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Vigilance for veterinary medicinal products

Annual report 2021

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Swissmedic, Swiss Agency for Therapeutic Products
Veterinary Medicines Department
Hallerstrasse 7
3012 Bern
Switzerland
www.swissmedic.ch

Editors/contacts
Cedric Müntener, Veterinary Assessor

Layout and typesetting
Swissmedic, Communication Department

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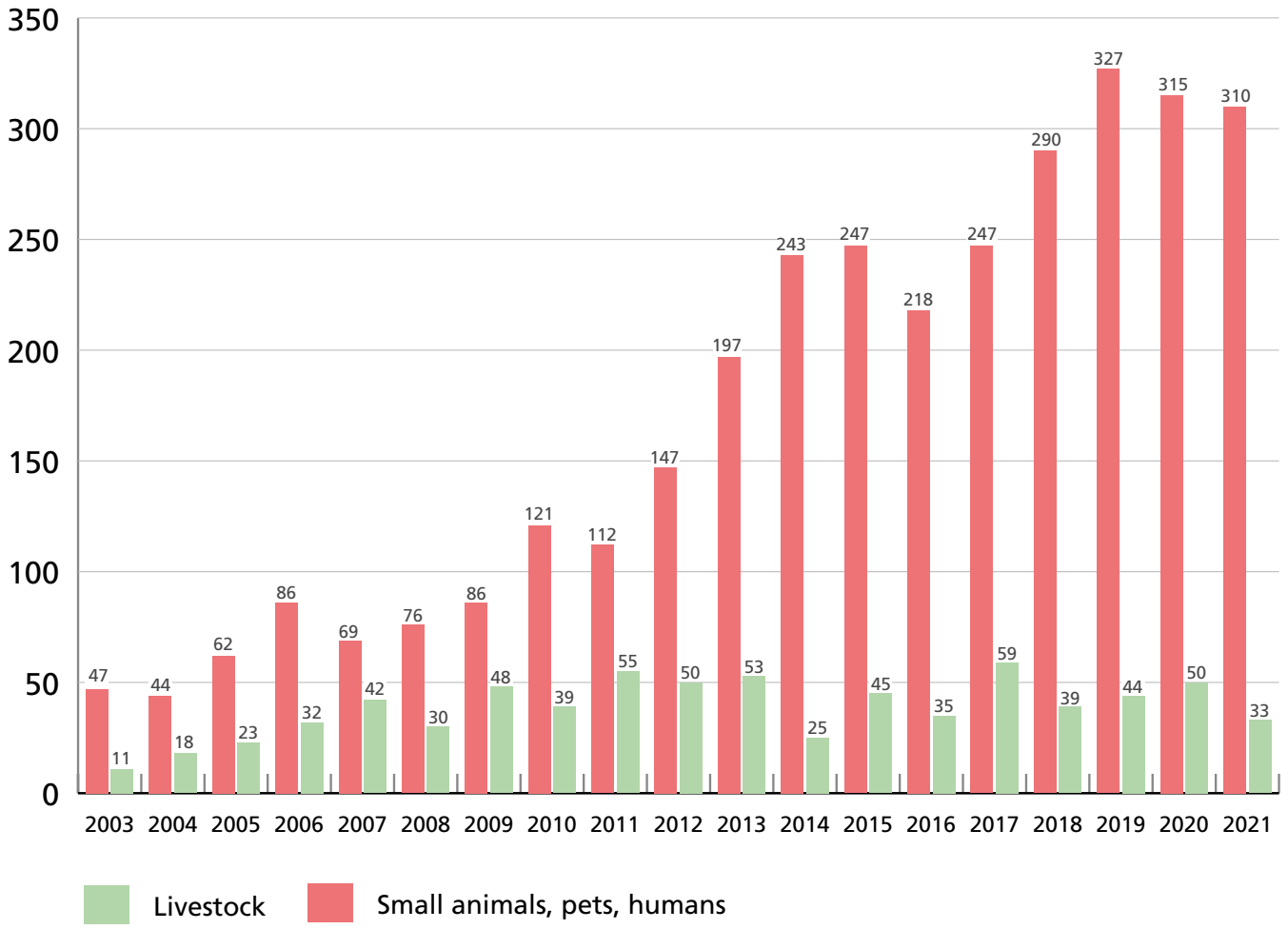
Summary of adverse reactions reported in Switzerland in 2021

A summary of the main points

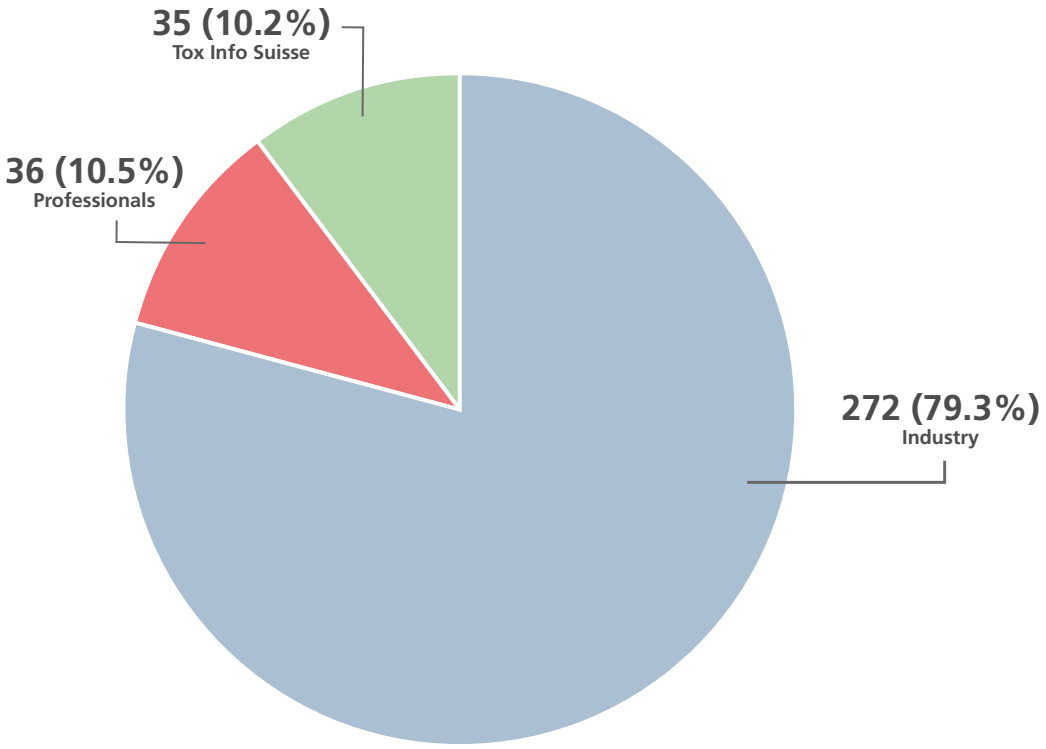
- Slight decrease of 3.4% in reports received
- Most frequently affected species: 218 dogs, 85 cats, 23 cows/cattle/calves
- Most frequent medicinal product types: antiparasitics (127), hormone products (83), products to modulate the nervous system (43), anti-infectives (30)
- 95 cases of suspected lack of efficacy, largely for antiparasitics and hormone products
- 35 cases passed on by Tox Info Suisse
- 19 cases of accidental ingestion of flavoured tablets by dogs/cats
- 104 cases of human exposure to veterinary medicinal products
- 13 signal procedures concluded



Development of the number of notifications submitted between 2003 and 2021, divided into small animals/pets/users and livestock.

A total of 343 reports were submitted to Swissmedic in 2021, representing a decrease of 3.4% compared to 2020. A certain fluctuation in the number of reports is due to many factors and is normal for a spontaneous reporting system. A larger fluctuation in the number of reports was observed between 2019 and 2020 in France, which possesses a well-established pharmacovigilance system, with a recorded decrease of 9% (to a total of 4,198 reports in 2020)[i].

The French authority ANSES mentions the various measures taken to curb the COVID pandemic as a possible factor responsible for this reduction. An even greater decrease of 14% was recorded in the United Kingdom in the same years 2019-2020, where a total of 6,139 reports were submitted in 2021[ii].



Distribution of notifications submitted in 2021 by source.

As in previous years, most of the reports were submitted by marketing authorisation holders. These do not refer to cases from clinical trials, but rather to cases reported by practising veterinarians. This pattern has been observed for years both in Switzerland and various European countries. In Germany, for example, submissions by marketing authorisation holders accounted for 83% of the reports in 2021 (1,202 reports out of a total of 1,442)[iii].

The distribution across the affected animal species (Table) has remained almost unchanged in recent years. Small animals make up the largest group (88% of all reports), with 218 adverse reaction reports in dogs and 85 in cats. They are followed in descending order by cattle/cows/calves with 23 reports, and by reports concerning horses or adverse reactions in users, each accounting for 5 reports. Fewer than five reports were received throughout the year for all the other animal species. The high percentage of reports of adverse reactions in small animals has been observed for years and is also a feature of the pharmacovigilance systems in other countries. In the United Kingdom, small animals account for 76% of the total, with corresponding figures of approx. 70% in France and 73% in Germany.

Among the adverse reactions in persons using the products, three submitted reports involved contact with the solution of a spot-on antiparasitic product. Due to its formulation, the solution leaves a «sticky feeling» on the fingers. Although this could create the impression that such contact is harmless, it should be noted that the wearing of gloves due to possible (potentially serious) reactions in users is explicitly recommended in the Information for healthcare professionals and the package leaflet for the product.

The classification of reports by medicinal product types (Table) also shows a consistent pattern over the years. Antiparasitics dominate, with 127 reports (37% of the total). As in previous years, this group includes 36 reports of suspected

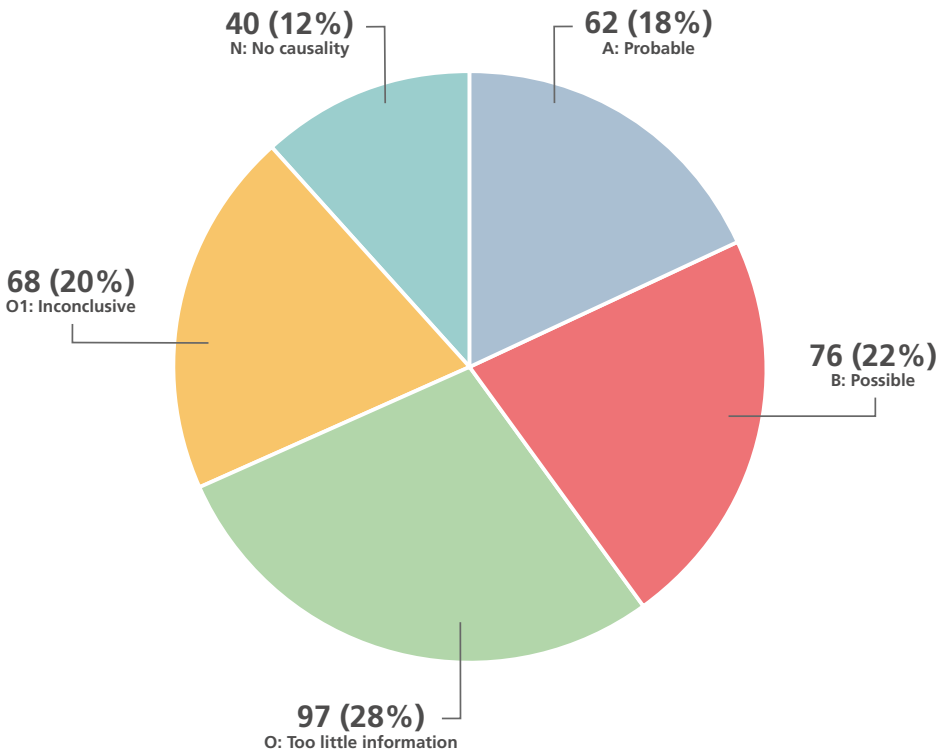
lack of efficacy against ticks. This seemingly high number can be explained mainly by the fact that veterinary medicinal products containing an active substance from the class of isoxazolines (afoxolaner, fluralaner, sarolaner or lotilaner) do not possess a repellent effect against ticks. To be subjected to the antiparasitic effect, the ticks must first come into contact with the blood of the host, after which they can take up to 48 hours to die. It is possible, therefore, to discover ticks (dead or alive) on dogs or cats, without needing to call into question the efficacy of the product.
Veterinary medicinal products containing hormones were the second-largest group, with 83 reports. A considerable proportion (43%) of reports in this group also concerned a suspected lack of efficacy of a veterinary medicinal product, in this case for temporary reduction of fertility in male dogs. In most of these cases, the owners noticed an absence

Medicine category by ATCvet code	Dog	Cat	Livestock	All species
QA: Alimentary tract and metabolism	1 (0.5%)	2 (2.4%)	4 (12.5%)	7 (2.0%)
QC: Cardiovascular system	10 (4.6%)	1 (1.2%)	0 (0.0%)	11 (3.2%)
QD: Dermatologicals	4 (1.8%)	0 (0.0%)	0 (0.0%)	4 (1.2%)
QG: Genitourinary system, sex hormones	2 (0.9%)	0 (0.0%)	1 (3.1%)	3 (0.9%)
QH: Hormonal preparations (excl. sex hormones and insulins)	68 (31.2%)	15 (17.6%)	0 (0.0%)	83 (24.2%)
QJ: Anti-infectives	8 (3.7%)	4 (4.7%)	18 (56.3%)	30 (8.7%)
QL: Antineoplastic and immunomodulating agents	1 (0.5%)	1 (1.2%)	0 (0.0%)	3 (0.9%)
QM: Musculoskeletal system	10 (4.6%)	5 (5.9%)	1 (3.1%)	16 (4.7%)
QN: Nervous system	29 (13.3%)	10 (11.8%)	4 (12.5%)	43 (12.5%)
QP: Antiparasitics	81 (37.2%)	40 (47.1%)	2 (6.3%)	127 (37.0%)
QS: Sensory organs	3 (1.4%)	0 (0.0%)	0 (0.0%)	3 (0.9%)
«QZ»: Reconverted veterinary medicinal products	1 (0.5%)	7 (8.2%)	2 (6.3%)	13 (13.8%)
Total	**218 (100%)**	**85 (100%)**	**32 (100%)**	**343 (100%)**

Distribution of adverse reactions reported in 2021, arranged by ATCvet code and providing specific data for dogs, cats and livestock. The fictitious code QZ makes it possible to specifically group adverse drug reaction reports involving reconverted products (i.e. not used for the authorised animal species and/or indication).

of any change in sexual behaviour or the size of the testes. In this context, these findings are regularly interpreted as evidence of inefficacy. But it should be noted that the active substance produces its effect only after a few weeks and that the male dog can be assumed to be infertile only after several days. The blood testosterone level needs to be measured before an objective assessment can be made of the effect of the veterinary medicinal product. In 24 of the reported cases, the testosterone level was below the threshold for a fertile male dog, while lack of efficacy was confirmed in the remaining cases.

The third largest group in 2021 was that of veterinary medicinal products for treating the nervous system. A large number of cases in this group concerned two therapeutic approaches for the treatment of osteoarthritis-related pain in dogs and cats. As a result of the mode of action of the monoclonal antibodies against nerve growth factor (NGF) contained in the respective veterinary medicines, both of the relevant products are classified under the ATCvet code QN. A higher reporting rate can basically be attributed to the fact that both veterinary medicinal products were recently launched on the market. This effect was first described for anti-inflammatory drugs in 1987 by Weber and is now named after him. He showed that the reporting rate of adverse events increases during the first 2-3 years after market launch, followed by a sharp decline in the following years[iv]. 15 reports in total describe adverse reactions such as itching, diarrhoea, hyperactivity or polyuria in dogs or itching and polyuria in cats. In 2021, insufficient information was available for these two veterinary medicinal products to identify any trends or safety signals.



Distribution of reports submitted in 2021 by causality.

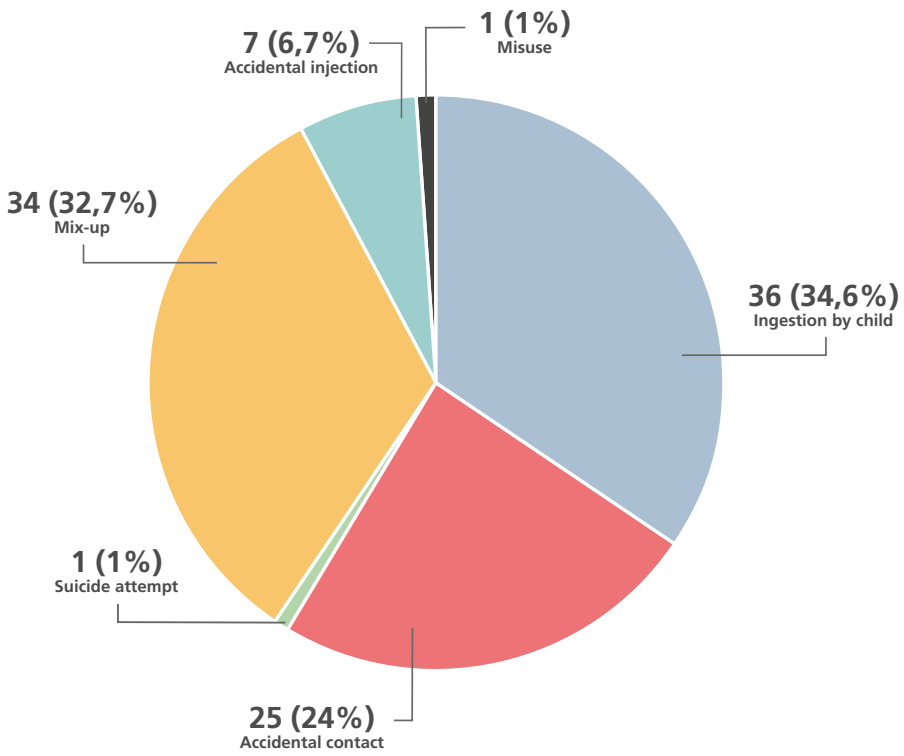
For 62 reports (18% of the total) it was possible to establish a clear link between the use of a product and the adverse reaction ("probable" causality); in 76 cases (22%) at least one possible alternative cause was identified ("possible" causality); and in 68 cases (20%) it was possible to rule out unequivocally a relationship between the product and the adverse reaction. This category included the reports on the veterinary medicinal product for inducing temporary infertility in male dogs, since their testosterone levels were clearly below the threshold for normal fertility. In the remaining 97 cases (28%), there was too little information to determine causality definitively.

Reports from Tox Info Suisse

Adverse reactions to veterinary medicinal products in animals

Overall, 35 cases satisfied the minimum criteria for reports (unambiguous identification of the patient, veterinary medicinal product and reaction) and were passed on to Swissmedic by Tox Info Suisse as part of a contractual agreement. 19 cases concerned the repeatedly mentioned accidental ingestion of flavoured tablets. These primarily involved veterinary medicinal products for administration over a prolonged period such as anti-inflammatory drugs, products for the treatment of hypo- or hyperthyroidism and, in isolated cases, antibiotics and antiparasitics. Although overdoses can be substantial (e.g. a 17-fold overdose with the anti-inflammatory product carprofen), they are often tolerated without any consequences. In one case, 11 tablets of an antibiotic, together with the blisters, were eaten by a dog while, in another case, a dog may have ingested as many as 90 tablets of a heart drug. Vomiting was induced, and the animal subsequently showed no symptoms.

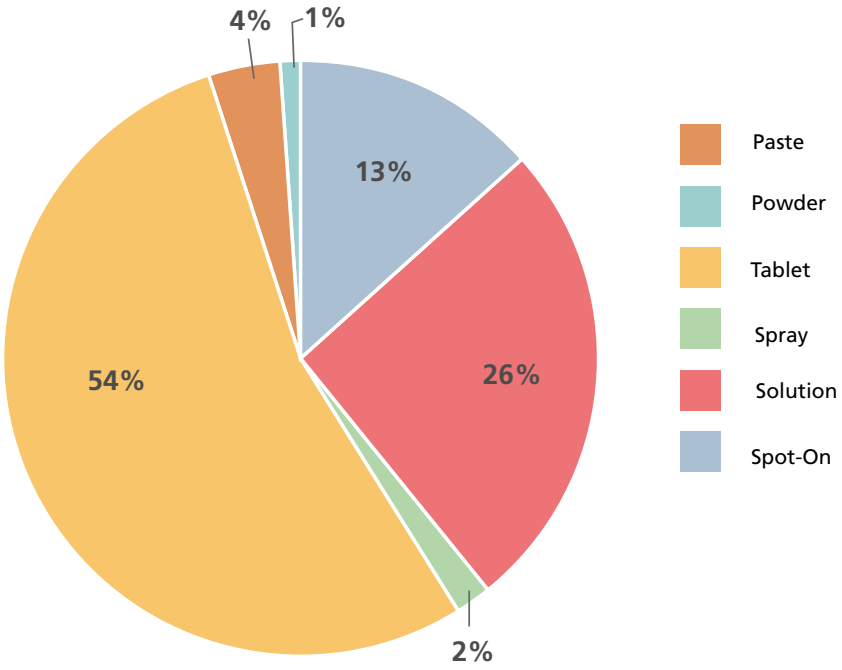
Human exposure to veterinary medicinal products



Distribution of cases of human exposure to veterinary medicinal products submitted in 2021, presented by type of exposure

104 cases were recorded: 36 (34.6%) described the ingestion of veterinary medicinal products by children, 25 (24%) accidental contact with a veterinary medicinal product by adults and 34 cases (32.7%) were attributed to a mix-up between a human and a veterinary medicinal product. In addition, there were seven cases (6.7%) of accidental self-injection. These cases cover a very broad spectrum of veterinary medicinal products, and those for long-term treatments (e.g. anti-inflammatory agents, treatment of hypo- or hyperthyroidism, anti-allergy drugs, treatment of Cushing's disease in horses) are reported more frequently. In most cases there were no symptoms, and the calls to Tox Info Suisse primarily originated from animal owners as a precautionary measure. In one case, a child who had already suffered from «parasites and diarrhoea for a long time» was intentionally «treated» with 2 g of a horse wormer paste (corresponding to approx. 37 mg ivermectin). No symptoms were reported.

The reports of drug ingestion by children included the case of an antiparasitic in the spot-on form: The cat was treated and the cat's fur was subsequently licked by the 5-year-old daughter. No symptoms were noted. Further similar cases were reported after the application of a solution. Several cases in which empty pipettes or syringes were placed in the mouth by a child following the treatment of an animal have also been reported. It cannot be stressed enough that veterinary medicinal products and corresponding applicators must be stored and discarded out of the reach of children.



Distribution of cases of human exposure to veterinary medicinal products submitted in 2021, presented by pharmaceutical form of the veterinary medicinal product

The classification of exposures by dosage form shows that tablets, solutions and spot-on pipettes were most frequently involved. This largely refers to veterinary medicinal products that are administered by the animal owners themselves e.g. antiparasitics. Exposures to solutions for injection tended to occur in a veterinary practice or during administration by a veterinarian.

In several cases involving accidental contact, the animal owner was reported to have attempted to open a spot-on pipette of an antiparasitic with their teeth, thereby causing some of the solution to leak into the mouth. Since certain solutions can, in very rare cases, cause anaphylactic reactions, this practice is strongly discouraged. The correct procedure for opening such pipettes is presented in the product information with pictograms. In other cases, attempts were made to open a container by other inappropriate methods, resulting in skin contact with the solution. All cases remained asymptomatic. One pet owner had also attempted to halve an antibiotic tablet for her cat «with her teeth, since a knife had proved unsuccessful». The owner had reported a «strange taste» in her mouth. Finally, there were several cases of eye contact with various solutions as a result of struggling animals. The cases remained largely asymptomatic. In such cases, the affected eye should be irrigated with plenty of water as the top priority. The cases of accidental self-injection mainly involved solutions containing antibiotics or vaccines. These cases were asymptomatic.

Conclusion

The number of reports in 2021 was subject to the natural fluctuations of a spontaneous reporting system. Pharmacovigilance for veterinary medicinal products remains an important tool for improving the safety of such products and for reducing the risks to the individuals who use them. Every report submitted can make a crucial contribution to this end.

Many reports of exposure passed on by Tox Info Suisse may appear anecdotal, but these should be viewed in the context of improving safety for the users and their families. They are important for an efficient pharmacovigilance system because they cover an additional spectrum of incidents with veterinary medicinal products. For example, they help identify possible risks to those in close contact with animal patients arising from incorrect uses or abuses of veterinary medicinal products.

At the end of this report, we would like to thank all practising veterinarians and all other reporters who have taken the time, during the course of the year, to submit reports on observed adverse reactions.

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Swissmedic, Swiss Agency for Therapeutic Products
Veterinary Medicines Department
Hallerstrasse 7
3012 Bern
Switzerland
www.swissmedic.ch