The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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FINAL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE:

REVISED RAPID ALERT SYSTEM (RAS) AND NON URGENT INFORMATION SYSTEM (NUIS) IN VETERINARY PHARMACOVIGILANCE

DISCUSSION OF THE REVISION AT PHARMACOVIGILANCE WORKING PARTY	JULY 1999
ADOPTION BY CVMP	AUGUST 1999

BACKGROUND

The revision of this guideline was considered necessary to reflect in particular the new developments in the field of information technology with regard to the efficient electronic exchange of Rapid Alerts and Non-Urgent Information.

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**NOTE FOR GUIDANCE ON RAPID ALERT SYSTEM (RAS)
AND NON URGENT INFORMATION SYSTEM (NUIS)
IN VETERINARY PHARMACOVIGILANCE**

I. INTRODUCTION:

During the marketing period of a veterinary medicinal product urgent measures to safeguard animal or public health or the environment may be necessary. Within the European system of pharmacovigilance it is essential that information concerning safety hazards possibly resulting in major changes to the marketing authorisation status or withdrawal of a product, is exchanged between the Member States, the European Agency for the Evaluation of Medicinal Products (EMEA) and the European Commission (EC) with the appropriate degree of urgency

An early exchange of information will enable the Competent Authorities of Member States to initiate data research and seek specialist expertise so that necessary decisions may be taken as soon as possible.

To support the rapid notification of safety concerns and the exchange of information required to take the necessary decisions, the Competent Authorities of Member States and European Free Trade Association (EFTA) countries concerned (Iceland, Liechtenstein and Norway), the EMEA and the EC operate the Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in accordance with the procedure laid down in this guideline.

In the event that a recall of a product or a product batch is necessary, the procedures outlined in the document, 'Compilation of Community Procedures on Administrative Collaboration and Harmonization of Inspections' shall apply.

II. PURPOSE:

The purpose of the Rapid Alert System (RAS) is to alert, with the appropriate degree of urgency, other Member States, EFTA countries concerned, the EMEA and the European Commission and about newly available pharmacovigilance data for veterinary medicinal products which indicate that action could be needed urgently to protect animal or public health. It is essential that communication of such a problem occurs at an early stage, normally before a decision is taken in a Member State.

The Non Urgent Information System (NUIS) is established to support the collection and exchange of pharmacovigilance information between the Competent Authorities of Member States, the EC and the EMEA which does not fulfil the criteria for a Rapid Alert.

In both cases, the RAS and the NUIS, the issue may then be discussed in a broad manner

- at the CVMP Working Party on Veterinary Pharmacovigilance on the basis of an assessment report,
- in the CVMP,
- or formalised within procedures laid down in Article 20 and 21 of Council Directive 81/851/EEC of 28 September 1981 as amended or Article 40 of Council Regulation (EEC) No. 2309/93 of 22 July 1993, as amended.

III. SCOPE:

The RAS should primarily be used in problems or concerns relating to safety and efficacy concerns of veterinary medicinal products authorised according to

- Council Directive 65/65/EEC of 26 January 1965 as amended and Council Directive 81/851/EEC of 28 September 1981 as amended,
- Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended.

The system must not be saturated by the exchange of less urgent information. For this purpose the Non-Urgent Information-System should be used.

Rapid alerts regarding quality problems of a veterinary medicinal product not related to safety or efficacy concerns are not considered in this guideline. Those Rapid Alerts must be handled as laid down in the document III/5698/94-EN as is referred to in the introduction.

IV. CRITERIA:

IV.1. Rapid Alert System

The RAS should be used when a Member State has concern about a change in the balance between risks and benefits of a veterinary medicinal product that could require major changes in the status of the marketing authorisation such as:

- the urgent variation, suspension or withdrawal of the marketing authorisation,
- the recall of the medicinal product from the market,
- changes in the Summary of Product Characteristics (SPC) such as[1]
  - the introduction of new contraindications,
  - the introduction of new warnings,
  - the reduction in the recommended dose,
  - the restriction in the indications,
  - the restriction in the availability of the medicinal product and
- the need to inform Veterinary health care professionals (e.g. Vet. Practitioner, pharmacist etc) about an identified risk without delay.

Concerns about a change in the risk benefit balance of a medicinal product or an active ingredient authorised according to Council Directive 65/65/EEC of 26 January 1965 as amended and Council Directive 81/851/EEC of 28 September 1981 as amended or Council Regulation (EEC) No. 2309/93 of 22 July 1993 may be based on:

- a series of report(s) of unexpected and serious Adverse Drug Reactions (ADRs),
- reports of an expected ADR which suggest greater severity or long-term sequelae than known or which identify new risk factors,
- significant increase in the reporting rate of expected serious ADRs,
- evidence from studies (clinical trials or epidemiological studies) indicative of unexpected risk or a change in frequency or severity of a known risk,
- knowledge that the efficacy of a medicinal product is not established as assumed to date,
- evidence that the risks of a particular product are greater than alternatives with similar efficacy.

IV.2. Non Urgent Information System

[1] With regard to Article 42h of Council Directive 81/851/EEC of 28 September 1981 as amended, these criteria define a significant variation of the SPC.

For the exchange of potential concerns that do not fulfil the RAS criteria as defined above, the NUIS should be used. It refers e.g. to

- Pharmacovigilance data, which do not require immediate or urgent action and/or where additional information is required from other Member States to support the evaluation of a potential concern,

- Provision of pharmacovigilance information, which does not require a response.

V. PROCEDURE:

Normally the case relating to the suspicion or concern is formulated by one Member State after evaluation of the data available in that Member State or the receipt of any other relevant important information that should be shared with other Member States, the EFTA countries concerned, the EMEA and the EC. This should also include any action initiated by the Marketing Authorisation Holder(s) (MAHs).

V.1. Sending a Rapid Alert or Non-Urgent Information

In accordance with Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended, Article 46, the EMEA, in consultation with Member States and the European Commission, has set up a data-processing network (EudraNet) for the rapid transmission of data between the EU Competent Authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding medicinal products marketed in the Community.

Following the successful piloting between Member States, the EC and the EMEA, the electronic submission shall replace the Telefax system used in past to exchange this kind of information. However, in case of urgency e.g. EudraNet access is not available or the network is down, the former Telefax system should be used as alternative. The electronic communication with partners that are not connected via EudraNet has to be performed in a way that guarantees security and confidentiality of the data exchanged.

The establishment of pre-defined data formats is essential to ensure the collection of similar data, aid in exchange of information among the Member States, and assist the common evaluation. Proposed forms are enclosed with this guideline. Templates are available on the EudraNet homepage http://eudranet.eudra.org/ and can be accessed via the established Pharmacovigilance domain.

To send the form, the established Rapid Alert (RA) or NUI (Non Urgent Information) address lists (Veterinary RA + Veterinary NUIS) and mailboxes should be used which refer to the contact points within the Competent Authorities of Member States, the EMEA and the EC. The EudraNet E-mail policy IT-SOP 9724 in the latest version applies accordingly.

<u>If using the RAS/NUIS the Member State should comply with the following rules:</u>

a) The template chosen must comply either with the Rapid Alert or the Non-Urgent Information System criteria.

b) Clear and concise information on the reasons for the Rapid Alert/Non-Urgent Information should be provided so that there is no need for clarification in the first instance.

c) The Competent Authority generating the Rapid Alert/Non-Urgent Information should transmit at least the minimal data listed in Annex I and template A.

d) Any information required from recipients should be specified clearly.

e) In the event a Telefax is sent it should be preferably typewritten; the size of the letters should be large enough to ensure that the text is satisfactory readable.

f) Annexes to the RAS/NUIS, considered to give sufficient details where necessary, should also be transmitted electronically, if available. The format to be used is the one specified in the EudraNet E-mail policy IT-SOP 9724 in the latest version. In case, the annexes are not available electronically, the form should be completed including a reference that the referred annexes would be submitted separately via Telefax; the form should be sent via the defined address list to the dedicated mailboxes. A print out of this completed form should be attached to the faxed annexes.

g) The Rapid Alert should be transmitted in case of a veterinary medicinal product authorised according to

- Council Directive 65/65/EEC of 26 January 1965 as amended and Council Directive 81/851/EEC of 28 September 1981 as amended – *nationally authorised veterinary medicinal products including those authorised through the mutual recognition procedure* - to the contact points of the Member States, the EFTA countries concerned, the EMEA and the EC,

- Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended – *centrally authorised medicinal products* - to the contact points of the Member States, the EFTA countries concerned, the EMEA, the EC and the Rapporteur.

- The Rapid alert should in any case also be provided to the chairman of the CVMP.

h) Non-Urgent Information should be transmitted in case of a veterinary medicinal product authorised according to

- Council Directive 65/65/EEC of 26 January 1965 as amended and Council Directive 81/851/EEC of 28 September 1981 as amended – *nationally authorised veterinary medicinal products* -to the contact points of the Member States, the EFTA countries concerned, the EMEA and the EC,

- Council Directive 65/65/EEC of 26 January 1965 as amended and Council Directive 81/851/EEC of 28 September 1981 as amended - *medicinal products authorised nationally through the mutual recognition procedure* - to the contact points of the RMS, all other Member States, the EFTA countries concerned, the EMEA and the EC,

- Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended – *centrally authorised medicinal products* - in the first instance only to the EMEA and the Rapporteur. The originator of the issue and the Rapporteur may request further information from other Member States.

- The Non-Urgent Information should in any case also be copied to the chairman of the CVMP.

i) If the fax is used it has to be transmitted to the established contact points as indicated above. A list of the fax numbers will be also accessible on the EudraNet homepage. Changes related to the fax numbers should be notified to the EMEA, the EC and the contact points in Member States and the EFTA countries concerned, immediately.

j) In case of urgency, when the Member State concerned has suspended the marketing authorisation of a medicinal product or withdrawn the drug from the market in order to protect animal or human health or the environment, the EMEA, the EC, all Member States and the EFTA countries concerned have to be informed at the latest on the following working day.

k) When a Rapid Alert is circulated

- Related to a medicinal product authorised according to Council Directive 65/65/EEC of 26 January 1965 as amended and Council Directive 81/851/EEC of 28 September 1981

as amended – *nationally authorised medicinal products* - the initiating Member State should inform the MAHs concerned in his country adequately and promptly. Receiving Member States are responsible for informing MAH(s) in their own country. Information on the MAH(s) may be given via associations of the MA holders both in the sending and receiving Member State.

- Related to a medicinal product authorised according to Council Directive 65/65/EEC of 26 January 1965 as amended and Council Directive 81/851/EEC of 28 September 1981 as amended – *medicinal products authorised nationally through the mutual recognition procedure* - the RMS should inform the MAH adequately and promptly.

- Related to a medicinal product authorised according to Council Regulation (EEC) No. 2309/93 of 22 July 1993 as amended – *centrally authorised medicinal products* - the EMEA Secretariat in agreement with the Rapporteur will promptly start an inquiry and information exchange with MAH(s).

l) According to the guideline on the 'Principles of Providing the World Health Organisation with Pharmacovigilance Information' (CPMP/PhVWP/053/98), Rapid Alerts will be sent for non-centrally authorised medicinal products by the Member States and for centrally authorised products by the EMEA in agreement with the EC if definitive measures related to the marketing authorisations of medicinal products (restriction, variation, suspension, withdrawal) are implemented by the competent authority or if the rapid alert informs about a public statement (positive or negative) made by the competent authority.

V.2. Responses to a Rapid Alert or Non-Urgent Information

Responses to a specific Rapid Alert should be sent only to the originating Member State and the EMEA no later than one week of receipt of the alert.

In case of a Non-Urgent Information requested answers should be provided to the originating Member State and the EMEA within the time frame indicated by the originator.

The template (see template B) to be used is the "ANSWER TO RAPID ALERT/NON-URGENT INFORMATION". The information requested by the generating Member State should be provided.

The EMEA will summarise the issues related to Rapid Alerts and Non-Urgent Information in the Drug Monitor, which will be discussed and updated at each meeting of the Pharmacovigilance Working Party.

V.3. Assessment of a Rapid Alert

An interim assessment report should be prepared within five weeks after transmission of the initial Rapid Alert

- for medicinal products authorised according to Council Directive 65/65/EEC of 26 January 1965 as amended and according to Council Directive 75/319/EEC of 20 May 1975 as amended – *nationally authorised medicinal products* – by the originating Member State taking into account all information received and collated from other Member States,

- for medicinal products authorised according to Council Directive 65/65/EEC of 26 January 1965 as amended and according to Council Directive 75/319/EEC of 20 May 1975 as amended – *medicinal products authorised nationally through the mutual recognition procedure* - any risk evaluation should normally be carried out by the RMS unless other arrangements are agreed with Member States. In each case agreement needs to be reached on the responsibility for the management of the alert and the risk/benefit assessment by the RMS, or originator CMS, or jointly.

- for medicinal products authorised according to Council Regulation (EEC) No. 2309/93 of 22 July 1993 – *centrally authorised medicinal products* - the Rapporteur should work closely with the originator of the alert to evaluate the issue. Agreement needs to be reached in each case on the responsibility for the risk/benefit assessment report, by the Rapporteur or the originating Member State, or jointly.

When the collated information provides evidence of a serious safety concern a full risk/benefit assessment report for consideration by the Pharmacovigilance Working Party and/or CVMP should be prepared.

The assessment report should follow the format and content of the guideline on Pharmacovigilance Assessment Reports (Annex II) and following the template (Annex III).
The assessment report should be sent to all Competent Authorities in Member States, the EFTA countries concerned, the EMEA and the EC and should be discussed at the next meeting of the Pharmacovigilance Working Party.

The assessment report should be distributed electronically using the defined Vet-Pharmacovigilance address list and the established mailboxes as indicated in the EudraNet E-mail policy in the latest version. The electronic communication with partners that are not connected via EudraNet has to be performed in a way that guarantees security and confidentiality of the data exchanged. Consideration will need to be given to whether the matter is of Community interest and should be referred under Article 20 and 21 of Council Directive (EEC) 81/851 of 28 September 1981 as amended.

V.4. Assessment of Non-Urgent Information

On the basis of the Drug Monitor the Pharmacovigilance Working Party will discuss all topics exchanged via the Non-Urgent Information System and will agree on a case to case basis how to process the issue. In the event the preparation of an assessment report is considered necessary the same assessment procedure applies as indicated for a Rapid Alert (chapter V.3.).

Annex I

Information for transmission of information about detected signals
Minimal data that should be filled in every case

1. Identification:

- Type of message categories: Rapid Alert/Non-urgent Message
- Reference:
- From:
- To:
- Date:

2. Veterinary Medicinal Product

- Brandname(s):
- Active substance(s): (INN, DCI)
  ★ - Centrally Authorised Product,
  ❑ - Nationally Authorised Product,
  ✣ - Mutual Recognition Product,
  ◆ - Product which has been subject to a referral process
- Pharmaceutical form and dosage (if appropriate):
- Marketing authorisation holder(s)
- Manufacturer (if essential)

3. Reason for Alert

- Source of information: Spontaneous reports/Post-Authorisation Study/Clinical Trial/Pre-clinical Study, others
- summarised evidence relevant to alert

4. Actions

- Action(s) proposed
- Action(s) taken (steps taken to collect more information at a national level and temporary steps taken to limit risks)

5. Information exchange

- Information required

Annex II

Guideline on Pharmacovigilance Assessment Reports

Format and content

I. Introduction

This section should clarify why the assessment has been undertaken.

II. Assessment of risks

This section will be specifically devoted to the safety concern under evaluation. It should encompass all relevant sources of information, including spontaneous reports, including death, published literature, studies (pre-marketing clinical trials, post-marketing studies, epidemiological studies and intensive monitoring data):

a) characterise the problem (nature, severity, outcome);
b) assess causal association;
c) estimate frequency and comparative frequency, where possible;
d) provide evidence of risk factors

III. Assessment of benefits

It should take into account the following, where known:

a) the nature of the diseases/signs for which the medicine is indicated (e.g. fatal, life-threatening, economic importance.)

b) absolute efficacy, as judged by controlled clinical trials

c) relative efficacy, as judged by studies comparing efficacy with that of appropriate alternative treatment(s)

d) the characteristics of the population exposed to the medicine

IV. Overall risk-benefit assessment

This section includes:

a) an overall benefit/risk analysis in the context of the safety problem under assessment and relevant comparative safety with other drugs in the same class or for the same therapeutic indication;

b) discussion of the optional actions for improving the risk-benefit ratio

c) proposed actions for responding to the safety issue.

Annex III

TEMPLATE FOR

FINAL ASSESSMENT REPORT FOLLOWING THE RAPID ALERT

OF

< ACTIVE INGREDIENT >

<The INN name should be used>

Status: < for INFORMATION >

Reference No < >

From: <Member State>

Date: <dd-mm-yy>

Signature: <.....>

Name: <.....>

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BACKGROUND INFORMATION

Starting Point
Referral to national advisory board
The proceedings of the national inquiries
Alerting the Member States
Involvement of the CVMP Pharmacovigilance Working Party

SCIENTIFIC DISCUSSION

Overview of the safety concerns
Overview of benefits
Overall risk - benefit assessment

PROPOSED ACTIONS / ACTIONS TAKEN

National variation of marketing authorisation
National suspension of the marketing authorisation
National withdrawal of the marketing authorisation
Referral to CVMP

ANNEXES

ABSTRACT OF THE ALERT PROCEDURE AND PRODUCT PROFILE (on one page)

Alerting Member State

Problem/Subject

Veterinary Medicinal Product

- INN name
- Brand name(s)
- Company
- Strength(s)
- Pharmaceutical form(s)
- Route of administration
- Therapeutic Classification (ATC-Vet code)
- Marketing authorisation holder

Animals Involved

Indications

Reason for Alert

Proposed action or action taken

BACKGROUND INFORMATION ON THE PROCEDURE

Starting Point

- When
- By whom
- The concern
- The drug
- The source of the concern
  (e.g. case reports from spontaneous reporting, epidemiological study)

Referral to the National Advisory Board

- When
- Which matter
- National procedure for actions to be taken

The proceedings of the National inquires

- When
- On which problem
- On which substance
- Involvement of the marketing authorisation holders
  ⇒ Time frame
  ⇒ Explanations of the MAH(s) in writing/orally

Alerting the Member States

- When, by (e.g. Fax, e-mail)
- On which problem
- On which INN-name
- Call for (e.g.)
  ⇒ case reports
  ⇒ details of legal status in the Member State
  ⇒ information on supply and use
- Answers received from

Involvement of the Veterinary Pharmacovigilance Working Party

- The subject was
  ⇒ presented by, when
  ⇒ discussed on, when
- Additional explanations of the MAH(s) were given
  ⇒ when
  ⇒ in writing (expert report)
  ⇒ orally
- Assessment reports were prepared
  ⇒ by , when
  ⇒ reviewed, updated, finalised
- A report of the Veterinary Pharmacovigilance Working party was given
  ⇒ when
  ⇒ to (e.g. the CVMP, the MAH, others)

SCIENTIFIC DISCUSSION

- Overview of the safety concerns
  ⇒ Adverse drug reactions
  ⇒ Risk of correct treatment (e.g. defined populations at risk)
  ⇒ Risk of inappropriate treatment (if applicable)

- Overall risk - benefit assessment
  ⇒ of drug under consideration
  ⇒ place on the market
  ⇒ compared to alternative treatment(s)

PROPOSED ACTIONS / ACTIONS TAKEN

- Variation of the marketing authorisation
  ⇒ Proposed conditions of supply and use
  ⇒ Proposed warnings to animal health professionals and/or animal owners
  ⇒ Proposed changes of the SPC or parts of it
  ⇒ Provision of further evaluation for the MAH(s)

- Suspension of the marketing authorisation
  ⇒ from, to
  ⇒ with obligation to fulfil in between

- Withdrawal of the marketing authorisation
  ⇒ in force from
  ⇒ recall of products on the market is included and monitoring of the recall process

- Referral to CVMP
  ⇒ Community interest involved

ANNEXES

(Annexes if appropriate,)

Template A

Logo and name of the Competent Authority of the Member State/EMEA

<RAPID ALERT | NON-URGENT INFORMATION> **IN VETERINARY PHARMACOVIGILANCE**		
Reference:	N° of attachments:	Date:
FROM:		
TO: (ALL) MEMBER STATES EFTA countries concerned EMEA EUROPEAN COMMISSION CHAIR-CVMP RAPPORTEUR (if applicable) RMS (if applicable)		

SUBJECT:

Please fill in the appropriate fields

Brandname(s): <*select* ★ | ❑ | ✣ | ◆>

International Non-proprietary Name (INN, DCI) or Class: <*select* ★ | ❑ | ✣ | ◆>

Strength(s):

Pharmaceutical Form(s) and Dosage(s):

Route of Administration(s):

Therapeutic Classification (ATC code):

Marketing Authorisation Holder:

Indication(s):

**REASONS FOR <*ALERT	NON-URGENT INFORMATION*>:** (Relevant Summarised Evidence) (Text)	
Source of Information:	Please select: Spontaneous Reports Post Marketing Study Clinical Trial Preclinical Study Other (please indicate)
PROPOSED ACTION AND ACTION TAKEN: (Text)	
INFORMATION REQUESTED: (Text)	

ADDITIONAL INFORMATION: (Text)
Please respond by --/--/--
Name of person responsible for sending message:

Template B

Logo and name of the Competent Authority of the Member State/EMEA

**ANSWER TO <*RAPID ALERT	NON-URGENT INFORMATION*> IN VETERINARY PHARMACOVIGILANCE**		
Reference:	N^{o} of attachments:	Date:
FROM:		
IN ANSWER TO THE ORIGINAL MESSAGE FROM <*MEMBER STATE*> DATED --/--/-- TO: (ALL) MEMBER STATES EFTA Countries concerned EMEA EUROPEAN COMMISSION CHAIR-CVMP RAPPORTEUR (if applicable) RMS (if applicable)		

Respond requested by originator for --/--/--

SUBJECT:

Please fill in the appropriate fields

Brandname(s): <*select* ★ | ❑ | ✣ | ◆>

International Non-proprietary Name (INN) or Class: <*select* ★ | ❑ | ✣ | ◆>

Strength(s):

Pharmaceutical Form(s) and Dosage(s):

Route(s) of Administration:

Therapeutic Classification (ATC code):

Marketing Authorisation Holder:

Indication(s):

**ANSWER TO <*RAPID ALERT	NON-URGENT INFORMATION*>:** (Text)
PROPOSED ACTION AND ACTION TAKEN: (Text)
ADDITIONAL INFORMATION: (Text)
Name of person responsible for sending message: