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Committee for Medicinal Products for Veterinary Use (CVMP)

Public bulletin - Veterinary pharmacovigilance 2010

1. Introduction

This is the 8th bulletin from the European Medicines Agency on veterinary pharmacovigilance activities, covering the year 2010. 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 the EU, adverse event reports to all authorised veterinary medicinal products (VMPs) are collected by national competent authorities and then collated in a single database: EudraVigilance Veterinary. This database also includes adverse event reports from outside the EU provided by the marketing authorisation holders when products have been used that relate to products authorised in the EU.

The database now contains more than 50,000 adverse event reports, and important progress was made in 2010 on the development of additional data-analysis tools, which is a relatively new field of expertise for veterinary medicinal products. At present the main responsibility of the Agency in relation to the post-marketing follow-up of authorised products remains in relation to the group of products that have been authorised via the EU centralised procedure. This document mainly describes the outcome of the surveillance of these products that accounted for a total of 4,250 adverse event reports assessed and 118 periodic safety update reports (PSURs) in 2010. The surveillance of all other VMPs authorised within the EU is taking place at Member State level. When necessary, procedures exist where the Agency and its scientific committees become involved in the surveillance of such products (see section 3), and this document also gives an overview of the outcome of pharmacovigilance matters that have been considered during 2010 by the Committee for Medicinal Products for Veterinary Use (CVMP) and its Pharmacovigilance Working Party (PhVWP-V).

It is anticipated for 2011 that the analysis and discussions on EU product surveillance will be further harmonised within the European network in order to benefit from the pool of information in view of better surveillance. There is also a major revision of the EudraVigilance Veterinary system ongoing and expected to be available by the end of 2013, with as specific objective the possibility for increased access and feedback to the veterinary professionals in the EU.

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

2. Centrally authorised products

2.1. Spontaneous reports of serious suspected adverse reactions and human adverse reactions

A total of 4,474 serious suspected adverse reaction reports in animals (4,250) and reports of human adverse reactions (224) related to the exposure to centrally authorised veterinary products were received and processed in 2010. 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 2009. Of the 4,250 suspected adverse reactions in animals, 2,812 were for companion animals and 1,438 for food-producing animals. For companion animals, suspected adverse reactions were most frequently reported in dogs (1,710) and cats (1,021). The 1,438 reports received for food-producing animals (mainly in cattle, pigs and ovine, with the highest number in cattle) represent almost three times the 487 reports received in 2009. The reason for this increase was mainly due to targeted reporting related to the authorisation of further vaccines for the prevention of Bluetongue.

Of all the reports received in 2010, 2,210 (2,161 concerning animal reactions and 49 concerning human reactions) have occurred in EU/EEA countries. Most of the reports received from third countries were from the United States (88%) and Canada (6%). The remaining reports were received from other third countries, including Australia, Japan, Switzerland, Brazil and South Africa.

Table 1. Centrally authorised products. Summary statistics on expedited reports by target species, excluding reports in humans. (Reports received between 21 December 2009 and 18 December 2010.)

	Treated animals included in the reports (n)	Affected animals included in the reports (n)	Total expedited reports (n)
Food-producing animals	***377,641***	***173,875***	***1,438***
Cattle/Bovine	98,847	5,707	1,093
Pigs/Porcine	115,445	21,914	189
Sheep/Ovine	19,383	3,130	93
Horses/Equine	70	53	47
Goat/Caprine	336	63	8
Chickens/Avian	143,000	143,000	2
Rabbit	553	1	1
Other food-producing animals	7	7	5
Companion animals	***3,324***	***3,075***	***2,812***
Dogs/Canine	1,977	1,813	1,710
Cats/Feline	1,233	1,148	1,021
Rabbit	51	51	21
Other companion animals	63	63	60
All	**380,965**	**176,950**	**4,250**

Approximately 30% of the reports included in Table 1 were received following the use of non-steroidal anti-inflammatory drugs (NSAIDs), and 30% following the use of vaccines; reports following the use of antiparasitic substances and antimicrobials represent approximately 10% each. The remaining reports relate to a wide range of categories, including anaesthetics, antiemetics, anticancer, hormone-based and peripherally acting antiobesity products.

A total of 224 adverse events in humans following exposure to a veterinary medicinal product were reported during 2010. This represents approximately 5% of the total of reports received. The majority of reported events resulted from exposure to topically administered products for use against parasites (approximately 50%) or the result of accidental self-injection by practitioners or owners during vaccinations or other administration of injectable products (approximately the remaining 50%).

No urgent risk management measures were considered necessary for centrally auhtorised product following analysis of the serious suspected adverse reports received in 2010.

2.2. Periodic safety update reports (PSURs) – centrally authorised products

Companies have the legal obligation to periodically provide summary reports on the safety of their products. These periodic safety update reports (PSURs) discuss the overview of all adverse events (serious as well as non-serious) that were recorded during the period and also include information on other aspects, such as possible environmental issues or residue violations. The PSURs conclude with the current benefit/risk status of the product, and on this basis the CVMP may consider and require that amendments to the product literature are necessary (e.g. addition of a warning to the product literature).

A total of 112 PSURs and 6 PSUR addendum reports were received in 2010. During the year, the assessment process was completed for a total of 100 PSURs and PSUR addendum reports. 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. However, based on the available reports it was considered necessary for the following 6 products to require changes and/or additions to be made to the summary of product characteristics (SPC) and the product literature:

Cerenia: The following addition to the adverse reaction section of the product literature was recommended for Cerenia Injectable 10 mg/ml: "Pain at injection site may occur. In very rare cases, anaphylactic type reactions (allergic oedema, urticaria, erythema, collapse, dyspnoea, pale mucous membranes) may occur."

Ingelvac Circoflex: The following statement for inclusion in Section 4.6 Adverse reactions of the SPC and product literature was proposed by the MAH: "On very rare occasions anaphylactic reactions may occur and should be treated symptomatically."

Profender: The following information was proposed by the company to be included or changed in the product literature:

Section 4.5 Special precautions for use (Special precautions for use in animals):

"Administer only to fasted dogs. For example: ~~o~~Overnight fasting ~~is recommended~~ if the dog is to be treated in the morning. ~~Food may be given~~ No food should be given until 4 hours ~~or more~~ after treatment."

Section 4.6 Adverse Reactions:

~~"None~~

Transient slight digestive tract disorders (e.g. hypersalivation, vomiting) were observed in very rare cases.

Especially if fasting requirements were not followed slight transient neurological disorders (e.g. tremor, incoordination) were observed in very rare cases. These signs may be more severe (e.g. convulsion) in mdr1 mutant (-/-) Collies, Shelties and Australian Shepherds.

Specific antidotes are not known."

Section 4.10 Overdose:

"Transient muscular tremors, incoordination and depression were occasionally observed when the veterinary product was administered at overdoses of up to 5 times the recommended dose. In mdr1 mutant (-/-) Collies the margin of safety appears lower compared to the normal dog population, with mild transient tremor and/or ataxia occasionally observed after twice the recommended dose, in dogs fasted as recommended.

The symptoms were completely self-resolving without any treatment. Feeding can increase the incidence and intensity of such overdose symptoms and occasionally vomiting may occur.

Specific antidotes are not known."

Convenia: The following amendment (in bold) to the product literature was proposed by the MAH and recommended for inclusion under Section 4.2 Indications for Use, specifying the target species of the SPC and product literature: "For use **only** for the following infections which require prolonged treatment. The antimicrobial activity of Convenia following a single injection lasts for up to 14 days."

Improvac: Amendment to the product literature was required: "In very rare cases anaphylactoid type reactions (dyspnoea, collapse, cyanosis and hyper salivation associated with or without muscle twitching or emesis) have been observed within a few minutes after the first vaccination with duration up to 30 minutes. In a small number of animals death occurred following the reaction, however most animals recovered without treatment and did not appear to react to subsequent vaccinations."

Advocate: The following amendments to the product literature were recommended:

SPC section 4.6 Adverse reactions: "If the animal licks the application site after treatment, transient neurological signs (most of which are transient) may be observed in very rare cases infrequently (see section 4.10)."

SPC section 4.10 Overdose: "After accidental oral ingestion or overdose, transient neurological signs (most of which are transient) such as ataxia, generalised tremors, ocular signs (dilated pupils, little pupillary reflex, nystagmus), abnormal respiration, salivation and vomiting may occur in very rare cases infrequently."

Package leaflet section 6 Adverse reactions: "In very rare cases (e.g. if the animal licks the application site after treatment or in case of overdose), transient neurological signs (most of which are transient) such as ataxia, generalised tremors, ocular signs (dilated pupils, little papillary reflex, nystagmus), abnormal respiration, salivation and vomiting may occur."

3. Rapid alert / non-urgent information notifications / Article 78 procedures and other community procedures related to pharmacovigilance matters

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 2010 than in the previous years by the Member States. One rapid alert was triggered in 2010 leading to a procedure under Article 78 of Directive 2001/82/EC, concerning Pregsure BVD, and one new non-urgent information issue was raised, while other non-urgent information procedures initiated in the years before have been followed up or closed in 2010, as detailed below.

Bovine Neonatal Pancytopaenia

A non-urgent information procedure (NUI) was initiated in March 2009 in relation to reports in various Member States on spontaneous haemorrhagic diathesis or prolonged bleeding in young calves, subsequently named 'Bovine Neonatal Pancytopaenia', for which a risk factor was identified as the use of a particular vaccine against Bovine Virus Diarrhoea in their dams. A rapid alert (RA) for this vaccine, Pregsure BVD, was therefore circulated which subsequently led to a procedure under Article 78 of Directive 2001/82/EC. The CVMP adopted an opinion concluding that the marketing authorisations for Pregsure BVD and associated names should be suspended until scientific evidence is available to demonstrate that the administration of the vaccine to dams according to authorised conditions of use does not lead to an increased risk of bovine neonatal pancytopenia or that risk-mitigation measures ensuring the safe use of the product can be implemented.

T-61 VMP for euthanasia containing embutramide, mebenzonium iodide and tetracaine hydrochloride

A non-urgent information procedure (NUI) triggered in 2009 concerning a product containing embutramide, mebenzonium iodide and tetracaine hydrochloride for euthanasia in several animal species, following reports of suspected lack of expected efficacy in animals, had been followed up as well in consideration of the persisting concerns raised by some national competent authorities following assessment of related periodic safety update reports (from 2003-2009) specially regarding suspected lack of expected efficacy (delayed euthanasia). The Agency was informed that a variation of the marketing authorisation in order to restrict the intravenous administration to animals under anaesthesia, to add a contraindication concerning the use of the products in pregnant animals and to restrict the use for veterinarians only is being presented in the respective Member States where the product is authorised.

Nuflor - Florfenicol injectable and oral solution VMPs

A non-urgent information procedure (NUI) was triggered by Denmark in 2009 related to an injectable and oral solution product containing florfenicol following the finding of reproductive system disorders recorded during a clinical study of eradication of *Actinobacillus pleauropneumoniae* (off-label indication). The Agency was informed that an agreement was reached between the concerned Member State authorities and the marketing authorisation holder to include a warning in the summary of product characteristics to prevent the use of the product in pregnant sows.

Live bacterial vaccines against *Chlamydophila abortus* 1B strain in sheep

A new non-urgent information procedure was initiated in May 2010 concerning live bacterial vaccines for sheep based on an attenuated temperature-sensitive mutant of *Chlamydophila abortus* 1B strain.

The NUI request was circulated following a publication from the Moredun Research Institute of Edinburgh that reported the identification of vaccine strains in abortion material from vaccinated ewes using new genotyping techniques. The benefit-risk evaluation of the concerned products was still considered favourable and the importance of vaccination against enzootic abortion was reiterated. However, discussion is ongoing in relation to potential inclusion of warnings in the product literature to reflect the above findings.

Retrovirus RD114 in relation to live attenuated vaccines for use in dogs and cats

The Committee discussed findings from a recent scientific publication reporting the presence of the feline endogenous retrovirus RD114 in some vaccines produced on feline cell lines. The Committee adopted an opinion concluding that the benefit/risk balance for these products remains strongly positive, but that consideration needs to be given to amending the requirements for authorisation with respect to testing for, and if possible eliminating, such viruses from live attenuated vaccines.

Vectin - ivermectin chewable tablets for horses

Following reports from Germany related to the accidental ingestion by dogs of ivermectin chewable tablets intended for horses, the German authorities informed that the marketing authorisation is being varied and the product literature amended with the following additional warning in the Member States where the product is authorised:

"Vectin is registered for horses and should not be used in other animal species. After the administration of ivermectin to dogs, cases of intolerance with fatal outcome have been reported. Dogs or cats may be adversely affected by the ivermectin in this product if they are allowed to ingest dropped or discarded tablets or have access to the used packaging material."