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Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE[1]

EMEA PUBLIC BULLETIN 2004 ON VETERINARY PHARMACOVIGILANCE[2]

Introduction

This is the second EMEA bulletin on veterinary pharmacovigilance activities, covering the year 2004. It is aimed at improving communication to all stakeholders but particularly to veterinary health professionals, on the surveillance of the safety of veterinary medicines in the EU. A glossary of the terminology used in this report in accordance with that referenced in EU legislation, is included.

Pharmacovigilance for veterinary medicinal products

The main responsibility of the EMEA and its veterinary scientific committee, the CVMP, in post marketing surveillance of veterinary medicinal products in the EU concerns those products, which reach the market by authorisation through the centralised procedure[3]. However, veterinary pharmacovigilance experts from the competent authorities of the Member States in their capacity as delegates to the CVMP Pharmacovigilance Working Party[4] regularly meet at the EMEA, and in addition to assessing pharmacovigilance issues for centrally authorised products referred to the Working Party by CVMP, they also discuss and agree approaches to pharmacovigilance issues related to nationally authorised and mutually recognised products[3] that are of specific interest to Member States.

Spontaneous reports of serious suspected adverse reactions – centrally authorised products

In 2004, a total of 187 spontaneous reports of suspected adverse reactions[5] to centrally authorised veterinary products occurring in the EU were reported to the EMEA. A single report may relate to one or more animals, which is why the number of reacting animals is higher than the number of reports mentioned in this text. Of these reports, 177 related to animals involving a total of 224 reacting individuals. Forty of the reports were not considered serious and are therefore not discussed further in this paper. Most frequently spontaneous reports were received for non-steroidal anti-inflammatory drugs (NSAIDs), endectocides and vaccines, mainly for companion animals, many of which were combination vaccines. For some of the spontaneous reports the available data indicated other, more likely causes for the reported reaction than the medicinal product involved, and for a larger number of reports the available information did not allow a conclusion on the causal relationship to the medicinal product involved. Forty-seven of the 137 remaining reports resulted in death of the treated animal(s), involving 93 animals in total, and including 10 cases of euthanasia due to poor prognosis for recovery. One report in pigs related to the death of 45 animals caused by a known interaction between the pleuromutilin antibiotic involved and ionophores; simultaneous use of the two classes of products is a contraindication that is clearly detailed on the product label. The remaining 48 deaths or euthanasia cases were due to a number of reasons and in many cases a clear causal relationship to the product involved could not be established, particularly where vaccines were involved. For NSAIDs, death or euthanasia occurred after aggravated known side effects in particular gastrointestinal signs such as haemorrhagic diarrhoea in more than 50% of the reports. For the endectocides there were some reports on death or euthanasia, around 40% of which involved fits or ataxia.

As distressing as the death of an animal is to its owner, such spontaneous reports must be put in relation to the amount of products sold to allow valid conclusions regarding benefits and risks afforded by the products concerned. This information is regularly provided by MAHs as part of Periodic Safety Update Reports (see below).

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The remaining reports on serious adverse reactions in animals involved mainly serious cases of known side effects, such as gastrointestinal signs for NSAIDs or aggravated injection site reactions or allergic reactions for vaccines. For 2 of the 4 vaccines for which reports on adverse reactions had been received, 4 cases (2 each) of injection site sarcoma in cats were reported. In the case of the endectocides 12 reports related to ataxia and other signs of neurological deficits, and 2 reports to collapse. Such signs are generally known to occur in relation with use of endectocides of the avermectin/milbemycin classes of compounds. In those few instances where unexpected reactions were reported, the overall information available was insufficient to allow conclusions whether the observed reactions were caused by the product(s) used or not.

Ten cases of human exposure involving 3 centrally authorised products were reported, 3 of which remained asymptomatic. Of the 7 remaining cases 5 involved local skin reactions or sensation disturbances, 1 headache and 1 excessive nasal discharge.

In addition to the reports from the EU also reports that occurred in countries outside the EU were received. In most instances the reports did not necessitate any changes to the marketing authorisation. However, for one product the SPC was amended during the renewal further to additional studies carried out by the MAH in consequence of suspected lack of efficacy reports from countries outside the EU in relation to one of the indications authorised in the EU. The product was still found to be effective for the indication, however to a somewhat lower extent than predicted from the clinical studies submitted for authorisation.

Periodic Safety Update Reports (PSURs)[6] – centrally authorised products

A total of 45 PSURs for centrally authorised products were submitted, generally according to the required format and in a timely manner. After consideration of all suspected adverse reactions detailed in these reports, the CVMP found it unnecessary to change the Risk/Benefit analysis for any of the products concerned.

Pharmacovigilance for other products

Micotil 300: After a first report of a fatality in the USA due to suspected accidental injection of the product, the CVMP Pharmacovigilance Working Party agreed revised warning statement in early 2004, endorsed by CVMP, for implementation by the Marketing Authorisation Holder for the nationally authorised products. After a second similar report from outside the EU, France referred the matter to CVMP to consider what actions would be required in the EU to ensure safe use of the product, under provisions in EU law addressing matters of safety in terms of community interest. In December the CVMP concluded that with appropriate safety warnings and additional measures to ensure user safety the benefits of Micotil continue to outweigh the risks. The recommendations made by CVMP include strengthened safety warnings, a restriction of use to veterinary surgeons only and advice on suitable treatment options in the very infrequent event of accidental administration. The EMEA will publish a more detailed report, once the European Commission has adopted a legally binding decision on this issue.

Issues of specific interest to Member States: Topics in 2004 focused on the reorganization of general exchange of pharmacovigilance information via the CVMP Pharmacovigilance Working Party, identification of safety concerns in relation to specific products (3 new Non-urgent safety information requests were exchanged) and agreeing harmonised warning statements suitable for implementation in each concerned Member State, as well as rapid exchange of warnings regarding serious concerns (1 new Rapid Alert was sent out in 2004; it related to Micotil and preceded the referral to CVMP. Discussions continued in relation to 1 rapid alert sent out in 2003). 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.

General pharmacovigilance reporting

As already reported in the 2003 bulletin, the EMEA, CVMP and the CVMP Pharmacovigilance Working Party remain concerned that, although the EMEA has issued opinions for over 50 products for many species of farm animals as well as companion animals, adverse reactions were mostly reported in companion animals. Very few reports were received in particular for centrally authorised pig or poultry vaccines. Use of any medicinal product bears with it a certain risk of adverse reactions and whilst it might be argued that newer products are increasingly well tolerated and more effective, the current reporting level for pigs and poultry is noticeably lower than practical experience in the

field would suggest is the case. The support of veterinary practitioners is essential in order to maximise reporting, and therefore specific initiatives were launched in 2004 by the CVMP and its Working Party that are aimed at this group (see **Pharmacovigilance guidelines** below). In addition the EMEA has been very active at key meetings with many of its stakeholders, particularly the veterinary pharmaceutical industry (IFAH Europe) and the Federation of Veterinarians in Europe (FVE) in promoting good pharmacovigilance practice to encourage a strong reporting culture.

Pharmacovigilance guidelines

The CVMP published a number of guidance documents during the year to assist the veterinary pharmaceutical industry and Member States' pharmacovigilance schemes[7] in the collection, evaluation and transmission of adverse reaction reports for veterinary medicines. Many of the documents published in 2004 continued to focus on harmonisation of data evaluation and transmission, and final preparations to introduce electronic reporting (see **EudraVigilance Veterinary** below). In 2004, work began on a simple, concise guide to veterinary pharmacovigilance in the EU following publication of a concept paper describing the project and collection of comments. The guide will address veterinary practitioners and other veterinary health professionals, and intends to clarify the organisation of veterinary adverse reaction monitoring systems in the EU and the reporting requirements per se. Interested parties such as the FVE and IFAH Europe will be closely consulted in the drafting of the guide in order to ensure that it is clear for the intended audience and can be implemented easily and in a practical way. A suspected adverse reaction reporting form for use by veterinarians and other veterinary health professionals has been released for consultation. Once finalised, this form shall replace existing, rather diverse national forms and facilitate reporting of suspected reactions. The documents are published on the EMEA website http://www.emea.eu.int/index/indexv1.htm, Guidance documents/Pharmacovigilance/Guidance and Reporting.

EudraVigilance Veterinary

Full implementation of EudraVigilance Veterinary (http://eudravigilance.emea.eu.int/veterinary), the EU system for electronic reporting of suspected adverse reactions to veterinary medicines (to replace the current paper based system), is on track. A revised test system became available on 6 September 2004, and the production system (i.e. the actual reporting system) was released on 18 October 2004. The majority of the national authorities of EU member states have pledged to switch over to electronic reporting as of 1 January 2005. The veterinary pharmaceutical industry, which will be a valuable major participant in electronic reporting of suspected adverse reactions, is closely involved in the implementation process. The system for electronic reporting will provide an effective way of analysing suspected adverse reactions to ensure implementation of risk management for veterinary medicines once they have been authorised.

Training of Assessors

In November 2004 a workshop was held on causality assessment in veterinary pharmacovigilance. The workshop was attended by assessors from Member States' Competent Authorities, from veterinary pharmaceutical industry and by delegates from the FVE. It successfully served to train in the application of a new guideline on causality assessment published in April 2004 and to foster common understanding between authorities and industry.

EU enlargement 2004

Delegates from the 10 new EU Member States successfully integrated into the EMEA work structure and actively participate at the meeting of the CVMP Pharmacovigilance Working Party.

GLOSSARY

[1] **Committee for Medicinal Products for Veterinary Use (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] **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.

[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.

[7] **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.