The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

EMEA/CVMP/359/04

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS[1]

EMEA PUBLIC BULLETIN 2003 ON VETERINARY PHARMACOVIGILANCE[2]

Introduction

The EMEA aims to improve communication to the public, in particular to veterinary health professionals, regarding the surveillance of the safety of veterinary medicines in the EU. Thus, a bulletin summarising the actions of the EMEA to ensure the continued safety and efficacy of authorised veterinary medicines is to be issued annually. This is now the first EMEA bulletin on veterinary pharmacovigilance activities, and should be viewed as a prelude to further comprehensive reports providing an analysis of adverse reactions to centrally approved products, which will be published by the Agency in 2005 and beyond, once the electronic reporting system for the EU, Eudravigilance, becomes fully operational A glossary of the terminology used in this report in accordance with that referenced in EU legislation, is attached.

Pharmacovigilance for veterinary medicinal products

The main responsibilities of the EMEA in post marketing surveillance of veterinary medicinal products in the EU concerns those products which reach the market following authorisation by the centralised procedure[3]. Some 250 spontaneous reports of serious adverse reactions[4] to a number of centrally authorised veterinary products were received during the year 2003, mainly concerning non-steroidal anti-inflammatory drugs, endectocides and combination vaccines for companion animals. Most of the reports detail events, which are listed as possible reactions in the Summary Of Product Characteristics (SPC), and are recognised possible adverse effects. A total of 43 Periodic Safety Update Reports (PSURs)[5] for centrally authorised products were generally submitted according to the required format and in a timely manner. After consideration of all spontaneous and periodic reports, the CVMP with one exception found it unnecessary to consider the Risk/Benefit analysis for any of the products concerned. In the case of a non-steroidal anti-inflammatory for dogs, the CVMP considered in September 2003 that the warning statements should be amended in order to provide more information on the occurrence of adverse reactions, in an attempt to reduce their incidence.

The CVMP, being aware of concerns regarding reports of tumours at injection sites in cats, referred the matter for consideration to both the Pharmacovigilance[6] and Immunologicals[7] Working Parties for expert advice. As a result of their considerations and recommendations the Committee published an advisory notice to veterinary surgeons on development of fibrosarcomas (a malignant, invasive tumour or form of cancer), at sites of injection of veterinary medicinal products in cats. This issue had been widely discussed in the veterinary community and vaccines in particular have been linked to fibrosarcoma development in cats. The CVMP took great care to emphasise that modern vaccines continue to represent the only safe and effective means of protecting cats against serious infectious diseases and this should be taken fully into account in any discussion between veterinary surgeons and cat owners. The full text is available at http://www.emea.eu.int/pdfs/vet/press/pp/020503en.pdf.

Although the EMEA and its scientific committee the CVMP has issued opinions for over 50 products for many species of farm animals as well as companion animals, the adverse reactions reported were mostly in companion animals. This might be expected as experience suggests that pet owners may be more vigilant of their animals after treatment by the veterinarian than the stock owner. In particular for pig or poultry vaccines very few reports were received and this is a matter of some concern to the CVMP. Use of any medicinal product bears with it a certain risk of adverse reactions and whilst it might be argued that newer products are becoming increasingly well tolerated and more effective, the current reporting level for pigs and poultry is noticeably lower than practical experience in the field

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would suggest is the case. The CVMP and its Working Party are committed to work with the member states competent authorities to promote better reporting of adverse events in these livestock sectors through improved pharmacovigilance practices. In order to maximise reporting, the support of veterinary practitioners will be essential.

Member states' veterinary pharmacovigilance experts acting in their capacity as expert delegates to the CVMP Pharmacovigilance Working Party regularly meet at the EMEA. In addition to assessing pharmacovigilance issues relating to centrally authorised products, they also discuss and agree approaches to pharmacovigilance issues related to nationally authorized and mutually recognized products[3] that are of specific interest to member states. Topics in 2003 ranged from a general exchange of pharmacovigilance information, identifying safety concerns in relation to specific products and agreeing harmonized warning statements suitable for implementation in each concerned member state, to rapid exchange of warnings regarding serious concerns. CVMP is always informed at the plenary meetings on any such issue and the approach agreed by the member states' pharmacovigilance experts. For national products any implementing action lies at member state level.

The CVMP also published a number of guidance documents during the year to assist the veterinary pharmaceutical industry and member states' pharmacovigilance schemes[8] in the collection, evaluation and transmission of adverse reaction reports for veterinary medicines. In 2003 work focussed on harmonisation of data evaluation and transmission, and preparations to introduce electronic reporting, which is expected to greatly facilitate adverse event reporting in the Community. The *Guideline on data elements for electronic submission of adverse reaction reports to veterinary medicinal products* (EMEA/CVMP/065/03), the *common EU reporting form for serious adverse reactions to veterinary medicinal products for marketing authorisation holders* (EMEA/CVMP/601/02), the *Guideline on causality assessment for adverse reactions to veterinary medicinal products* (EMEA/CVMP/552/03), and the *List of breeds and species for electronic reporting of adverse reactions* (EMEA/CVMP/553/03) are available at the EMEA website http://www.emea.eu.int/index/indexv1.htm, Guidance documents/Pharmacovigilance/Guidance and Reporting.

EudraVigilance

Currently pharmacovigilance schemes of EU member states and in pharmaceutical industry function by means of paper reports. To improve communication with all partners that need to be involved, once an animal owner or veterinarian or another concerned person has reported an adverse reaction, be it for example to a member state pharmacovigilance scheme on paper or by telephone to a pharmaceutical company, the information on the adverse reaction will be exchange electronically in future. Initially the exchange will take place between member states' pharmacovigilance schemes and pharmaceutical industry. The system for electronic reporting of adverse reactions to veterinary medicines in the EU, EudraVigilance Veterinary, has now reached a crucial stage with testing underway and full implementation planned for by end 2004.

Preparation of the EU enlargement in 2004

At the beginning of 2003 there were concerns that the application of pharmacovigilance in the 10 new countries was still rather heterogeneous and that further work was required to optimise the systems in place. In preparation of the enlargement of the European Union in 2004 a second in a series of workshops dedicated to veterinary pharmacovigilance was held as part of the European programme to prepare the new countries in the pharmaceutical sector for accession; this being the Pan European Regulatory Forum (PERF)[9]. Delegates attended from all the new countries with the aim to enable the future member states to build up their veterinary pharmacovigilance systems to be compliant with the standards expected in accordance with EU legislation and guidelines.

GLOSSARY

[1] **Committee for Veterinary Medicinal Products (CVMP):** the Committee of the EMEA responsible for preparing the scientific opinions of the Agency on any question relating to the evaluation of veterinary medicinal products; in the context of this document in particular relating to safety, efficacy after marketing.

[2] **Pharmacovigilance:** the surveillance of medicinal products after authorisation to ensure their continued safety and efficacy. A major aim of pharmacovigilance is to ensure that products remain safe during use under field

conditions and that they remain effective. This is achieved by reporting adverse reactions (see below) to veterinary medicines (irrespective of the procedure for authorisation as described below) to the veterinary pharmacovigilance schemes established in each member state (see below). Initial reporters may be the animal owners or the veterinary surgeon involved (among others). Reporters may choose to contact the pharmaceutical company, who is then obliged to notify the member state's pharmacovigilance scheme, or they may choose to report directly to the member state's pharmacovigilance scheme, which in turn is obliged to inform the pharmaceutical company (personal details may be withheld upon request). Member states' pharmacovigilance schemes are obliged to inform the EMEA of adverse reactions on centrally authorised (see below) veterinary products that were reported to them. It is important to note that in general not one individual report will provide sufficient scientific grounds for action (e.g. changes in warnings), most often several similar reports will indicate the emergence of a specific issue.

[3] 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. by means of the **mutual recognition procedure** of the original national authorisation in more than one MS.

[4] **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.

[5] **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.

[6] **Veterinary Pharmacovigilance Working Party**: An advisory group to the CVMP on pharmacovigilance. Advice to CVMP on pharmacovigilance issues and development of guidance documents for CVMP is its main function, but the working party also serves as a discussion forum for member states in order to promote harmonised approaches to pharmacovigilance for nationally authorised and mutually recognised products.

[7] **Veterinary Immunologicals Working Party**: An advisory group to the CVMP on immunological veterinary medicinal products (IVMPs). Its main tasks are revision of existing and creation of new guidelines relating to IVMPs, examination of other questions on IVMPs and related issues.

[8] **Member State's pharmacovigilance schemes**: Each Member State is obliged to establish a veterinary pharmacovigilance scheme or system. This system shall be used to collect information useful in the surveillance of veterinary medicinal products, in particular on adverse reactions in animals and in human beings related to the use of veterinary medicinal products, and to evaluate such information scientifically. Such information shall be collated with available data on the sale and prescription of veterinary medicinal products. In practical terms it means that animal owners, veterinarians on anyone else concerned may report any adverse reaction to a veterinary medicine directly to the pharmacovigilance scheme of the Member State where the reaction occurred (in most cases where the person lives). Alternatively, as explained above, they may choose to report a reaction to the pharmaceutical company (Marketing Authorisation Holder), who then is obliged to inform the Member State's pharmacovigilance scheme.

[9] **Pan European Regulatory Forum (PERF)**: The Pan European Regulatory Forum (PERF) on Pharmaceuticals was a project financed from European Commission funds, with the ultimate aim to achieve transposition of all technical regulations and European technical acts regarding medicinal products into the national legislation of the future member states. There were three phases of PERF throughout 1999-2000, 2001-2002 and 2003. Details are available from the PERF website at http://perf.eudra.org.