

Therapeutic gaps in the Horse sector

Hearing of 20/11/23

Participants: Laurent Mangold (Vice-President AVEF, antibiotic expert, veterinary practitioner in Argonnay), Claire Scicluna (AVEF therapeutic commission, veterinary practitioner in Oise)

Excused: Charles-François Louf (President AVEF, veterinary practitioner in Vosges), Marie-Noëlle Lemouland (representative of SNGTV), Séverine Boullier (Professor ENVT, representative of CSMV), Stephan Zientera (Anses Head of the laboratory at Maisons-Alfort – Dozulé),

for the ANMV: L. Baduel, B. Leroux, M. Salery, H. Ait Lbacha, S.Rougier, L. Fabry

Reminder of the responsibility for the comments made during the hearing and reported in this report:

- The identification of therapeutic gaps (and details of situations expressed and alternatives considered) is the responsibility of the representatives of the veterinary profession
- The ANMV provides additional information or answers to the technical and regulatory questions addressed. These supplements are systematically preceded by "Info ANMV : ... to distinguish the origin of the words expressed.

Table summarising the comments of the representatives of the veterinary profession (*new elements since the last hearing – in blue*):

Disease	Problem encountered: PhV: Pharmacovigilance (efficacy or safety perceived as unsatisfactory) Disp: Availability, shortage Reg: Regulatory (cascade application, withdrawal period, restricted access) 0 VMP: Absence of <u>appropriate</u> veterinary medicinal products (VMPs) 0 TS: Lack of therapeutic solution	Problem Type: PhV, Disp, Reg 0 VMP 0 TS	Alternatives identified	PRIORITIES Major: M minor: m (see p8)
IV injectable penicillins_ for intensive care.	Need for non-critical ATB (penicillin sodium or amoxi-cilline) that can be administered <u>IV</u> . There should be a 1st line ATB that does not risk laying horses on the ground and is injectable by the IV route <i>For reference:</i> MA discontinued for CLAMOXYL 5G in 2009. PENETAVET stopped. BELCOPENI 5 (Benzylpenicillin sodium + colistimethate, for all species, and slow IV) no more marketed since 2017. "Cascade" use of drugs for cattle impossible for various reasons: - pénéthamate (STOP M, PENETHAMATE, PENETHAONE, PERMACYL, REVOZYN): indicated in IM only and contraindicated in IV (suspensions). - Penicillin procaine and benzathine unusable: risk of neurological reactions (procaine), significant shock if the product passes into the blood during injection with a risk of a very violent reaction by the animal (unacceptable for any valuable horse) and local reactions and pain ++ during IM injection.	0 VMP Disp/ Reg	Use of critical antibiotics: marbofloxacin, EXCENEL or COBACTAN is forbidden. Purchase of "human" penicillin sodium possible at Panpharma, but out of price. Access to "human" Clamoxyl denied by Panpharma. ANMV info: see information on the ANSM website: - CLAMOXYL 1g shortage since 05/04/22 - supply tensions since 10/10/22: "Amoxicillin, alone or in combination with clavulanic acid, is subject to high pressure or even shortage. They concern the whole of Europe."	M n° 1 or 2

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	<p>Inappropriate dosages on SPC for penicillins ("see 100 publications in the US"): experience of therapeutic failures with 10 days at a SPC dosage, resolved in 3 days of the same treatment with an increased dose.</p> <p>Dosage to be reviewed (see Elodie Lallemand's work at ENVT) No PhV statements as the problem is well known and vets are not used to making statements for lack of efficacy.</p> <p>ANMV note: It is important to report this type of declaration of lack of efficacy to the ANMV, in order to have data that justify the need to update the dosages.</p> <p>The authorities are aware of the need to revise the dosages of certain "old" ATBs but the implementation also depends on the investments to be made to carry out the studies necessary to justify new dosages and assess the impacts in terms of withdrawal period (WP), antibiotic resistance (ABR) and environmental safety.</p> <p>ANMV post-meeting info: Since the publication in 2017 of the ANSES report on the review of the dosages of old antibiotics, work with the European Medicines Agency (EMA) is underway. At the Committee for Veterinary Medicinal Products (CVMP) in December 2023, a questionnaire was adopted, with the aim of collecting evidence of lack of efficacy of antibiotics at the authorised dose. This questionnaire will soon be sent to many stakeholders, including the Federation of European Veterinarians (FVE). The aforementioned observations can be reported and documented in this reflection in order to feed into the prioritisation exercise for substances to be reviewed. The deadline for responding to the European questionnaire is 1 June 2024.</p>	PhV	<p>ANMV post-meeting note: For equines, one of the objectives of the Ecoantibio 3 plan is to better assess exposure by considering the specificities of the sector and to continue to promote the reasoned use of antibiotics.</p> <p>The ANMV is also a pilot of Action 14, which aims to consolidate existing antibiotic exposure indicators and also to improve and optimise these indicators by animal sector and sub-category, by putting in place an indicator more suited to the specific characteristics of certain sectors such as the equine sector. The collection of usage data via Calypso should ultimately make it possible to assess exposure by sector more precisely.</p>	
Leptospirosis	<p>Vaccine exists in the US (Zoetis). Would avoid antibiotic treatments.</p> <p>Resurgence of seropositive horses according to some opinions from the field. It is a zoonosis with compulsory declaration in humans (since 24/08/23), but with a low zoonotic risk.</p>	0 VMP	<p>Curative treatment: tetracycline, penicillins or doxycycline.</p> <p>⇒ Registration of the US vaccine to be promoted in the EU (market > West Nile vaccine and ≈ ½ influenza market). See RESPE epidemiological data, EU & US figures.</p>	<p>M n° 2*, 3 or 4</p>

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	Clinical expression of the infection related to the direct action of leptospira, rare according to ENV, poorly detected in the acute phase.		Monitoring network planned with RFSA, involving AVEF, RESPE, AFVAC & QualitéVet. * "To make progress", it is important to think about the vaccine (which exists in the USA), at least to ensure consistency in the work at the RFSA and with the Ecoantibio plan (reduction in the use of antibiotics in equine). ANMV info: no request of import authorisation recorded neither new marketing authorisations since last meeting	
Tetanus	Marketing discontinuation by Boehringer Ingelheim (formerly Merial) of their tetanus serum. Unacceptable situation: veterinarians must let mares die from tetanus. Why no obligation to sell marketing authorisations? ANMV info: since the last meeting: recurring disruptions on Equip artevac; disruptions then discontinuation of the marketing of equine trivalent serum and anti-tetanus serum 300 => only Tetaniserum 150 remains: very, very fragile situation.	1 VMP	More than just one specialty, less dosed, marketed by CEVA: TETANISERUM 150. If any shortage occurred: no alternative. However, the horse is the most sensitive species to tetanus. There is no more tetanus toxin.	M n° 1, 2 or 4
Shock	SOLUMEDROL (methylprednisolone) stopped	(0 VMP)	Dexamethasone but with risks of laminitis	M n° 3 or 4
Osteoarthritis	Wish to have injectable ZEEL and TRAUMEEL: do not forget that we need simple, cheap and non-harmful products to relieve the horse's osteoarthritis. Some homeopathic specialities mentioned opposite are regularly used in France, but do not have MA. Some have a MA in countries other than France.	Reg	Traumeel gel obtained MA in France 3 years ago. Homeopathic specialities, particularly arnica-based, with references in humans and animals, including horses for several decades. Products manufactured by the Heel laboratory in Germany and available abroad. These products are useful for the treatment of synovitis, joint and paravertebral pain in horses, including in the long term, without the deleterious effects of corticosteroids on cartilage, and at a reasonable cost. The regularisation of the status of these products would allow the situation to be regularised when they are used in the field. Clinical studies for an objective evaluation of efficacy in practice may be put in place if necessary to support the dossiers.	M n° 5 or m
Asthma	Problems with administration of ASERVO => pharmacovigilance reports to be made. Non-recyclable device + high cost...	PhV	Autologous treatments (interleukin) => specify which devices and/or which molecules: prepared by the 'Animal Immune' company that has gone bankrupt. Experience of a vet on 8	M n° 5 or m

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	<p>Desire for further solutions and clarification of what is known as "asthma".</p> <p>ASERVO is often no longer used due to disappointments about efficacy or adverse effects on horses or users, due to difficulty in application.</p> <p>ANMV Info: It is important to report to ANMV this type of declarations of lack of efficacy or adverse events on the horses or on the user.</p>		<p>horses with variable results)</p> <p>=> continue to work on blood derivatives</p> <p>Field use of "Boldair" inhaler of pine essences.</p> <p>Why are there no medical devices that can be used in horses in France, unlike in other European countries? It is important to find a solution for these treatments that ultimately customers buy and do on their own, while veterinarians cannot prescribe or use them, as this would be outside the legislative framework.</p> <p>ANMV info: no new MA since last meeting. There is currently no status for animal health medical devices.</p>	
Abscesses or chronic corneal ulcers	<p>Frequent shortages for the available eye drops or ointments. Ophthalmic ointment for dogs with ciclosporin with too low concentration (0.2% instead of 2% desired)</p> <p>ANMV Info: sterile eye drops are ordered to be manufactured by certain hospitals with substances that are not legally authorised in veterinary medicine (e.g. voriconazole, 5 FU, mitomycin C, ceftazidime, amphotericin B)</p>	Disp	<p>Prescription of "reinforced eye drops" (highly concentrated) in extemporaneous preparation with enilconazole + gentamicin + NAC.</p>	m
Induction lactation	<p>Need for a veterinary medicine (small market).</p> <p>Anecdotal and a solution exists in human medicine</p>	0 VMP	<p>Domperidone is less effective but works.</p> <p>Human drug: sulpiride (injectable form stopped, only available in tablets).</p>	m
Botulism (very rare)	<p>No vaccine or equine serum available</p> <p>Very rare.</p>	0 VMP	<p>Possible import of an ANTRAVAX bovine vaccine</p> <p>ANMV info: no import requests since last meeting</p> <p>Bovine serum</p>	m
Chemical castration	<p>Vaccine reactions with IMPROVAC (not reported as known and predictable). There is currently no strong demand but there is a risk of coming in a general context of taking animal welfare into account. Limited market but responding to societal demand.</p> <p>Only IMPROVAC bottle available from 100 to 1000 doses (10*50 doses = €800) => Use of a bottle shared between several veterinary practices...</p>	0 VMP	<p>IMPROVAC (it is already a solution, even if it is expensive).</p> <p>Report the declarations of adverse events. There is EQUITY in Australia and NZ (less AEs than IMPROVAC?).</p> <p>ANMV Info: Improvac was concerned by a EU signal in August 2022 concerning mortality in horses: 4 cases between 01/12/19-30/06/22. In 2 cases, this followed an anaphylactic reaction. In the other 2 cases, anaphylaxis is strongly suspected. Section 3.5 of the SPC has been updated to add a warning for use in horses. All AEs combined in horses, there</p>	m

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			are in total (up to now) 18 cases in the European database, of which 11 in EU but no cases in FR.	
Respiratory tract mycoses	Nystatin? no antifungal drugs in veto inhalation.	0 VMP		m

Therapeutic gap: resolution in progress with existing solution	Initial problem	Type of problem	Solution / Alternatives Reason for: Resolution in progress / Removal of the therapeutic gap	Initial GAP priority Major: M minor: m
Rhodococcosis	Expected vaccine. Avoid the use of critical antibiotics. Veterinary erythromycin not always effective and risk of diarrhoea in the foal. Efficacy of self-vaccines to be evaluated. <i>Pay attention to diagnosis</i>		See sheet AVEF => Péni Genta. According to ATB Gram. Framework reviewed in the ATB good practices In curative mode: human: azithromycin/ tulathromycin + Rifampicin. ANMV info: no new MA granted since last meeting	m
Piroplasmosis	CARBESIA: the withdrawal period of 213 days for cattle is not applicable in practice.			
Myosites	Vit E not very effective. A dantrolene-based VMP would be a plus. ANMV info: list of essential substances under evaluation in EU		Increasingly rare myosites (thanks to food supplements) Animal Health or Human M: Dantrolene (DANTRIUM)	
Antibiotic against anaerobes (pleuropneumonia)	Need for a metronidazole-based (IV?) VMP <i>Only for horses not intended for human consumption</i> ANMV info: no new MA granted since last meeting		OK for oral route (50 mg/kg/3x per day) Active substance (powder) could be purchased at vet distributors for extemporaneous preparations Human MP (tablets)	
Mycotic keratitis	Need for a VMP suitable for ophthalmic application. Rare problems ANMV info: no new MA granted since last meeting		M human injectables: natamycin or fungizone	
Alpha2agonist antagonist (detomidine)	A VMP would be welcome. (interest?) ANMV info: no new MA granted since last meeting		Atipamezole OK	
Chondroprotection	Triamcinolone is the only corticosteroid considered as chondroprotective (with appropriate dose) for intraarticular injection. No such VMP for horses. The VMP CANITEDAROL- dog, cat based on triamcinolone diacetate is no longer marketed. The chondroprotective effect seems controversial according to the latest scientific publications.	(0 VMP)	VMP with triamcinolone available in the US => why not in Eu? Human medicine based on triamcinolone acetonide (Kenacort Unidose <u>40</u> or 80 mg accessible in pharmacies, €6-7)	M n° 2

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	<p>If necessary, inform the EMA of the value of its inclusion on the list of essential substances for equidae.</p> <p>ANMV Info: There is a dog/cat VMP approved in NL (no MA in France): Cortalone, 10 mg/mL suspended voor injected voor honden with katten.</p> <p>Post-meeting note: If this is of interest to some practitioners, it is possible to send import authorisation requests to the ANMV. But no LMR status => butcher sector excluded.</p>		<p>New VMPs with stem cells (Articell Forte and Horstem) with different indications (osteoarthritis and cost +++).</p>	
<p>Chondroprotection (Synvet access)</p>	<p>The distribution of Synvet in France has been suspended: can it be obtained in Belgium or should an import request be made?</p> <p>Reminder: just one other VMP with hyaluronic acid (HYONATE): if shortage => possible use of only 1 human medicine via the cascade.</p> <p>+ Problem with the multipuncture HYONATE bottle => intra-articular risks, for some. When is an MA for single-dose HYONATE for intra-articular inj., IV & IM? Human medical devices in single-dose syringes, more satisfactory for some veterinarians, less expensive but prohibited for veterinary use for regulatory reasons.</p>	<p>Disp</p>	<p>ANMV Info: Synvet has a marketing authorisation in France, it is therefore possible to obtain one from Belgium without using an import request (if labelling in French).</p>	<p>M n° 2</p>

For reference: Other questions/requests (from the last meeting of 19/10/21):

- **Difficulties in the veterinary use of products without MA, legally not authorised in the first line** when VMPs exist, e.g.:
 - Hyaluronic acid in single-dose syringe (medical devices for humans – see above)
 - Sarapin used as an analgesic during neuralgia, back pain (used in humans in the US).
ANMV info: as this is a plant, refer to ongoing work on phytotherapy
 - Athramid Vet (medical device in the US – polyacrylamide hydrogel), without MA in EU.
MA in Australia: possible request for import authorisation
- Use of homeopathic drugs to be clarified / recent positioning of CNOV
- Access to the BCG in pharmacies for sarcoids
Info from Rémy Steinbrecher sent by CI Scicluna on 05/01/22: “the CSP company, which operates this specialty and the company for which I work, receives regular requests from veterinarians for the use of this specialty.
We can respond favourably to their request, without calling into question the public health programme for vaccinating young children at risk of tuberculosis. »
Info L. Mangold of 06/01/22: “Information taken from the reference persons in my team, this product is actually used and gives good results (testimonial). Clearly

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widely used in Belgium. "

ANMV Info: The drug BCG AJ Vaccines (100 times less concentrated than other specialties for oncology purposes) is authorised in France for humans and is not included in a restricted prescription category. It is therefore accessible to veterinarians by order for professional use from a retail pharmacy. DGS info of May 2022: the supply of veterinarians with this product is not possible due to the quota.

- RELAQUINE: administration difficulties with the bottle, which replaced the syringes (much more suitable, even if air bubbles were found during quality controls on the market because without consequences in this case). Very useful product (must be kept). It is important to consult the AVEF prior to proposals for such changes in presentation by the MA holder.

ANMV info: There are alternatives in syringe packaging i.e. Promased & Tranquigel

- Undeclared / anticipated shortages

ANMV post-meeting note => information to be systematically reported to the ANMV as soon as possible (internet address: DQ_ANMV@anses.fr) by MAH but also by vets, if necessary.

- Doxycycline: bioavailability/efficacy in horses? long oral treatment practices (Lyme) => substantive work to be planned on this subject

Library info: Yung-Fu Chang et al (2005) suggest a better efficacy of oxytetracycline at 5 mg/kg/d compared to 10 mg/kg/d doxycycline and 2.2 mg/kg/d ceftiofur. No clinical justification, but only on the basis of necropsy, PCR and serology. n=16, i.e. four ponies per group.

- Issues with borderline claims on non-drugs

ANMV post-meeting note => Internet address for declaration and management by the ANMV (Market Surveillance Unit): usm@anses.fr

ANMV info: no issues reported to ANMV since last meeting

- Complicated access to centralised AMMs *via* iRCP which returns to the site of the EMA which is not very easy to use

ANMV post-meeting note => detailed procedure by clicking on the top right of the screen (to the left of the question mark) on "[RCP of centralised AMMs](#)"

It would be necessary to have easy and fast access to withdrawal periods when prescribing VMPs submitted through the centralised procedure.

ANMV info: a "tutorial" is being written and will be put online soon.

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Prioritisation of gaps by representatives of the veterinary profession (excluding ANMV)

Prioritisation according to external participants	Laurent Mangold	Charles-François Louf (excused absent)	Claire Scicluna	Marie-Noëlle Lemouland (excused absent)	Séverine Boullier	Stephan Zientera (excused absent)	PRIORITIES in 2021 Major: M minor: m
Gaps identified							
IV injectable penicillins for intensive care	M n°1	M n°1	M n°1	M n°1	M n°2	M n°1	M n°1
Leptospirosis	M n°2	M n°2	M n°2 ("to get things moving")	M n°3	M n°4	M n°3	m
Tetanus	M n°4	M n°4	M n°4	M n°2	M n°1	M n°2	(Gap not mentioned)
Shock	M n°3	M n°3	M n°3	M n°4	M n°3	M n°4	(Gap not mentioned)
Osteoarthritis	M n°5	M n°5	M n°5	m	m	m	(Gap not mentioned)
Asthma	m	m	m	M n°5	M n°5	M n°5	m
Chondroprotection	m	m	Resolved ("SYNVET available, even if not distributed in FR")	m	m	m	M n°2
Abscesses or chronic corneal ulcers	m	m	m	m	m	m	(Gap not mentioned)
Induction lactation	m	m	m	m	m	m	m
Botulism (very rare)	m	m	m	m	m	m	m
Chemical castration	m	m	m	m	m	m	m
Mycoses respiratory tract	m	m	m	m	m	m	(Gap not mentioned)

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Changes in gaps since the last meeting in October 2021:

Favorable trend for:

- Chondroprotection, concerning access to Synvet, possible from Belgium without import authorisation, due to the existence of MA in France

Less favorable trend for:

- Leptospirosis, a notifiable zoonosis in humans since 08/24/23, to be considered as a major gap to raise awareness of the vaccine requirement (exists in the US)

Addition of several major or minor gaps:

- tetanus (very fragile situation with only one anti-tetanus serum left), shock (discontinuation of methylprednisolone), osteoarthritis (MA request in France for injectable or oral homeopathic medicinal products), abscesses or chronic corneal ulcers (concern for availability), respiratory tract mycoses

	Meeting of 19/10/21	Meeting of 20/11/23
MAJOR priorities	<ol style="list-style-type: none"> 1. Non-critical IV injectable antibiotics for intensive care 2. Chondroprotection 	<ol style="list-style-type: none"> 1. IV injectable penicillins for intensive care 2. Leptospirosis 3. Tetanus 4. Shock 5. Osteoarthritis or Asthma
minor priorities	<ul style="list-style-type: none"> • Leptospirosis • Asthma • Induction lactation • Botulism • Chemical castration 	<ul style="list-style-type: none"> • Induction lactation • Botulism • Chemical castration + Abscesses or chronic corneal ulcers + Respiratory tract mycosis
Resolution in progress	<ul style="list-style-type: none"> • Rhodococcosis • Piroplasmosis • Myosites • Antibiotic against anaerobes (pleuropneumonia) • Mycotic keratitis • 2-agonist αantagonist (detomidine) 	<ul style="list-style-type: none"> • Rhodococcosis • Piroplasmosis • Myosites • Antibiotic against anaerobes (pleuropneumonia) • Mycotic keratitis • 2-agonist αantagonist (detomidine)
Existing solution	<ul style="list-style-type: none"> • Immunostimulator 	<ul style="list-style-type: none"> ☑ Chondroprotection (Synvet access) : import possible from Belgium, without authorisation request (MA in Fr)