European Medicines Agency
Veterinary Medicines and Inspections

EMEA/CVMP/PhVWP/73213/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

EMEA PUBLIC BULLETIN 2006 ON VETERINARY PHARMACOVIGILANCE

Introduction

This is the fourth EMEA bulletin on veterinary pharmacovigilance activities, covering the year 2006. It is aimed at improving communication with stakeholders and particularly veterinary health professionals on the surveillance of the safety of veterinary medicines in the EU. For an extended glossary of the terminology used in this report please refer to the EMEA public bulletin 2005 on veterinary pharmacovigilance[1].

Pharmacovigilance for veterinary medicinal products in the EU

The main responsibility of the **European Medicines Agency (EMEA)** and its **veterinary scientific committee, the Committee for Medicinal Products for Veterinary Use (CVMP)**, in post marketing surveillance of veterinary medicinal products in the EU is for products that reach the market by authorisation through the centralised procedure[2]. In addition, the **CVMP Pharmacovigilance Working Party**[3] **(PhVWP-V)** regularly meets at the EMEA. The mandate of the PhVWP-V now enables the group to form the scientific platform on pharmacovigilance of all veterinary medicinal products. Experts on veterinary pharmacovigilance from the competent authorities of each Member State contribute to this forum. This expert group assesses pharmacovigilance issues for centrally authorised products on behalf of CVMP as well as for products that have been authorised by the Member States via the national or decentralised procedures, or the procedure of mutual recognition[2].

Major progress was achieved in 2006 regarding a pan-European scheme for risk-management of all veterinary medicinal products independent of their marketing authorisation procedure. The European Surveillance Strategy (ESS) group for veterinary medicinal products of the Heads of Veterinary Medicine Agencies - of which the EMEA became a member in late 2005 - developed an action plan aiming towards better harmonisation of regulatory approaches in pharmacovigilance between competent regulatory authorities of the Community, and work sharing between these authorities and plans for necessary procedures to achieve this. Furthermore, the ESS group is dedicated to promoting veterinary pharmacovigilance.

Late in 2005, a **revised pharmaceutical legislation** came into force[4]. The legislation now puts more emphasis on the safety of products, through pharmacovigilance. The new provisions encourage prompt reporting especially of those suspected adverse reactions[5], which are serious and unexpected in animals, and those occurring in human beings. The scope of pharmacovigilance now also includes compulsory reporting of suspected transmission of infectious agents through use of veterinary medicinal products. Other changes include improving communication on safety of veterinary medicines by sharing information on adverse reactions. For this purpose, a central EU database has been established to allow for full electronic reporting and use of this database has now become obligatory for all marketing authorization holders as well as competent authorities within the EU.

All suspected adverse reactions reports received by a marketing authorisation holder are collected, collated and evaluated. A Periodic Safety Update Report (PSUR)[6] is a product-specific document evaluating the safety of the product in practical use. The PSUR is prepared for each product on all reports received during a specified period and submitted to relevant competent authorities at predetermined intervals. The PSURs are initially submitted at 6-monthly or 1-yearly intervals. After the first four to five years of experience of use, the PSURs are then usually submitted at 3-year

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

intervals as long as the product is available, unless more frequent reporting is triggered by safety concerns.

In addition, marketing authorisation holders must report serious suspected adverse reactions in animals and suspected human adverse reactions after exposure to a veterinary medicinal product via an expedited route. Within a period of 15 days after receipt of the report it is evaluated and forwarded to the competent authority to ensure surveillance of the safety profile of the product and to enable rapid triggering of necessary actions. Each report is evaluated to identify is a causal relationship exists between the suspected adverse reaction and the veterinary medicinal product. This contributes to a continuous assessment of the **balance between risks and benefits** of the product in use.

Spontaneous reports of serious suspected adverse reactions and human adverse reactions – centrally authorised products

Overall, the number of suspected adverse reactions (including deaths) reported to EMEA in 2006 was approximately twice that received in 2005. This increase may reflect greater awareness for the reporting of suspected adverse reactions.

A total of 738 spontaneous serious suspected adverse reaction reports in animals or reports of human adverse reactions to centrally authorised veterinary products was received in 2006[1]. Of these, 300 were from EU countries, a relative increase of 33% compared with the EU reports received in the previous year[1]. In 2006, 438 reports were received from countries outside the EU, predominantly from the United States (US) and Canada. For an assessment of safety or efficacy of a veterinary medicinal product, or a comparison between such products, the data relating to suspected adverse reactions from the spontaneous reporting system are not normally enough to establish beyond doubt that the suspected adverse reaction was caused by the veterinary medicinal product.

Table 1 shows the numbers of expedited reports by target species, excluding reports in humans. A single report may relate to one or more animals. Of all the reports received in 2006, 638 concerned suspected adverse reactions in animals, which was over twice the number of expedited reports received in 2005.

Table 1. Summary statistics on expedited reports by target species, excluding reports in humans (2006)*

	Treated animals that were included in the reports (n)	**Affected animals (n)**	**Animals that died or were euthanised (n)**	**Total, expedited reports (n)**
Food producing animals	***2,251***	***559***	***76***	***53***
Cattle (*bovine*)	1,476	399	61	31
Horse (*equine*)	38	32	9	18
Pig (*porcine*)	737	128	6	4
Companion animals	***725***	***661***	***451***	***585***
Dog (*canine*)	421	406	299	380
Cat (*feline*)	299	250	148	200
Rabbits and hares	2	2	1	2
Rodents	3	3	3	3
All	**2,976**	**1,220**	**527**	**638**

* Reports received between 1 January 2006 and 14 December 2006

Suspected adverse reactions in dogs (n = 380) and cats (n = 200) were most frequently reported. The reports received in 2006, identified a total of 2,976 treated animals, of which 1,220 showed suspected adverse reactions. A total of 527 deaths in animals were reported. These events must be put in relation

[1] Reports received between 1 January 2006 and 14 December 2006

to the amount of products sold to allow valid conclusions regarding benefits and risks afforded by the products concerned, and to the fact that animals receiving medicines are often very ill and may die from causes unrelated to treatment. This information is regularly provided by MAHs as part of Periodic Safety Update Reports (PSURs).

There were 53 reports relating to food-producing animals – cattle, pigs and horses – which related to the treatment of 2,251 animals, of which 559 showed suspected adverse reactions. The low number of reports in food-producing animals is consistent with previous years. The high number of treated animals of which only approximately a quarter showed suspected adverse reactions is explained by the fact that farm animals are seldom treated individually but rather in groups.

Approximately three-quarters (479 of 638) of the animal reports were received following the use of non-steroidal anti-inflammatory drugs (NSAIDs) and antiparasitics.
Following the use of NSAIDS, the most frequently reported suspected adverse reactions reported involved the gastrointestinal tract e.g. vomiting and diarrhoea. Neurological and gastro-intestinal clinical signs were reported most frequently in reports relating to the use of antiparasitics.

A total of 100 reactions in humans following exposure to a veterinary medicinal product were reported during 2006. None of these were fatal. The majority of these resulted from accidental exposure to two products. One of these contains an antiparasitic substance and the most frequent reaction observed was skin irritation. The other contains a non-selective monoamine re-uptake inhibitor, frequently associated with cognitive disorders (including nausea and dizziness).

Periodic Safety Update Reports (PSURs) – centrally authorised products

A total of 52 new PSURs for centrally authorised products were received and the assessment process was completed for a total number of 41 PSURs during 2006. After consideration of all pharmacovigilance data detailed in the 41 assessed PSURs, the CVMP concluded that the risk/benefit balance was in favour of the concerned products. On the basis of eleven PSURs regulatory action was required. Amendments of the product literature were recommended or additional data requested for the concerned products. Addition of new adverse reactions was the most commonly recommended amendment of the product literature, followed by recommendations concerning the expected frequency of known adverse reactions. None of these recommended amendments were considered urgent. Following assessment of four PSURs, additional PSURs were requested for different products for more frequent monitoring of the safety of the product.

Pharmacovigilance for other than centrally authorised products

Rapid Alert and Non Urgent Information Systems

The system that has been established in previous years for Member States to enable early detection, rapid notification and exchange of relevant information of safety concerns was used less frequently in 2006 than in 2005 by the Member States. A total of eleven new issues were brought to the attention of the PhVWP-V, none of which concerned centrally authorised products. Seven were related to quality issues and five of these were circulated as rapid alerts . The PhVWP-V considered that no further action was required for these in relation to pharmacovigilance. A separate system is available for communication of rapid alerts relating to quality defects. Information may, however, be processed through both systems simultaneously in cases where the link to pharmacovigilance cannot initially be ruled out.

Two non-urgent matters were also considered. Firstly, the possibility of teratogenic effects of products containing benzimidazoles (a group of antiparasitic substances) was discussed and may be considered further by the PhVWP-V. On a European level no need for regulatory action has been identified. Secondly, skin reactions to products containing fipronil (an antiparasitic substance that is applied on the skin) have been identified. Having consulted the national pharmacovigilance databases and EudraVigilance Veterinary, it was noted that the high reporting frequency appeared only in one country. A possible explanation to the high frequency is that local veterinarians are aware both of the reporting system and the occurrence of such reactions.

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 CVMP.

During the year, the competent authority of The Netherlands consulted the PhVWP-V on a published case report in a human concerning one product containing a substance of the group of alpha2-adrenoreceptor agonists. These substances are used for sedation and analgesia in several animal species. The patient experienced cardiovascular and central nervous system effects after accidental self-injection. The PhVWP-V also contributed to a European survey of precautionary measures relevant to nationally authorised products containing alpha2-adrenoreceptor agonists. The survey concluded that these were heterogenous throughout the EU.

After consultation with the PhVWP-V, the Dutch authority notified the CVMP of a lack of sufficient precautionary measures for 21 Dutch authorisations of injectable products containing an alpha2-adrenoreceptor agonist. The concern related to the special precautions for use concerning user safety to minimise the risks associated with accidental self-injections, or skin, eye or oral exposure, and to give information to pregnant women handling the products as well as to doctors that eventually may treat these patients. The CVMP after having consulted the marketing authorisation holders and considered the available data, recommended a set of new precautionary measures relating to user safety to be reflected in the product literature of the products concerned. The CVMP further concluded that these precautionary measures also apply to other products containing alpha2-adrenoreceptor agonists. Late in 2006, the opinion was forwarded to the European Commission for a decision on further action.

Referral procedures

The referral procedure for **Micotil 300** (tilmicosin) injectable solution[1] was completed in 2006. This product contains an antimicrobial used exclusively in animals to treat respiratory diseases such as pneumonia in cattle and sheep. The procedure was started in 2004, triggered by accidental events involving two farmers who died in the US following unintended self-injection while treating their cows. Following scientific assessment of the matter by the CVMP in consultation with the PhVWP-V, the European Commission tightened the rules for the use of Micotil in the EU by harmonising and strengthening the precautionary measures in the product information and deciding that Micotil should only be administered by veterinarians.

Other than centrally authorised products

During the year, the PhVWP-V also discussed adverse reactions relating to various vaccines.
A subgroup of the Working Party was formed to focus on injection site sarcoma in cats in light of reports received over the past years on these suspected adverse reactions and ongoing research projects. The PhVWP are seeking to raise the profile of injection site sarcoma in cats for consideration during the coming year. Such sarcomas, whilst serious for the individual animal, need to be kept in context with the overall very positive outcome of the assessment of benefits and risks for the veterinary medicinal products involved.

An apparently high incidence of post-vaccination reactions was reported in German pinschers, which led to the discussion of possible breed-related susceptibility in dogs. The susceptibility may be related to an immunological defect, however, data is still required to provide supporting evidence before any firm conclusions can be drawn.

European guidance on Pharmacovigilance

There was continuous activity in preparation of guidance not only for marketing authorisation holders but also for veterinarians in relation to pharmacovigilance. Further, several matters of principle were discussed by the PhVWP-V throughout the year to create and maintain harmonisation on approaches within the Community. Draft and final guidance is published at the EMEA website (http://www.emea.europa.eu) or at the European Commission website (http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm).

A Simple Guide to Veterinary Pharmacovigilance in the EU was finalised and published during the year. This guide is aimed at veterinarians and other animal health professionals. It explains the concept and importance of pharmacovigilance, the reporting system for suspected adverse reactions, and the use of the reported data. The English version of the guide has been published on the EMEA website and will be published and circulated by Member States in their national language(s).

A revision of the major guidance on procedures for marketing authorisation holders in relation to pharmacovigilance for veterinary medicinal products was in consultation. This guidance aids the marketing authorisation holders to implement practical procedures involved in complying with the legislation concerning pharmacovigilance.

A guideline for marketing authorisation holders for monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections by marketing authorisation holders was prepared and published for consultation during the year. The document clarifies the expected level of detail of procedures within a pharmacovigilance system and how inspections of these systems will be carried out. The final guidance is expected to be published in early 2007.

During the year a guideline on assessments and management of PSURs was in development. The guideline will include procedures for and aspects of risk/benefit assessment and will be finalised for public consultation in the new year.

The PhVWP-V also contributed to the revision of guidance on the Summary of Product Characteristics for pharmaceutical and immunological veterinary medicinal products. According to this guideline, future product literature should include numerical and qualitative information on the incidence of suspected adverse reactions for the veterinary medicinal products.

A suspected adverse reaction reporting form for use by veterinarians and other animal health professionals that had been finalised in 2005 was translated into all EU languages and published on the EMEA web site. This form will replace existing national forms and will facilitate reporting of suspected reactions in the EU. Further, an electronic form for veterinarians was created and will be tested in practice with volunteering veterinarians in a few Member States in early 2007 before finalisation.

To achieve and maintain harmonisation, approaches to assessment of off-label use and lack of efficacy were discussed by the PhVWP-V and the conclusions to be drawn will be integrated in appropriate guidelines in the new year.

EudraVigilance Veterinary

EudraVigilance Veterinary, the EU system for electronic reporting of suspected adverse reactions to veterinary medicines (to replace the current paper based system), became the main tool for reporting by national authorities in 2006 (see further https://eudravigilance.emea.europa.eu/veterinary/). In order to progress direct electronic reporting by the veterinary pharmaceutical industry, which became a legal requirement in November 2005, a further simplified electronic reporting tool was developed and released in 2006 mainly for use by smaller companies within the Member States. Many resources were also spent on the development of the Data Warehouse that is a tool to facilitate the continuous monitoring the safety of veterinary medicinal products by analysing the data contained in EudraVigilance Veterinary.

The veterinary pharmaceutical industry's major players have further used 2006 to set-up and test their internal systems of reporting to the EU central database. The number of marketing authorisation holders actively using either the gateway or the web reporting tool for actual reporting in 2006 was disappointing. It is however expected that many more companies will move to electronic reporting in early 2007. Further software and operating procedures are under development in relation to the analysis and the release of the data. Member States have come to an agreement in 2006 on the input of data from nationally authorised products to the product dictionary which is essential for any analysis at the level of single active substances, or groups of such.

EU enlargement 2007

The integration of Observers from the two Candidate Countries (Bulgaria and Romania) into the EMEA work structure - including meetings of the PhVWP-V - was successfully continued during 2006.

GLOSSARY

[1] **EMEA public bulletin 2005 on veterinary pharmacovigilance.** Doc.Ref.No EMEA/226674/2005. Available on the EMEA website http://www.emea.europa.eu/pdfs/vet/phvwp/22667406en.pdf

[2] Authorisation procedures in the EU for veterinary medicines

1. **Centralised procedure**: The EMEA by means of the CVMP evaluates veterinary medicinal products that are authorised by the centralised procedure, whereby marketing authorisation is granted simultaneously in all EU Member States (MS). This procedure is mandatory for highly innovative products or products derived from gene technology in order to ensure a uniform standard for the evaluation of such products. The centralised procedure may be chosen for other innovative products.

Alternatively veterinary medicinal products may be authorised by

2. **national procedure** in one MS only or

3. in accordance with the **decentralised procedure** where national authorisations are desired in several MS simultaneously

4. by means of the **mutual recognition procedure** of an original national authorisation in more than one MS

[3] **CVMP Pharmacovigilance Working Party**: An advisory group to the CVMP on veterinary pharmacovigilance. Its main function is to provide advice to CVMP on pharmacovigilance issues and to develop guidance documents on veterinary pharmacovigilance on behalf of CVMP, but the Working Party also serves as a discussion forum for Member States to promote harmonised approaches to pharmacovigilance for nationally authorised and mutually recognised products.

[4] **New legislation**: Directive 2004/28/EC of the European Parliament and of the Council amending Directive 2001/82/EC on the community code relating to veterinary medicinal products. Regulation (EC) No 726/2004 of the European Parliament and of The Council laying down Community procedures for the authorisation of and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

[5] **Adverse reaction**: A reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

Serious adverse reaction: An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or which results in permanent or prolonged signs in the animals treated.

Unexpected adverse reaction: An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of the product characteristics.

Human adverse reaction: A reaction which is noxious and unintended and which occurs in a human being following exposure to a veterinary medicine**.**

Spontaneous reaction reports: Reports submitted to the MAH or the Competent authority soon after their occurrence and reported onwards in compliance with legal requirements (if serious, within 15 days).

[6] **Periodic Safety Update Reports (PSURs):** regular update reports submitted by pharmaceutical companies to the supervisory authorities concerned (member states where the product is authorised and the EMEA for centrally authorised products) on a given veterinary medicinal product at certain defined intervals. These reports include a scientific evaluation of the reactions and an evaluation of any changes to the benefits and risks afforded by the product.