

## VETERINARY MEDICINAL PRODUCTS FOR FLUID THERAPY IN CASE OF DIARRHOEA

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Additional Notes	The objective of this document is to provide specific guidance in respect of the documentation of the efficacy of new veterinary medicinal products suitable for fluid therapy to influence concurrent diarrhoea. It should be read in conjunction with Directive 81/852/EEC as amended, and the note for guidance on <i>Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union</i> .

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# VETERINARY MEDICINAL PRODUCTS FOR FLUID THERAPY IN CASE OF DIARRHOEA

## 1. INTRODUCTION

For the purpose of this guideline the following definitions shall apply:

Fluid therapy:

The purpose of fluid therapy is to correct dehydration and/or electrolyte imbalances and/or metabolic imbalances and, if need be, energy losses. Such therapy additionally controls the incidence and severity of diarrhoea.

Veterinary medicinal product:

Veterinary medicinal products suitable for fluid therapy in the presence of diarrhoea are solutions for parenteral and oral administration containing electrolyte(s) only or electrolyte(s) with other compounds (e.g. glucose, glycine).

New veterinary medicinal products developed for fluid therapy to influence concurrent diarrhoea will have to satisfy all the usual requirements of approval. This guideline is not intended to replace the note for guidance: *Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union*, but to provide specific guidance in respect of the documentation of the efficacy of such veterinary medicinal products, and should be read together with Directive 81/852/EEC and the note for guidance: *Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union*. As multiple associations of electrolytes etc., such veterinary medicinal products also come under the category of fixed combinations.

However, it is necessary to consider this kind of product as an exception amongst fixed combinations as far as demonstrating the interest of the combination of electrolytes and nutrients is concerned. In fact, any demonstration aiming to compare the separate activities of each of these ingredients is irrelevant, because the combination of different components in a solution for fluid therapy is justified by the parallel losses and imbalances quantified in the animal suffering from diarrhoea. Therefore the applicant should justify, by literature review, product formulation with respect to essential nutrients (electrolyte, glucose, glycine).

Other ingredients claimed to be active which are not essential nutrients for the intended animal, e.g. soluble fibre for preruminant calves, must satisfy the requirements on fixed combination products.

## 2. STUDIES CONCERNING THE EFFECTS OF FLUID THERAPY ON THE TARGET ANIMAL

### 2.1 Experimental conditions

Where possible, the studies shall be performed on each target species in comparison with groups receiving products approved in accordance with requirements of Directive 81/852/EEC by a Member State of the European Union (positive control group). Trials should indicate untreated control groups to evaluate the rate of spontaneous cure of diarrhoea. The exclusion

of untreated control groups must be justified. The trials should be designed in such a way that the type of diarrhoea and concurrent therapy, if necessary, is the same for groups intended to be compared.

The observation period should cover a pre-treatment, a treatment and a post-treatment period of time suitable to control the evolution of the disease and, if claimed, of recovery.

If necessary, a wide variety of feeding and rearing conditions in accordance with standard practice in the European Union should be covered (e.g. intensive husbandry with feeding by milk or milk replacer and extensive husbandry with feeding by cow suckling a calf).

The tests performed must be described individually in detail and in accordance with Directive 81/852/EEC and the note for guidance: *Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union*.

## 2.2 Clinical trials

The clinical trials should prove that the fluid therapy is effective for the purpose claimed and is harmless to the intended animal. They should be performed taking into consideration the results of preclinical trials on target animal pharmacology conducted in accordance with the requirements of the note for guidance: *Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union*.

The rationale for the selection of the type of solution (kind and composition of active ingredients), the concentration (osmolarity of the solution and osmolarity of its electrolyte-components) and quantity of solution (dose level) and the dose intervals claimed to be optimally effective should be explained and justified for each indication claimed. The studies should demonstrate the effects of the final product.

The purpose of these studies is also to demonstrate the therapeutic range, possible adverse effects occurring under correct usage of the veterinary medicinal product taking into account different physiological conditions (e.g. neonatal) and the results of the preclinical studies.

In addition, local tolerance of products intended for parenteral administration should be examined.

Any further negative effects which occur during the experiment and the time of their appearance must be documented. However, generation of data should be decided on a case by case basis taking into consideration the choice of more suitable and/or additional parameters.

### 2.2.1 Pre-treatment period

Animal descriptive data should include rearing condition, breed, age, sex, and, if applicable, yield of animal produce, nutritional composition of the individual daily ration in terms of quality and quantity, physiological condition.

Case history and the results of clinical examination should be well documented (especially clinical signs such as the behaviour and appearance of the animal, body temperature, duration and frequency of diarrhoea, consistency and colour of stools, frequency of urination, colour of urine, possible vomiting, presence and character of thirst, fluid and dietary intake, suckling reflex, turgor of skin, nature and colour of mucous membranes and sciera, odour of the breath, and weight loss or gain, preceding therapy). These factors may be identified by a pre-defined scoring system.

Laboratory examination should include blood analysis, haematocrit, Na<sup>+</sup>, K<sup>+</sup>, Cl, HCO<sub>3</sub>, blood pH and blood glucose. From case to case further examinations in view of differential diagnosis and composition of active ingredients of the product may be necessary.

The diagnosis should be explained (differential diagnosis) and the disease should be reported in terms of clinical features, for example rated as degree of dehydration, hypo-, iso- or hypertonic dehydration, as justified by haematocrit, acid/base, pH disturbance, electrolyte imbalance etc., and by the degree of diarrhoea (using the relevant parameters mentioned above).

### 2.2.2 Treatment period

Fluid therapy, whether or not associated with a concurrent treatment (e.g. with antimicrobials) is to be initiated on diagnosis so that it will be possible to elucidate the degree of self-cure.

During treatment animals are to be checked for clinical signs and observations recorded. Samples of blood should be collected for laboratory diagnosis (see above for methods and parameters). In addition the feeding regimen must be reported in detail. The systemic tolerance of fluid therapy should be examined taking into account:

- extensive observation of behaviour, respiratory, digestive and cardiovascular functions;
- local irritancy at the injection site.

### 2.2.3 Post-treatment period

Animals are to be checked for clinical signs of remission and the observations should be recorded. The relevant physiological parameters should be monitored also by laboratory examination of blood (for clinical and laboratory parameters see above). Further samples should be taken at the end of the treatment period and again a few days later when the animal has resumed normal feeding.

## 2.3 Evaluation of the clinical response

Survival/mortality of treated and control groups should be documented.

An effective method for evaluation of the success of fluid therapy is the application of clinical judgement based on clinical and laboratory examination. A return to normal of clinical signs presented by the patient (e.g. turgor of the skin, eyeball etc.), improvement of consistency of faeces and of the various physiological parameters being monitored (e.g. haematocrit, ionogramm, alkaline reserves) indicate success of treatment.

The interval from treatment to desired clinical response should be reported.

Groups should be compared at least with regard to desired clinical response and the period until clinical response.