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Committee for Medicinal Products for Veterinary Use (CVMP)

Veterinary pharmacovigilance 2011

Public bulletin

1. Introduction

This is the 9th bulletin from the European Medicines Agency on veterinary pharmacovigilance activities, covering the year 2011. The aim of this bulletin is to contribute to the public communication on veterinary medicinal products, particularly on the surveillance of the adverse events and safety issues of veterinary medicines in the European Union (EU). 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 and evaluated by national competent authorities and then, when they report serious events like death, life-threatening reactions or permanent lesions, they are collated in a single database: EudraVigilance Veterinary. This database also includes reports of serious and unexpected adverse events that occurred outside the EU, reported by the marketing authorisation holders of products that are considered to be similar to products authorised in the EU. EudraVigilance Veterinary is also increasingly used for collecting reports considered non-serious, which allows for a more complete surveillance using the available electronic analysis tools.

Electronic reporting became mandatory in November 2005, and the database now contains more than 67,000 adverse event reports, of which approximately 45,000 occurred within the EU and 22,000 outside the EU. At present, one of the main responsibilities of the Agency concerns pharmacovigilance of centrally authorised products. This document mainly describes the outcome of the surveillance of these products, which accounted for a total of 4,888 adverse event reports and a total of 132 periodic safety update reports (PSURs) or PSUR addendum reports received in 2011.

The surveillance of all other VMPs authorised within the EU takes place at Member State level. Procedures exist whereby the Agency and its scientific committees, where necessary, become involved in the surveillance of such products, and this document also gives an overview of the outcome of pharmacovigilance matters that have been considered during 2011 by the Agency's Committee for Medicinal Products for Veterinary Use (CVMP) and its Pharmacovigilance Working Party (PhVWP-V).

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2. Centrally authorised products

2.1. Spontaneous reports of adverse events in animals and humans

A total of 4,888 reports of adverse events in animals (4,629) and adverse reactions in humans (259) related to exposure to centrally authorised veterinary products were received and processed in 2011.

The adverse event reports received concerned 88 products, which is approximately 70% of the 126 centrally authorised products with a valid marketing authorisation recorded at the end of 2011.

Table 1 shows the numbers of reports by target animal 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 table gives raw figures of reports received, irrespective of their causality assessment. Furthermore, no conclusion on the incidence of the adverse event can be drawn without the corresponding sales figures.

There was a slight decrease of serious adverse event reports in 2011. There was, however, a higher number of non-serious adverse events reported. Of the 4,629 reports in animals, 3,973 concerned companion animals, most frequently dogs (2,648) and cats (1,288), and 656 concerned food-producing animals. Compared to 2010, these numbers show an increase in reporting concerning companion animals and a decrease in reporting concerning food-producing animals. This is probably attributable to a lower use in 2011 of vaccines for the prevention of bluetongue, which represented the large majority of reports in 2010 for cattle.

Of all the reports received in 2011, 2,010 occurred in EU/EEA countries, of which 1,963 concerned animal adverse events and 47 concerned human adverse events. Most of the 2,878 reports received from third countries (2,236 concerning animals and 212 concerning humans) were from the United States (84%) and Canada (8%), with the remainder being from Australia, Japan, New Zealand, Switzerland, Mexico, Brazil, South Africa, South Korea, Turkey, Chile, Gabon, Israel, Jordan, Malaysia, Panama, Philippines, Russia and Thailand.

Table 1. Centrally authorised products: Summary statistics on reports by target species, excluding reports in humans. (Reports received between 19 December 2010 and 31 December 2011.)

	Treated animals included in the reports (n)	Affected animals included in the reports (n)	Total reports (n)
Food-producing animals	***659,931***	***49,675***	***656***
Cattle/bovine	27,222	5,994	313
Pigs/porcine	144,204	22,473	193
Sheep/ovine	5,746	98	25
Horses/equine	1,420	180	109
Goats/caprine	2,794	1,350	6
Chickens/avian	478,544	19,579	9
Other (donkeys/asinine)	1	1	1
Companion animals	***5,636***	***4,317***	***3,973***
Dogs/canine	3,056	2,789	2,648
Cats/feline	2,485	1,436	1,288
Rabbits	18	15	15
Other	77	77	22
All	**665,567**	**54,992**	**4,629**

Approximately 30% of the reports included in Table 1 were received following the use of non-steroidal anti-inflammatory drugs (NSAIDs) and another 25% following the use of antiparasitic substances, while antimicrobials represent approximately 15%. Compared to 2010, there was a significant decrease from 30% to 10% in the number of reports related to vaccines. The remaining reports related to other product categories, including anaesthetics, antiemetics, anticancer, hormone-based and a peripherally acting antiobesity product.

A total of 259 adverse events in humans following exposure to a veterinary medicinal product were reported during 2011. This represents approximately 5% of all reports received, which is in line with the data recorded in previous years. Approximately 50% of these events resulted from exposure to topically administered antiparasiticides and the other 50% from accidental self-injection of vaccines or other injectable products. It needs to be stressed that, in contrast to reports in animals, all reports of adverse events in humans need to be expedited, as they are considered serious, even if they involve only mild and transient symptoms.

It should be noted that the above reported percentages of occurrence of reported adverse events to the category of products relates only to the analysis of reports for centrally authorised products (community marketing authorisation) and may not reflect the relative occurrence of events observed for the other veterinary medicinal products authorised in the different EU countries.

A new surveillance procedure that makes full use of electronic analysis tools for the periodic surveillance of all centrally authorised products was initiated in August 2011. Investigation of 72 products was completed in 2011 for one or more suspected emerging signals per product. However, no urgent risk-management measures were considered necessary for centrally authorised products following analysis of the suspected adverse reports received in 2011.

2.2. Periodic safety update reports — 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 and evaluate the overview of all adverse events (serious as well as non-serious) that were recorded during the period. They provide information on the frequency of occurrence of adverse events: the total amount of product sold and estimated number of animals treated are put into relation to the number of animals affected by an adverse event. They also include information on other aspects, such as suspected lack of efficacy, environmental issues or residue violations. The PSURs conclude with the current benefit-risk balance of the product, and on this basis, the CVMP may consider and require that amendments to the product literature, e.g. addition of a warning, are necessary.

A total of 132 PSURs or PSUR addendum reports were received in 2011. During the year, the assessment process was completed for a total of 121. After consideration of all pharmacovigilance data detailed in these reports, the CVMP concluded that the benefit-risk balance remained in favour of the concerned products. However, it was considered necessary to amend the summary of product characteristics (SPC) and product literature for 13 products, as detailed in Annex 1.

3. Rapid alerts, non-urgent information notifications, referrals under Article 78 and other Community procedures related to pharmacovigilance matters

The rapid alert and non-urgent information system was established for national competent authorities and the Agency for early detection and rapid notification of safety concerns, and for the exchange of pharmacovigilance information. These procedures are not restricted to centrally authorised products but are applicable to all veterinary medicinal products authorised within the European Union.

One non-urgent information issue that escalated to a rapid alert was triggered in 2011, leading to a procedure under Article 78 of Directive 2001/82/EC, concerning Hiprabovis Pneumos. A further 6 new, non-urgent information issues were raised; discussions on some of them have been closed without further action, while others are ongoing. Other non-urgent information procedures initiated in the years before have been followed up or closed in 2011. The most relevant issues discussed in 2011 are summarised below.

Pregsure BVD and bovine neonatal pancytopenia

Following the suspension of the marketing authorisations for Pregsure BVD and associated names in 2010, discussions continued at the PhVWP-V in 2011 in view of long term effects reporting of events of bovine neonatal pancytopenia that were received, and the potential need for further regulatory action.

The role of a long-lasting immune-mediated mechanism or the result of an effect triggered by administration of Pregsure BVD that could be reactivated following the use of other vaccines was considered. In addition, the role of the colostrum was further considered in relation to the hypothesis for an antibody-mediated pathogenesis for the syndrome.

Finally, the product was withdrawn by the marketing-authorisation holder (MAH) following the occurrence of events of bovine neonatal pancytopenia in third countries.

The PhVWP-V and the CVMP continuously monitor reports on this issue and discuss the possible need for development of specific guidance concerning cell lines and adjuvants used for vaccines.

Ovilis Enzovax and CEVAC Chlamydia: Live bacterial vaccines against *Chlamydophila abortus* 1B strain in sheep

A non-urgent information request was circulated in May 2010 concerning live bacterial vaccines for sheep based on an attenuated temperature-sensitive mutant of *Chlamydophila abortus* 1B strain. The non-urgent information request was circulated following a publication from the Moredun Research Institute of Edinburgh, which 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, the PhVWP-V were informed of the amendments of the SPC agreed for the concerned products. Section 4.6 of the summary of product characteristics and product literature were amended to: "In very rare cases abortions may occur where the vaccine strain can be identified".

Hiprabovis Pneumos Emulsion for injection for cattle (*Mannheimia haemolytica* biotype A serotype A1, inactivated cell free suspension containing leukotoxoid Ph. Eur. / inactivated *Histophilus somni* Bailie strain)

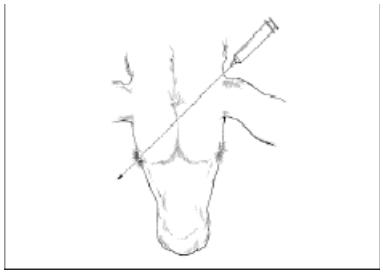
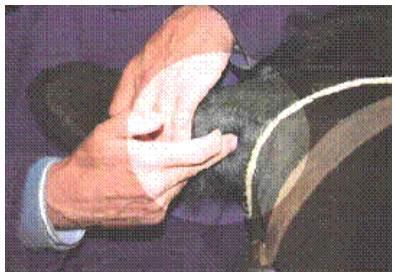
In March 2011, a non-urgent information request from Belgium was initially discussed following reports of anaphylactic-type reactions occurred in Belgium and leading to some deaths in treated cattle.

On 13 April 2011, the French national competent authority informed the Agency that the marketing authorisation had been suspended, due to pharmacovigilance concerns relating to increased frequency of anaphylactic-type events in animals. In accordance with Article 78 of Directive 2001/82/EC, the matter was referred to the CVMP following the suspension in France. The Committee concluded that the data available indicated an association between the anaphylactic-type adverse events and the product, and that the underlying cause for the adverse events could not yet be determined. Therefore, the CVMP recommended the suspension of the marketing authorisations for Hiprabovis pneumos emulsion for injection for cattle until a favourable benefit-risk balance for the product could be demonstrated. The recommendation was followed by a subsequent decision of the European Commission.

Annex 1

Lists of amendments recommended in 2011 following assessment of PSURs or summary bridging reports and PSUR addendum reports in renewal procedures.

Product	SPC section	Recommendation to MAH (addition, deletion or other changes **in bold**)
Cerenia	Section 4.5, Special precautions for use	**Injecting the product at refrigerated temperature may reduce pain at injection.**
Convenia	Section 4.6, Adverse reactions (frequency and seriousness)	**In very rare cases neurological signs and injection site reactions have been reported after the use of the product.**
Cortavance	Section 4.6, Adverse reactions (frequency and seriousness)	**Transient local reactions at the application site (erythema and/or pruritus) can occur in very rare cases (less than 1 in 10,000 animals).**
Ibaflin	Section 4.6, Adverse reactions (frequency and seriousness)	**In very rare cases retinotoxic effects such as blindness may occur in cats.**
Metacam and **Novem**	Section 4.6, Adverse reactions (frequency and seriousness)	*For presentations: Metacam 5 mg/ml solution for injection for dogs and cats, Metacam 0.5 mg/ml oral suspension for dogs, Metacam 0.5 mg/ml oral suspension for cats and Metacam 1 mg and 2.5 mg chewable tablets for dogs* Typical adverse drug reactions of NSAIDs such as loss of appetite, vomiting, diarrhoea, faecal occult blood, ~~**apathy**~~ **lethargy** and renal failure have occasionally been reported. **In very rare cases elevated liver enzymes have been reported.** **In dogs, in very rare cases haemorrhagic diarrhoea, haematemesis, and gastrointestinal ulceration have been reported.** **If adverse reactions occur, treatment should be discontinued and the advice of a veterinarian should be sought.**
		For presentations: Metacam 5 mg/ml solution for injection for cattle and pigs, Novem 5 mg/ml solution for injection for cattle and pigs, Metacam 20 mg/ml solution for injection for cattle, pigs and horses and Novem 20 mg/ml solution for injection for cattle and pigs In very rare cases anaphylactoid reactions **which may be serious or fatal may** occur and should be treated symptomatically.
		For presentation: Metacam 15 mg/ml oral suspension for horses **In very rare cases loss of appetite, lethargy, abdominal pain and colitis have been reported** In very rare cases anaphylactoid reactions **which may be serious or fatal** may occur and should be treated symptomatically. **If adverse reactions occur, treatment should be discontinued and the advice of a veterinarian should be sought.**

<table>
<tr><th>Product</th><th>SPC section</th><th>Recommendation to MAH (addition, deletion or other changes in bold)</th></tr>
<tr><td>Naxcel</td><td>Section 4.9, Amounts to be administered and administration route</td><td>Take appropriate precautions to avoid intra-arterial or intravenous injection, such as restraining appropriately the animal (chute or head restraint for example) and using appropriate needles [1 inch (2.54 cm) long; 16 gauge].
<table>
<tr><td>Figure 1. Subcutaneous administration of NAXCEL at the posterior aspect of the ear where it attaches to the head (base of ear). Diagram of the head showing the direction for the base of the ear injections administered toward the animal’s opposite eye.</td><td>Figure 2. Injection location for the subcutaneous administration of NAXCEL at the posterior aspect of the ear where it attaches to the head (base of ear).</td></tr>
<tr><td>  </td><td>  </td></tr>
</table>
The photo in figure 2 can be replaced by a corresponding drawing where the direction of the syringe is clearly highlighted, if appropriate.</td></tr>
<tr><td rowspan="2">Onsior</td><td>Section 4.6, Adverse reactions (frequency and seriousness)</td><td>Onsior 6 mg for cats tablet

Mild and transient diarrhoea, soft faeces or vomiting were commonly reported. In very rare cases, lethargy may be observed.</td></tr>
<tr><td>Section 4.6, Adverse reactions (frequency and seriousness)</td><td>Onsior 5, 10, 20 and 40 mg tablets for dogs

Gastrointestinal adverse events were reported very commonly, but most cases were mild and recovered without treatment. Vomiting and soft faeces were very common, decreased appetite and diarrhoea were common, and blood in the faeces was uncommon. In dogs treated up to 2 weeks no increases in liver enzyme activities were observed. However, with long-term treatment, increases in liver enzyme activities were common. In most cases there were no clinical signs and the liver enzyme activities either stabilised or decreased with continued treatment. Increases in liver enzyme activities associated with clinical signs of anorexia, apathy or vomiting were uncommon. In very rare cases, lethargy may be observed.</td></tr>
</table>

Product	SPC section	Recommendation to MAH (addition, deletion or other changes **in bold**)
Onsior	Section 4.6, Adverse reactions (frequency and seriousness)	*Onsior 20 mg/ml solution for injection for cats and dogs* Cats: gastrointestinal adverse events (such as vomiting) were very commonly reported, but most cases were mild and recovered without treatment. Diarrhoea or vomiting with blood were uncommon. Slight pain at injection **site** was very commonly reported. Moderate or severe pain at injection **site** was commonly reported. Dogs: gastrointestinal adverse events (such as vomiting) were commonly reported but most cases were mild and recovered without treatment. Diarrhoea, soft and dark faeces or reduced appetite were uncommon. Slight pain at injection **site** was commonly reported. Moderate or severe pain at injection **site** was uncommon.
Prac-Tic	Section 4.5, Special precautions for use	i) Special precautions for use in animals This veterinary medicinal product is for spot-on application only. Do not administer orally**, which can lead to overdose,** or via any other route. ii) Special precautions to be taken by the person administering the medicinal product to animals. **In case of contact with the product, irritation of skin and mucosa and numbness, which usually resolve spontaneously, may occur.**
	Section 4.6, Adverse reactions (frequency and seriousness)	**On very rare occasions the following have been reported:** **- application site and skin reactions (pruritus, hair change, dermatitis, erythema, alopecia, fur discoloration and greasy appearance of hair).** **- neurological reactions (ataxia and convulsions).** **- systemic reactions (lethargy).** **- digestive tract reactions (emesis and diarrhoea).** ~~**The following local reactions may be observed at the application site: fur discoloration, local alopecia or pruritus. Local cosmetic effects at the application site, such as a greasy appearance or clumpiness of hair are common. However, those signs disappear within 24 hours of the application.**~~
Promeris	Section 4.5, Special precautions for use	**The solvent in ProMeris may stain certain materials including leather, fabrics, plastics and finished surfaces. Allow the application site to dry before permitting contact with such materials.**
Promeris Duo	Section 4.5, Special precautions for use	**The solvent in ProMeris Duo may stain certain materials including leather, fabrics, plastics and finished surfaces. Allow the application site to dry before permitting contact with such materials**

Product	SPC section	Recommendation to MAH (addition, deletion or other changes **in bold**)
	Section 4.6, Adverse reactions (frequency and seriousness)	**In very rare cases, pemphigus foliaceous-like cutaneous signs have been reported. If pemphigus-like signs occur, further use of the product should be avoided. These signs are transient and reversible if prompt and appropriate treatment is administered**
Reconcile	Section 4.6, Adverse reactions (frequency and seriousness)	**Rare adverse events: panting**.
Trocoxil	Section 4.5, Special precautions for use	*Special precautions for use in animals:* Animals should undergo a thorough clinical examination before commencing treatment with Trocoxil **and appropriate laboratory tests to monitor haematology and clinical chemistry are recommended**. Animals with evidence of impaired renal and hepatic function or with evidence of protein or blood losing enteropathy are not suitable for treatment with Trocoxil. It is recommended to repeat the clinical examination one month after commencing treatment with Trocoxil and prior to administration of the third dose **with additional monitoring of clinical pathology as appropriate during treatment**. Ensure appropriate hydration and haemodynamic status when animals receiving Trocoxil undergo anaesthesia and/or surgical procedures or develop conditions which may result in dehydration or compromised haemodynamic status. **Patients with underlying renal disease may experience exacerbation or decompensation of their renal disease while on NSAID therapy**.
	Section 4.6, Adverse reactions (frequency and seriousness)	Adverse reactions **of the digestive tract** such as vomiting, diarrhoea **were commonly reported**, loss of appetite **haemorrhagic diarrhoea and melaena have been reported in uncommon cases**. **Gastrointestinal ulceration was reported in rare cases**. Apathy, degradation of renal biochemistry parameters and impaired renal function has been reported **in uncommon cases**. In rare cases these **adverse reactions** may be fatal. **Gastrointestinal protectants and parenteral fluids, as appropriate, may be required for animals that experienced gastrointestinal or renal adverse reactions**. Veterinarians should be aware that clinical signs of adverse reactions may continue when supportive therapy (such as gastro protectants) is discontinued.
Zubrin	Section 4.6, Adverse reactions (frequency and seriousness)	Typical undesirable side-effects associated with NSAIDs are vomiting, soft faeces/diarrhoea, blood in faeces, reduced appetite, lethargy and **renal disorders**. If there are such undesirable effects, treatment should be discontinued immediately.