EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 February 2010
EMA/CVMP/PhVWP/729768/2009
Committee for medicinal products for veterinary se (CVMP)

Veterinary pharmacovigilance 2009

Public bulletin

1. Executive summary

This is the seventh bulletin from the European Medicines Agency on veterinary pharmacovigilance activities, covering the year 2009. The aim of this bulletin is to contribute to the public communication on veterinary medicinal products, particularly on the surveillance of the safety of veterinary medicines in the European Union. It is addressed to all stakeholders, and particularly to veterinary health professionals. In order to give it wider diffusion, it is published in the veterinary pharmacovigilance section of the Agency's website, http://www.ema.europa.eu/htms/vet/phvwp/bulletins.htm, where further information and guidelines relating to veterinary pharmacovigilance are also available.

The numbers of serious adverse event and human adverse event reports increased in 2009, confirming the trend of the previous years. This increase is likely to indicate a continued increase in awareness of veterinary pharmacovigilance in the Union. The higher number of reports concerning food-producing animals represents a positive signal in this direction in the network of professionals who deal with livestock. Furthermore, the increased number of centrally authorised products reaching the market may also partly explain such increased reporting. Particularly, the authorisation of a certain number of new veterinary medicinal products for livestock immunisation has contributed to the enlargement of the panel of products under the responsibility of the Agency. The implementation of electronic reporting and the use of the central database, EudraVigilance Veterinary (EVVet), continued according to the action plan. A major milestone was achieved in 2009 with the operational implementation of the EVVet DataWareHouse (DWH), a tool for retrieving and analysing data from the central database.

Volume 9B on pharmacovigilance of medicinal products for veterinary use of the Rules Governing Medicinal Products in the European Union was released for public consultation by the European Commisssion in the third quarter of 2009, and will be finalised early in 2010.

2. Pharmacovigilance for veterinary medicines in the EU

The main responsibility of the Agency and its veterinary scientific committee, the Committee for Medicinal Products for Veterinary Use (CVMP), in post-marketing surveillance of veterinary medicinal products in the Union is for products that have reached the market by authorisation via the centralised procedure.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

The CVMP Pharmacovigilance Working Party (PhVWP-V) forms the core scientific platform on veterinary pharmacovigilance through experts from the EU competent authorities. The working party meets 6 times a year at the Agency. The PhVWP-V is part of the European regulatory network for the overall surveillance of adverse events to veterinary medicinal products authorised within the Union, irrespective of their original authorisation procedure. This expert group is in charge of the evaluation of pharmacovigilance issues concerning centrally authorised products on behalf of the CVMP, as well as products that have been authorised via the national, decentralised or mutual-recognition procedures.

The European Surveillance Strategy (ESS) group for veterinary medicinal products of the Heads of Veterinary Medicines Agencies (HMA-V) met in Copenhagen in March 2009 and October 2009. Virtual meetings took place on June 2009 and September 2009. The group refined its action plan for better harmonisation of regulatory approaches to pharmacovigilance between competent regulatory authorities of the Community. This year, the group focused on the evaluation of the pilot for worksharing on PSUR assessment between Member States, a project started in 2007 seeking to reduce the workload and the number of PSURs and harmonise submission schedules. The group agreed to recommend a consolidation phase for three years, with the aim of expanding the participation to include additional companies and all regulatory authorities.

2.1. Centrally authorised products

Spontaneous reports of serious suspected adverse reactions and human adverse reactions

A total of 3,129 spontaneous serious suspected adverse reaction reports in animals (2,858) and reports of human adverse reactions (271) to centrally authorised veterinary products were received and processed in 2009. Table 1 shows the numbers of reports by target species, excluding reports in humans. A single report may relate to one or more animals (especially for treatment concerning livestock) and to one or more products which may have been used concurrently. The rise in number of reports seen over recent years is clearly continuing, with approximately 40% more reports received than in 2008. This increase recorded in 2009 is still likely to reflect a greater awareness of the need to report suspected adverse reactions, rather than an absolute increase in the number of reactions occurring. Furthermore, the increased number of centrally authorised products reaching the market may also partly explain such increased reporting. Particularly, newly authorised veterinary medicinal products for livestock immunisation (e.g. against bluetongue and porcine circovirus) have contributed to enlarge the panel of products under the responsibility of the Agency. However, it is important to recognise that adverse reactions are still under-reported in general.

Of the 2,858 suspected adverse reactions in animals, 2,371 were for companion animals and 487 for food-producing animals.

For companion animals, suspected adverse reactions were most frequently reported in dogs (1,382) and cats (969).

The 487 reports received for food-producing animals (mainly in cattle, pigs and ovine, with the highest number in cattle) double the number of reports received in 2008. This increased number of reports in food-producing animals is considered to represent a positive signal in the awareness of pharmacovigilance in the network of professionals dealing with food-producing animals.

Of all the reports received in 2009, 1,145 (1,087 concerning animal reactions and 58 concerning human reactions) were from EU/EEA countries – up nearly 17% over the 972 EU/EEA reports received in the previous year[i]. A further 1,976 reports (1,763 concerning animal reactions and 213 concerning human reactions) were received from countries outside the EU. This is an increment of nearly 38% compared to the 1,279 non-EU reports received in 2008. Most of the reports received from third

countries were from the United States (91%) and Canada (4%), but partly also from Japan (2%), Australia, Brazil and other countries.

It should be underlined that the data relating to suspected adverse reactions from the spontaneous reporting system are not always enough to establish that a suspected adverse reaction was caused by the veterinary medicinal product. Additional information is sometimes necessary for an assessment of the safety or efficacy of a veterinary medicinal product.

The reporting of adverse events must be considered in relation to the amount of product sold, to allow valid conclusions to be drawn about the benefits and risks of the product concerned. Such an evaluation of the benefit-risk balance has to be regularly provided by marketing authorisation holders as part of their PSURs.

When examining Table 1, the types of products that are authorised via the centralised procedure must be taken into consideration. Since the range of centrally authorised products is a particular subset of the total range of products authorised within the Union, it is not a representative sample of the universe of veterinary medicinal products on the market throughout the Union. Therefore, it may not be meaningful to make direct comparisons between number of reports received for centrally authorised products and nationally authorised products.

Table 1. Centrally authorised products. Summary statistics on expedited reports by target species, excluding reports in humans. (Reports received between 15 December 2008 and 20 December 2009.)

	Treated animals that were included in the reports (n)	Affected animals that were included in the reports (n)	Total expedited reports (n)
Food-producing animals	***244,449***	***29,885***	***487***
Cattle/Bovine	25,654	5,395	270
Pigs/Porcine	73,721	15,595	116
Sheep/Ovine	19,385	1,201	78
Horses/Equine	37	12	11
Goat/caprine	51	15	6
Chickens/Avian	117,000	7,448	3
Other food-producing animals	8,601	219	3
Companion animals	***2,861***	***2,552***	***2,371***
Dogs/Canine	1,681	1,432	1,382
Cats/Feline	1,141	1,081	969
Rabbit	5	5	5
Other companion animals	34	34	15
All	**247,310**	**32,437**	**2,858**

Approximately 34% of these reports were received following the use of non-steroidal anti-inflammatory drugs (NSAIDs), 18% following the use of vaccines, 14% following the use of antiparasitic substances (both ectoparasiticides and endectoparasiticides), and another 6% following the use of antimicrobials. The remaining reports relate to a wide range of categories, including anaesthetics and peripherally acting antiobesity products.

A total of 271 adverse events in humans following exposure to a veterinary medicinal product were reported during 2009. This represents approximately 8% of the total received; the percentage

recorded in the year 2008 was 14%. None of the reactions were fatal. The majority of reactions resulted from exposure to topically administered products for use against parasites.

Periodic safety update reports (PSURs) – centrally authorised products

A total of 95 PSURs and 17 PSUR addendum reports for centrally authorised products were received in 2009. During the year, the assessment process was completed for a total of 108 of these reports. The assessment process for an additional 13 PSURs received in 2008 was also completed in 2009. After consideration of all pharmacovigilance data detailed in these PSURs, the CVMP concluded that the benefit-risk balance remained in favour of the concerned products. Regulatory action was required for one PSUR. In this instance, amendments to the product literature were recommended for the addition of new adverse reactions or modification of known ones.

2.2. Rapid alert and non-urgent information notifications

The system that has been established for national competent authorities and the Agency for early detection and rapid notification of safety concerns, and for exchange of relevant information, was used less frequently in 2009 than in 2008 by the Member States. Three rapid alerts were triggered in 2009 (all concerning quality defects only, without immediate concerns for pharmacovigilance), while a total of four new non-urgent information issues were raised, and two non-urgent information issues pending from 2008 were concluded in 2009.

In March, a follow-up discussion was held on the non-urgent information procedure triggered in 2007 after the off-label use in cats of various topically administered products containing permethrin, due to the persisting occurrence of reports of death in such off-label treatments and in view of a possible harmonisation of the product literature of the concerned products throughout the Union. The PhVWP-V concluded that the procedure under Art. 78 of Directive 2001/82/EC would not be applicable, and initiative for regulatory measures was entrusted to the individual Member States in which reported cases were most prevalent.

A non-urgent information procedure was initiated in March in relation to reports in various Member States on spontaneous haemorrhagic diathesis or prolonged bleeding in young calves following vaccination of dams against BVD. Extensive contacts have been established between experts in the field and concerned marketing authorisation holders to investigate the aetiology of the apparent syndrome and the possible link with vaccination. The investigation is ongoing and no conclusions have been reached yet.

Finally, again in March, a non-urgent information procedure was triggered concerning a product containing embutramide, mebenzonium iodide and tetracaine hydrochloride for euthanasia in several animal species, following reports of lack of expected efficacy in large animals. It was noted that most countries already have restricted the availability of the product only to veterinarians, and included a requirement for pre-anesthesia prior to administration. The PhVWP-V concluded that the procedure under Art. 78 of Directive 2001/82/EC.would not be applicable.

Following up a Non Urgent Information notice issued in 2007 in relation to the quality of vaccines produced on cell lines derived from cats, marketing authorisations holders continued their investigations into the potential presence, and significance, of nucleic acids from the endogenous feline retrovirus RD 114 to enable a risk assessment to be performed.

2.3. CVMP opinions on pharmacovigilance matters

In general, when a Member State considers, on the basis of pharmacovigilance data, that a marketing authorisation needs to be suspended, withdrawn or varied to restrict the indications or availability, amend the posology, add a contraindication or add a new precautionary measure, the issue is passed to the CVMP, according to the provision laid down under Article 78 of Directive 2001/82/EC.

No such procedure was triggered in 2009.

2.4. European guidance, focus groups, workshops and training on pharmacovigilance

There was continuous activity in the preparation of regulatory and scientific guidance on pharmacovigilance. In addition, several matters of principle were discussed by the PhVWP-V throughout the year to create and maintain harmonisation on approaches within the Union. Draft and final guidance is published on the Agency's website (http://www.ema.europa.eu) or on the European Commission's website (http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm).

The preparation for a Volume 9B of the Rules Governing Medicinal Products in the European Union – Pharmacovigilance of Medicinal Products for Veterinary Use – continued in 2009. The guidance was transferred to the European Commission for review, following which it was released for public consultation until October 2009. The document will be finalised in 2010, taking into consideration all the observations received.

Further to the publication in 2006 of the original English version of the Simple Guide to Veterinary Pharmacovigilance in the EU[ii], translated versions have been published by the following Member States to promote pharmacovigilance and safety-reporting: Austria, Belgium, Bulgaria, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Slovenia, Spain and Portugal.

3. EudraVigilance Veterinary

The central European Union database for electronic reporting of suspected adverse reactions to veterinary medicinal products recorded an increase in the number of entered reports in 2009. National competent authorities are using (EVVet), and since October 2008, submission of adverse events by marketing authorisation holders is only accepted via electronic means.

EVVet now contains over 33,000 adverse event reports in animals and about 2,100 reports of adverse events in humans. Thirty-two competent authorities are registered, as are 111 other organisations, including marketing authorisation holders and third parties.

The draft policy for access to EVVet data was released for public consultation[iii] in January 2009. A considerable number of comments have been received and are being prepared for discussion at the relevant meetings, prior to the revision of the guideline on access to the data in EVVet.

Development and improvements to EVVet continued in line with the action plan that was agreed between all partners to ensure a stable and secure system. A significant development stage of the DataWareHouse (DHW) was achieved in 2009 with the addition of new and improved query tools for analysis. Several training sessions for national competent authorities took place in 2009. Following the endorsement of a new standard operating procedure, the CVMP began in September 2009 to access EVVet data directly via the DWH for the monthly surveillance of expedited reports of adverse events related to centrally authorised veterinary medicinal products. A dedicated pilot group of PhVWP-V members is planning further use of DWH for surveillance purposes.

An Info day took place in October 2009 to present the DWH, its structure, use and development to veterinary pharmaceutical companies.

4. Challenges in 2010

In 2010, veterinary pharmacovigilance will further develop in line with the work programme of the PhVWP-V[iv] and within the framework of the ESS action plan, intended to be published on the HMA-V website[v]. The project on work-sharing between national competent authorities for the assessment of PSURs will go into a 3-year consolidation phase. Further challenges include: finalisation of Volume 9B; development of guidance and the concept of risk-management plans for veterinary medicinal products; and development of recommendations on the use of data contained in EVVet. A major update of EVVet (EVVET 3.x) will be initiated to improve data input, to harmonise it with international standards and to include a tracking system for surveillance.

References

[i] **EMEA public bulletin 2008 on veterinary pharmacovigilance (EMEA/CVMP/PhVWP/253196/2008)**: http://www.ema.europa.eu/pdfs/vet/phvwp/25319608en.pdf

[ii] **A Simple Guide to Veterinary Pharmacovigilance in the EU (EMEA/CVMP/PhVWP/110607/2005)**: http://www.ema.europa.eu/pdfs/vet/phvwp/11060705en.pdf

[iii] **Draft Eudravigilance Access Policy for Medicines for Veterinary Use (EMEA/113700/2008)** http://www.ema.europa.eu/pdfs/vet/euleg/11370008en.pdf

[iv] **CVMP Pharmacovigilance Working Party Work programme 2010 (EMEA/CVMP/PhVWP/201745/2009)**: http://www.ema.europa.eu/pdfs/vet/phvwp/PhVWPworkprogramme.pdf

[v] Information from **Heads of Veterinary Medicines Agencies** (HMA-V) is published on the HMA-V website: http://www.hma.eu/veterinary.html