



Adopted by FEEVA GA on 18 May 2017

Adopted by FVE GA on 9 June 2017

FEEVA / FVE position
for improving availability of medicines bringing added clinical benefit
for treatment in horses

Request to include tenoic acid, phenylbutazone for systemic use and tetracaine, tetryzoline, synephrine, rifamycine, polymyxine B for ophthalmic use on the list of substances bringing added clinical benefit for treatment in horses.

The therapeutic arsenal of medicines for horses (food-producing species in the European Union) is limited. Considering this, the EU has provided specific regulations for the horse industry to derogate from the principle that food animals can only be treated with active substances for which a Maximum Limit of Residues (MLR) has been established. Therefore, Regulation (EC) No 1950/2006 of 13 December 2006 in accordance with Directive 2001/82 / EC of the European Parliament and the Council on the Community code relating to veterinary medicinal, establishes a **list of essential substances** and **substances bringing added clinical benefit for the treatment of horses**.

The '**essential and clinical benefit list**' in Regulation 1950/2006 allows the treatment of horses whose meat or products are intended for human consumption with listed substances. Substances included in this list are considered as essential for the treatment of equine diseases and/or present additional clinical benefit, even if they don't have a defined MRL. In these cases, a **waiting period of six months** must be respected before sending treated animals for human consumption.

According to the legislation substances bringing added clinical benefit may be used, for the specific disease conditions, based on improved efficacy or safety or a major contribution to treatment compared to other products authorized for Equidae.

The French Equine Veterinary Association (AVEF) reported¹ that seven substances bringing additional clinical benefit to the treatment of horses because of their therapeutic

¹ AVEF 'Argumentaire relatif à l'extension de la liste des substances à bénéfice clinique supplémentaire' – available upon request (in French)

interest were missing in the 1950/2006 Regulation. The seven substances are listed in Annex I, with references to studies showing their clinical benefit.

The French authorities commissioned the French National Agency of Health Security of Food, Environment and Labour (ANSES) to assess whether or not, after the use at recommended doses and a waiting a period of 6 months, these substances don't have any significant risk for public health. In its opinion 2015-SA-0104 delivered on 31 March 2016, ANSES concluded that for seven substances "*the results of the evaluation show that 'the risk of these drugs for the consumer with a 6-month withdrawal period after administration in horses is considered acceptable, given the level reached which is well below the threshold of toxicological concern in humans.'*"

More details on the ANSES study can be found in Annex II.

Seen the added clinical benefit given by these seven substances and the ANSES opinion on their safety, FVE and FEEVA strongly advise the European Commission to extend its list of substances by including these medicines.

This is a necessary step to increasing the availability of medicines for horses. Although horses are a minor species, the availability of medicines should reflect their dual role in European society as a food-producing species and as companion animal in the economically important horse leisure and sport industry. Veterinarians and the horse industry are adamant that these additional medicines are essential in maintaining the health and welfare of European horses and it is hoped that introducing these new measures in the revised EU medicines legislation will facilitate this objective.

Annex I: Seven substances considered in the ANSES opinion

Product	Therapeutical Classification	Indication in horse	Added clinical benefit	Therapeutic regimen
Tenoic acid	Antiseptic, antimicrobial	Injectable antiseptic & antimicrobial adjuvant for systemic use in pulmonary infections	The only known product being antiseptic, expectorant and trophic working in synergy or even increasing the activity of the antibiotic in respiratory treatment ref : WEAS congress Calgary, C Scicluna (2013)	20 ml IV / horse 3 to 5 days
Phenylbutazone	Analgesic, antipyretic & non-steroidal anti-inflammatory agent	To alleviate pain pre- and post-operative and best treatment chronic laminitis	The only drug licensed and the most efficient drug for chronic laminitis in horses, one of the more painful and hardest pathology to manage, in which treating pain effectively and helping the horse with more comfort is major for welfare maintenance. Real interest in equine endotoxemia and potentialization of flunixin for better anti-inflammatory treatments. ref : The equine hospital, Kevin Corley (2009) ; Equine acute abdomen, N White (2009) ; Am J Vet R, KG Keegan (2008); Pharmacol Res, Berreta C (2005)	1-4 mg/kg pO or IV 5 to 10 days
Tetracaine	Anaesthetic	Local eye anesthetic used for diagnosis and surgery	The only known product inducing anesthesia very quickly, which allows to handle these painful animals which are difficult to handle safely.	Ophthalmic drops 1-2 drops, 3 to 15 days
Tetryzoline	Vasoconstrictor, Sympathomimetic agent	Induces vasoconstriction & antiseptic adjuvant when used locally in inflamed eyes	Local effect for faster and more efficient treatment than any other systemic anti-inflammatory therapy.	Ophthalmic drops 1-3 drops 3 to 15 days
Synephrine	Sympathomimetic agent with vasoconstrictor and decongestant properties	Induces vasoconstriction & antimicrobial adjuvant to help in treatment diffusion in eye infections	Local effect, for faster and more efficient treatment than any other anti-inflammatory systemic therapy and unique local antimicrobial synergy with or related antibiotics.	Ophthalmic drops 1-2 drops 3 to 15 days
Rifamycine and Polymyxine B	Antimicrobial	Antimicrobials treatment for local treatment in bacterial eye infections, bacterial keratitis and corneal ulcers.	Specific local treatment of specific bacterial eye infections, (e.g.Gram-negative infections) for topical use, allowing to reduce doses required for systemic treatment and so help in the fight against antibiotic resistance.	Ophthalmic drops 1-3 drops 3 to 15 days

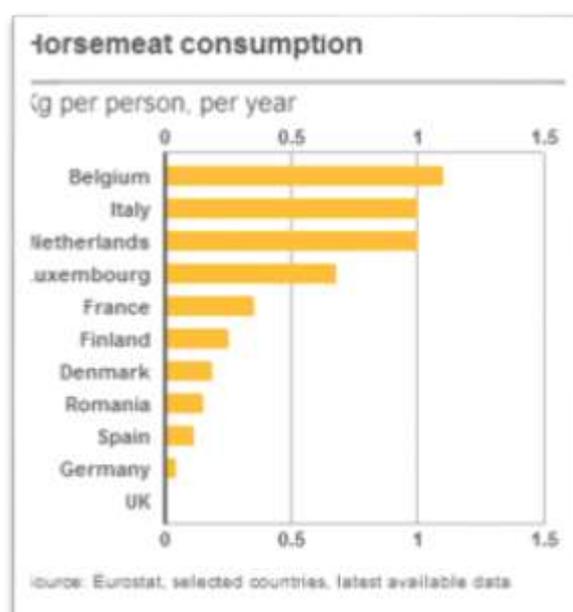
Annex II: About the toxic risk of seven drugs for the consumer

1- OPINION of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on the “Request concerning extension of the list of substances with additional clinical benefit to other substances of interest in equine medicine” (No 2015-SA-0104)

On 31 March 2016, ANSES released its opinion on the request concerning the extension of the list of substances with additional clinical benefit. They

The aim was not to establish MRL but rather to characterise consumer exposure 6 months after veterinary treatment and compare exposure with a toxicity reference value (TRV). Exposure of consumers was evaluated based on available concentrations observed in tissue for consumption or, if these data are not available, on the basis of plasma concentrations. In some cases, when there are no data for tissues or plasma, an overall approach to exposure is adopted whereby we considered that the entire amount administered is found in the animal. This is a pragmatic risk assessment tool that is based on the principle of establishing a human exposure threshold value for a chemical below which there is a very low probability of an appreciable risk to human health.

ANSES analysed the exposition risk for the consumer at 6 months (from tissues or plasmatic rates concentrations and/or global entire exposition) after systemic use of tenoxic acid and phenylbutazone at recommended dosages in horses, and the local ophthalmic use of tetracaine, tetrazoline, rifamycine, synephrine and polymyxine B, and compared it to a reference toxicological value (published or estimated at 1,5 mg/ people/day).



The full opinion can be found on <https://www.anses.fr/en/system/files/MV2015SA0104EN.pdf>

2- EFSA and EMA joint statement (2013)

In respect public health risk to phenylbutazone, EFSA and EMA² pointing out in 2013 that *‘the risk of carcinogenicity to humans from exposure was considered very low based on the available experimental data on organ toxicity and carcinogenicity, as well as on the low exposure levels and the infrequent exposure to phenylbutazone from horse meat or*

² <https://www.efsa.europa.eu/en/press/news/130415>

adulterated beef-based products'.

3- Scientific papers

- Phenylbutazone in horses and man : Properties relevant to safety of humans consuming horse meat containing phenylbutazone and its metabolites
P Lees, PL Toutain, Equine vet. Educ. (2013) 25 (11) 545-549
- Pharmacokinetics, pharmacodynamics, metabolism, toxicology and residues of phenylbutazone in humans and horses
P Lees, PL Toutain, The Veterinary Journal 196 (2013) 294–303