

Therapeutic deficiencies in the Dogs/Cats/NCA sector

Meeting of 15/12/2022

Participants: Jean François ROUSSELOT (AFVAC President, expertise in cardiology); Eric GUAGUERE (veterinary practitioner, dermatology specialist, AFVAC Vice-President); Sylvain LARRAT (veterinary practitioner, NCA specialist); Erik ASIMUS (ENVT lecturer, surgery specialist, AFVAC Continuing Education Vice-President); Christophe HUGNET (veterinary practitioner, CSMV representative). Excused: Séverine BOULLIER (ENVT, CSMV representative); Claude BEATA (veterinary practitioner, behaviour specialist); Dan ROSENBERG (veterinary practitioner, expertise in endocrinology, oncology), Claire Beaudu-Lange (veterinary practitioner, expertise in oncology)

of which ANMV Laure BADUEL, Mariette SALERY, Anne SAGNIER, Laurent FABRY, Jacques BIETRIX. Excused: Paule CARNAT-GAUTIER, Sophie BARRETEAU

General remarks:

Impact Reg 2019/6: A new update of the Appendices to the order of 08/08/12 amending the order of 29/10/09 listing drugs subject to restricted prescription is finally no longer relevant. Indeed, **the procedures for publishing the list of drugs with restricted prescription (RP) are currently being revised** by ANSM/ANMV/DGAL/DGS due to the articulation of the European Regulation 2019/6 with the national provisions relating to RP. **Progress expected in 2023.**

The drafting of arguments for the inclusion of new substances remains current, if this has not already been done, **as soon as the planned advances materialise.**

It should be noted that **antimicrobials reserved for humans cannot be prescribed** as part of the “cascade” (according to Art. 112.1.b).

The use of extemporaneous preparations remains possible (see Art. 112 1.c) and **is facilitated by the possibility of subcontracting to a retail pharmacy.**

Post-meeting notes

Pathology	Species concerned Dog (CN) Cat (CT) New pets (NCA)	Problem encountered by the sector*: PhV: Pharmacovigilance (perceived unsatisfactory efficacy or safety) Disp: Availability, shortage Reg: Regulatory (cascade application, waiting time, restricted access) 0 VMP: Absence of <u>appropriate</u> veterinary medicinal products 0 TS: Absence of therapeutic solution	*Type of problem PhV Disp Reg 0 VMP 0 TS	Alternatives identified	PRIORITIES: MAJOR: M minor: m
FIP (feline infectious peritonitis)	CT	No treatment available	Reg	GS-441524 (otherwise Remdesivir or Mutian X) The use of Remdesivir is already accepted in the UK	MAJOR Group 1
High-grade B lymphoma	CN	Wish for Tanovea in 1st line or relapse; registered for CNs in the USA (Elanco), no European marketing authorisation	0 VMP		MAJOR Group 1
EPO deficiency anemia (end-stage renal disease)	CN, CT	Darbopoietine not accessible (to avoid misuse of human drugs (HM) containing EPOs, particularly in the context of sports doping in humans). Not mentioned in Annex I of the order amending Art 5141 -112, an argument has been drafted for the addition of the injectable form to the list of RP drugs applications (transmission in March 2020)	Reg	Transfusion	MAJOR Group 2

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Vasoplegic shock	CN, CT	Norepinephrine in RP for dental use. Only accessible in CHUV. This medicinal product should be accessible to all veterinary care facilities. Otherwise, sometimes fatal for dogs/cats Argument sent on 04/12/20 by I. Goy-Thollot (VetAgroSup) for an application for inclusion in Appendix I. Progress expected in 2023 (see General Remarks above).	Reg	Adrenaline (but more species-dependent action). Norepinephrine only accessible in CHUV	MAJOR Group 2
Analgesia (cervical pruritus)	CT	Desire for veterinary anti-pruritis suitable for cats, when there is no response to existing analgesics (rapid effect of corticosteroids, slower for cyclosporine). No cat indication for oclacitinib (APOQUEL) due to side effects in this species.	(0) VMP	Gabapentin (human drug) oral route , but excipient poorly tolerated.	MAJOR Group 3
Difficulties accessing the drug					
Anti-cancer	CN, CT	Access to human drugs* subject to RP, reserved for hospital prescription (see general remarks in introduction => progress expected in 2023) *see opposite: substances proposed by ANMV (March 2020) for inclusion on list III in Article R. 5141-122 of the CSP.	Reg	Bleomycin*, dacarbazine*, epirubicin*, etoposide*, 5FU*, vinorelbine* , Gemcitabine, Procarbazine, Temozolomide, Actinomycin D, Mechlorethamine, Docetaxel, Bortezomib, Thalidomide. Recombinant asparaginase*	MAJOR (Difficult to classify)
Lymphoid leukemia	CN	Chlorambucil (CHLORAMINOPHENE) in hospital reserve (passage 01/07/19 on hospital prescription) "For the time being, we are managing to have some but it may be stock in the pharmacies". Claude Muller (11/12/22).	Reg	Simple, effective, well tolerated and inexpensive conventional chemotherapy.	MAJOR Group 2
Ventricular arrhythmias	CN	Oral Mexiletine not available (no access in France). Also requested by GEN AFVAC (17/05/22), even if it "will not solve the price problem"	Reg	Oral mexiletine (human drug - no equivalent VMPs available). Progress planned during 2023 on RP => rationale to be drafted, if necessary	MAJOR Group 3
New immunomodulators (immune glomerulopathy, idiopathic polyarthritis)	CN/CT	Mycophenolate mofetil and Leflunomide Need for alternatives or supplements to corticosteroids and cyclosporine in the event of failure, contraindication or need for combination. Particularly relevant in immune glomerulopathy and idiopathic polyarthritis respectively	0 VMP	No real alternative in terms of tolerance and efficacy	MAJOR Group 3
Mainly serious gastrointestinal infections, infections	CN, CT	Restricted prescription (RP) for metronidazole injection (IV) – uncommon.	Reg	Metronidazole IV (human drug) in a hospital emergency (access to RP)	minor

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caused by anaerobic bacteria		Also requested by GEN AFVAC (17/05/22) for the management of metabolic disorders and portosystemic shunt			
Hypoalbuminemia	CN, CT	Human albumin 5% IV: Not accessible	Reg		minor
Epilepticus status	CN, CT	Phenobarbital 200 mg/4 ml IV: Hospital reserve List II Also requested by GEN AFVAC (17/05/22) Midazolam IV: Hospital reserve, possible orders	Reg		minor
Epilepticus status (shunt)	CN, CT	Levetiracetam IV: Hospital reserve List I, possible orders. Also requested by GEN AFVAC (17/05/22)			minor
Dysuria (bladder atony)	CN, CT	Oral betanechol: not marketed in France, preparation possible in some pharmacies. Also requested by GEN AFVAC (05/17/22) for the treatment of detrusor hypotonia	0 VMP	Extemporaneous preparation of betanechol	minor
Dysuria	CN, CT	Oral alfuzosin: wish for a veterinary presentation	0 VMP	Prescription of the human drug (URION, XATRAL & generics)	minor
Gastric ulcers (antiacids)	CN, CT, NCA	No omeprazole with MA for CN, CT or NCA => Frequent cascade. Wish for a veterinary presentation	0 VMP	Omeprazole, pantoprazole IV and oral, esomeprazole (human drugs). "Cascade" prescription facilitated with NVR.	minor
Monovalent vaccine	CN, CT, NCA (ferret)	Monovalent vaccine does not exist for: C, H, P, Pi. However, the scientific durations of immunity are not the same, and this would prevent overvaccination in a context of opposition to vaccination in France. R, C and P in cats where the difference in duration of immunity is even more obvious than in dogs (almost 9 years on typhus, compared to about 3 years depending on the epidemiological conditions of the RC) Also true for distemper vaccine in ferrets – many allergic shocks during vaccination in this species with a multivalent vaccine, risk increased by unsuitable vaccines.	(0) VMP	The demand for monovalent vaccines is rather at odds with recent MAs, although the investment would be minimal to register a monovalent vaccine from a polyvalent vaccine dossier. However, this seems utopian for market rationales.	minor
APE fleas/ticks in tablets API Toxocara	CN, CT	Lack of targeted and not broad-spectrum presentations against: APE: fleas ± ticks in tablets API: against toxocarosis, nematocide alone (significant zoonotic risk), which would also be larvicide in tablets and spot-on, for dogs and cats while it only exists in combination with other actives	(0) VMP	Wish for monovalent parasiticides, which is rather at odds with recent Mas, although, as for vaccines, the investment would be minimal to register a monovalent from a polyvalent product dossier. However, this seems utopian for market rationales.	minor
Analgesia, well-being, quality of life	CN, CT	Oral buprenorphine, Tramadol LP, Cannabidiol extract: wish for a VMP	0 VMP	Dietary supplements with cannabidiol (without therapeutic claim, efficacy ?).	minor

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Bone healing (in the absence of fusion of the humeral condyles)	CN	Bone Morphogenetic Protein: unavailable	Disp		minor
Chemotherapy side effects	CN	Dexrazoxane, cardiac protector: Hospital reserve	Reg		minor
Hemorrhagic cystitis	CN	Mesna (prevention of haemorrhagic cystitis): Hospital reserve	Reg		minor
Inappropriate galenic or packaging					
Anti-fungal treatment (ringworm) of the environment	CT, NCA (guinea pig)	Had existed in vet practice (Clinafarm) but withdrawn. Rq: environmental treatment must be considered as a biocide rather than a veterinary medicine.		Enilconazole spray. Can be used in catteries but not suitable for the treatment in private home. This is also a real problem in general practices, especially as ringworm is a frequent zoonosis.	MAJOR Group 2
Anti-glaucoma	CN, CT	No veterinary anti-glaucoma products to be prescribed during chronic glaucoma while it is a frequent disease.	0 VMP	Prescription of human eye drops: TRUSOPT (dorzolamide), TIMOPTOL (timolol) or COSOPT (dorzolamide+timolol).	MAJOR Group 2
Anti-viral or immunosuppressing eye drops	CN, CT	Wish for antivirals, immunosuppressants, other than ciclosporin. In particular, a tacrolimus-based preparation would be interesting. Another formulation for dexamethasone as FRADEXAM contains dexamethasone phosphate and it seems that acetate (MAXIDROL) has better ocular penetration.	(0) VMP	FRADEXAM (see note opposite): the submission of a MA variation may be eligible for extended data protection (see Art 40.5 -Reg 2019/6)	MAJOR Group 3
Chronic inflammatory bowel disease	CN/CT	Wish for budesonide : far less side effects like Cushing's syndrome than prednisolone (very effective), but the human medicinal product is not adapted to pets (3 mg capsules too high dosage for pets)	PhV	Prednisolone	MAJOR Group 3
Anti-coagulant	CT	Very low palatability of clopidogrel in cats. Poor knowledge of its usefulness/effectiveness	0 VMP	Clopidogrel (22 human products + 2 in combination with aspirin). Long-term treatment => possible submission as "limited markets" dossier ?	minor
Anxiolytic	CT	Fluoxetine: mint presentation not suitable for cats.	0 VMP	Oral fluoxetine (RECONCILE)	minor
Localized bacterial infections	CN, CT	Wish for a veterinary antibiotic for topical application, other than fusidic acid (FORUDINE ointment for CN&CT, BETAFUSE gel for CN).	(0) VMP	Self-medication and misuse with risk of ABR. (ongoing work at CSMV about off-label practices for local antibiotherapy).	minor
Hepatocutaneous syndromes	CN	Wishes for a sugar-less amino acid solution for perfusion: only the solution for humans AMINOPLASMAL 25 (with sugars) is available in pharmacies.	0 VMP	AMINOPLASMAL 25 (for humans) – see opposite	minor

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Therapeutic gap : currently being resolved		Initial problem	Type of problem	Solution / Alternatives Reason for: Resolution in progress / Disappearance of the therapeutic gap	GAP initially MAJOR: M minor: m
with existing solution					
Bacterial infections	CN, CT	<p><i>Reminder:</i> No IV injection of non-critical ATBs (e.g. cefalexin, cefazolin): wish for a VMP with a non-modifiable price (1 HMP ordered from wholesalers).</p> <p>Eligible Art 40.5 of the Reg 2019/6, IF modification of pharmaceutical form, administration route or dosage</p>	Disp	<p>Order cefazolin IV now possible from the MAH.</p> <p><i>For reference:</i> Cefazolin IV not listed under restricted prescription (RP) but only restricted to collectivities (case of CIP code "5"). Information not well known by pharmacies who generally refuse to order such products.</p> <p>RILEXINE POWDER FOR INJECTION 1 G authorised for IV injection (see iRCP).</p> <p>IV injectable human drugs (if non-critical neither reserved ATB): Ampicillin inj. Delivered by pharmacies AUGMENTIN IV available, HS reactions more frequent than with cephalosporins.</p>	MAJOR group 1
Appetite-stimulating anxiolytic	CT	No oral mirtazapine accessible: reconditioning required	Disp	<p>Marketing of a VMP (MIRATAZ®) in Q1 2022.</p> <p><i>For info:</i> Mirtazapine ointment obtained centralised MA on 10/12/19.</p>	MAJOR

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Issues specific to NCA (new companion animals)					
Bacterial infections	Reptiles etc.)	No marketing authorisation/galenic suitable for first-line ATBs. Few PK/PD data on non critical ATBs, especially reptiles: study needed / waivers	(0) VMP	The only ATB VMPs approved for reptiles, birds, amphibians, rodents are with enrofloxacin (4 MA). RFSA already communicated (via minutes of the previous meeting) on the wish for applications of MA extension to those species for VMPs with other ATBs (e.g. tetracyclines, sulfa TMP, penicillins, amoxi-clavulanic acid).	MAJOR
	Rabbit, hen	Inappropriate packaging: e.g. ADJUSOL - 100mL -> treatment of 30kg of rabbit for 10 days or 1 rabbit of 1.5kg for 200d... Problem of deconditioning at the clinic = only possibility although not authorised => what to do? (less) good practices to be defined?	(0) VMP	MA for rabbit, chicken but inappropriate galenic or presentations. See J. Biatrix's ppt at the AFVAC 2022 conference. see best practices for the extemporaneous preparation of VMPs (possibility of subcontracting Art. L5143-9-1), but not possible in case of emergency.	MAJOR
	Rabbit	Need for antibiotic with good accumulation in pus/bone	0 VMP	Azithromycin	minor
Chlamydia	Birds	VMP approved for a powder for oral solution: permanent supplier shortage + inappropriate galenic. Need for an oral and injectable formulation (inj reserved for hospital use) According to iRCP, Doxycycline VMPs for poultry have inappropriate packaging: - Powder for drinking water: DOXIPULVIS 500 MG/G (SP Veterinaria), DOXYVETO-C 433 MG/G (VMD), GALLUDOXX 433 MG/G (Huvepharma), RONAXAN 500 MG/G (Dopharma) - Concentrate for oral solution: DOXSOL 10% (KARIZOO), SOLDOXIN 100 MG/ML (Vetpharma)	Disp	Doxycycline crushed tablets (DOXYTAB VET. 15 & 50 MG TABLETS FOR DOGS AND CATS) ORNICURE (Doxycycline from OROPHARMA) exists in 4x130 mg bags but the orders do not succeed... Shortages declared in 01/2021, then return on the market confirmed in 06/2021. Moreover, advertising is expensive for an antibiotic (esp. considering the initial registration costs when sales are of 2 units/month only!) Oxytetracyclines would be another option but their bioavailability is too variable.	MAJOR
Fish medicines	Fish	Over-the-counter sale of AB, API/APE, anaesthetics, formalin, malachite green etc. see for example https://www.koi-prestige.com/soin-du-koi/medicaments-poisson/	Reg	The only MA for fish (see iRCP) is FLUMIQUIL 3% powder (flumequine) Reg 2019/6: exemption from MA but mandatory registration => will help to better know (composition, instructions) and regulate these products. Pending adoption of the order being prepared and the implementing decree.	MAJOR

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Difficulties accessing the drug					
Respiratory aspergillosis	Parrots, falcons	Treatment of choice in the literature includes voriconazole ± amphotericin B for injection. However, voriconazole (VFEND) prescription is restricted (for fear of misuses ?). Wish for oral voriconazole (only 1 oral HMP: VFEND 40 mg/mL). Progress about RP expected in 2023 (see general remarks in introduction). Justification provided by Dr S. Larrat (post-meeting)	Reg	Itraconazole, but safer with voriconazole (VFEND) _ to be used sparingly.	MAJOR
Egg retention	Birds	Prepidil (topical gel) with restricted prescription (RP). Progress about RP expected in 2023 (see general remarks in introduction). Justification provided by Dr S. Larrat (post-meeting)	Reg	Surgery on dying animals...(no cervix dilation => abdominal lay). Purified pork sperm. Dinoprostone but not effective.	MAJOR
Heavy metal poisoning	Birds	Succimer (DMSA) with restricted prescription whereas Succimer PO is used at home in other countries	Reg	Ca EDTA injectable IM	minor
Analgesia	Rabbit, rodents	Buprenorphine long acting available in US - not available in Fr Butorphanol long acting - not available in Fr No oral Tramadol	PhV	Doubts about the actual efficacy of meloxicam (METACAM approved for guinea pigs) because pharmacodynamic studies showed a much higher required dose than the one mentioned in the SPC for rodents)	minor
Anaesthesia	Fish	Import of tricaine	Disp	Import from other EU member states	minor
Hypocalcaemia	Reptiles	Frequent "cascade" use		Ca gluconate Eligible Art 5.6 Reg 2019/6 if not subject to prescription	minor
Candidiosis	Birds	Frequent "cascade" use		Nystatin	minor
Inappropriate galenic or packaging					
Insulin	Ferret	Wish for diazoxide (PROGLICEM) for oral use. Available in humans but only in capsules (with restricted prescription) i.e inappropriate galenic for ferrets. Prevalence of the disease: 3 000/100 000 (3%) Progress about RP expected in 2023 (see general remarks in introduction). Needs justification to be drafted	Reg	Could be manufactured at the ENVA pharmacy Prednisolone tablets	MAJOR

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Vaccines for Marek disease and coccidiosis	Poultry	Inappropriate packaging: maintenance of diseases in backyards that could be prevented => use of antibiotics for treatment instead of vaccines for prevention. For info: 12 millions individual poultry (// 7 millions dogs): enthusiasm for Indian duck runners who consume slugs and are compatible with permaculture.	(0) VMP	Vaccines for intensive farming available only with 1000 or 5000 doses	MAJOR
API/APE (for red mites)	Poultry	Inappropriate packaging Small EXZOLT bottle = €150 (=> unpacking required), 50mL <=> 2x2tmts 7 days apart from approximately 80 hens	(0) VMP	Fluralaner (EXZOLT) Selamectin (STRONGHOLD kitten): but consumption of eggs prohibited (no MRL status)	MAJOR
Pituitary adenoma (prolactinoma)	Rat	VMP (cabergoline) not adequately dosed => too large volume mechanically impossible to administer to a rat (<=> 1 vial of 4 mL every 2 days). ⇒ Use of tablets for human medicine crushed by the owner who then has to handle the suspension and daily treatment. Non-compliance with the extemporaneous preparation GP (despite the facilitated option for subcontracting - Art. L5143-9-1).	(0) VMP	Preparation by pharmacy, but the reconditioning is complicated by the intermittent medicine availability and the lack of reactivity: in the meantime, risk of death of the rat.	MAJOR
Renal impairment	Ferret, rabbit, rodents, birds	Lack of an oral formulation for proper dosing / patient weight	0 VMP	Furosemide injection/tablet	minor
GnRH vaccine: sterilisation, adrenal disease of ferret, control of reproduction problems in poultry	Ferret, poultry	Unsuitable packaging: sold by 12*150mL. Scientific articles on Gonacon (US). No data on IMPROVAC.	0 VMP	Improvac	minor