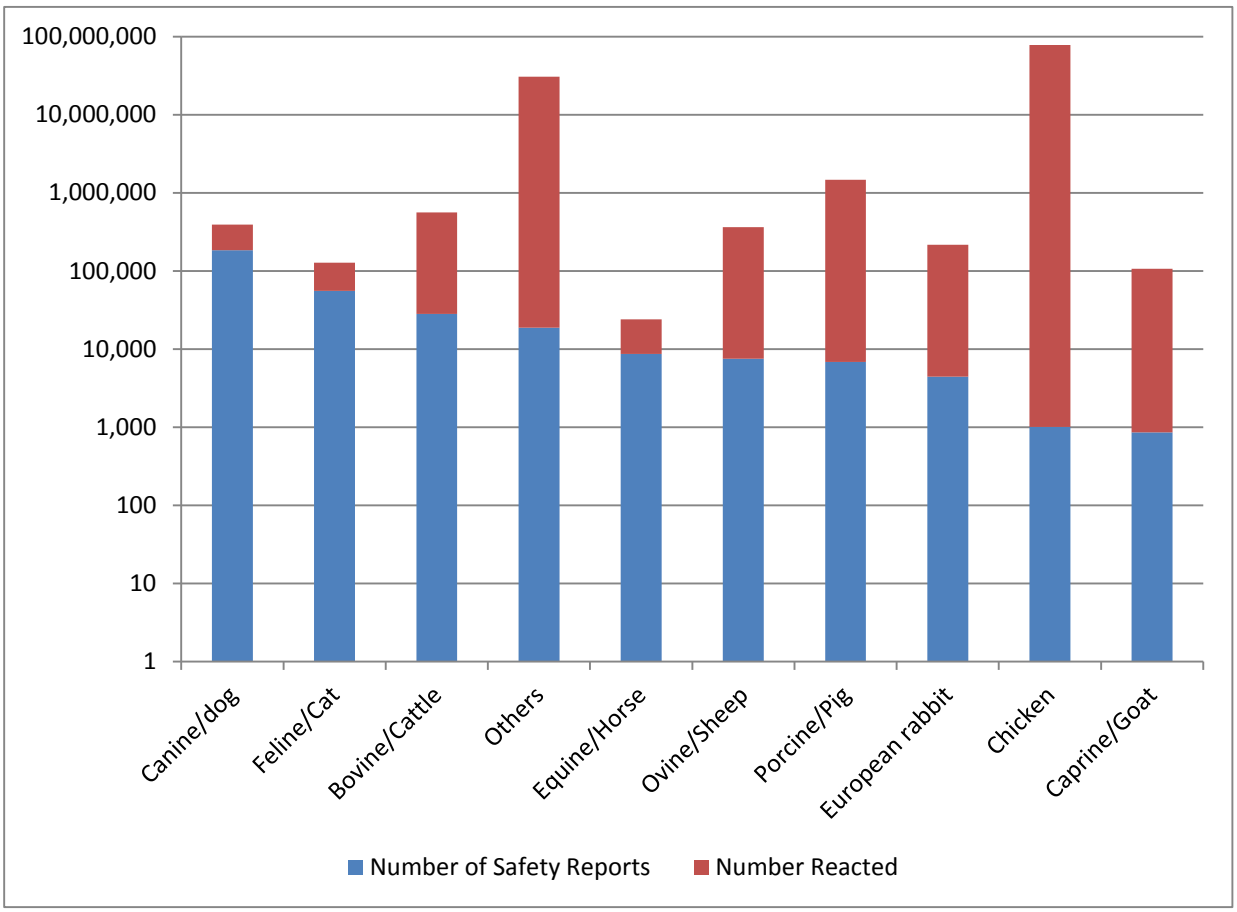


Figure 2. Total number of reports and animals affected by species in EVVet (1 January 2005-31 December 2018).

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 2018 is presented in the figure below.

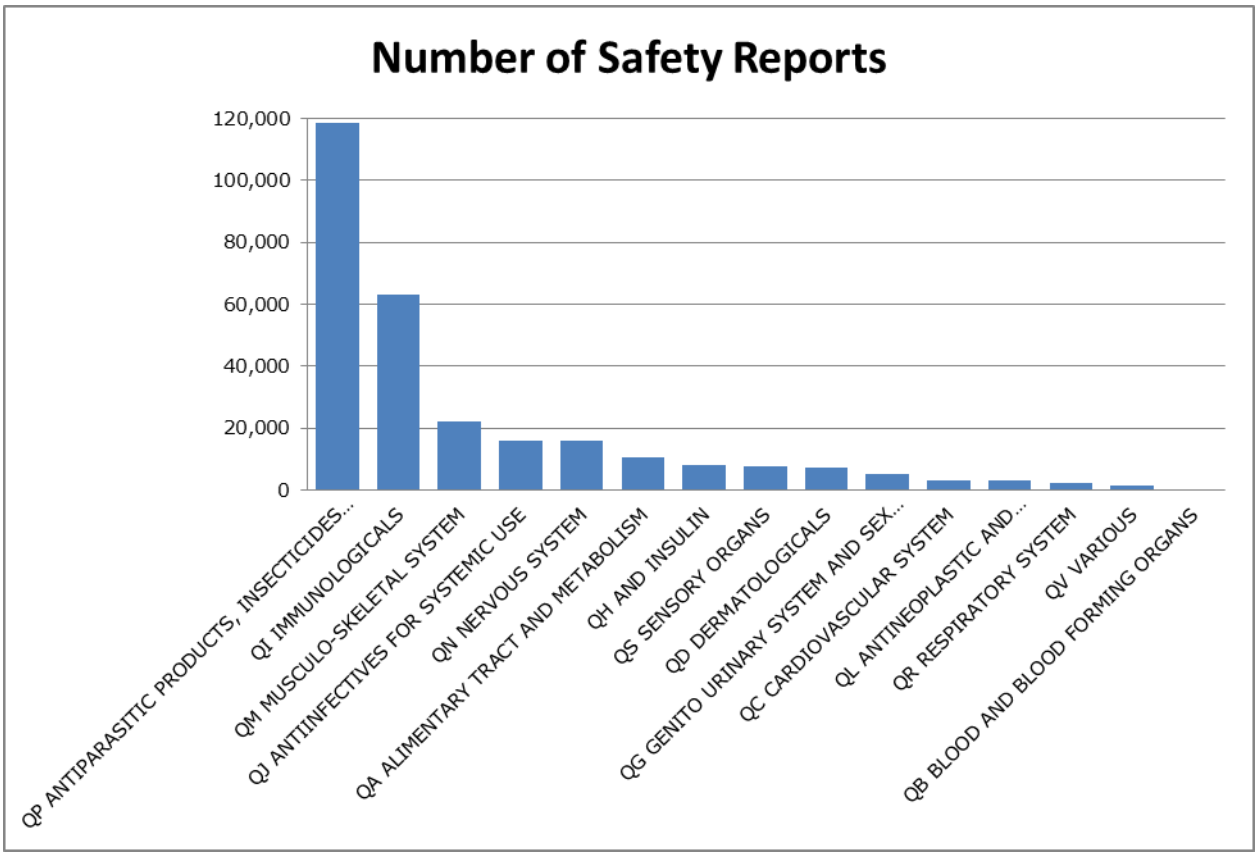


Figure 3. Total number of reports by ATCVet group in EVVet (1 January 2005-31 December 2018).