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Withdrawal Guidance Advisory

Withdrawal guidance of HISA's Anti-Doping and Medication Control (ADMC) Detection Times

March 20, 2023

Background:

The RMTC's Scientific Advisory Committee (SAC) has performed an analysis and, where data permits, developed withdrawal guidance associated with the ADMC Screening Limits and Detections Times of the schedule of RMTC Controlled Therapeutic Substances (CTS).

Withdrawal guidelines are for informational purposes only. It is advisable that this information should be used by horsemen in consultation with their attending veterinarian. The withdrawal guidelines do not constitute a guarantee or warranty.

Terms to know:

Screening Limit (SL) - Considered the decision limit used by the laboratories. If initial testing finds a concentration of a substance in a sample that is below the SL, the laboratory will not pursue the possible presence of a prohibited substance. If initial testing finds a concentration of a substance to be above the SL, the laboratory will pursue confirmatory analysis to solidify the positive finding.

Limit of Detection (LOD) – The lowest concentration of a substance that can be identified by the laboratory.

Restricted Administration Time (RAT) – A specified interval prior to a race during which the administration of a substance(s) is prohibited. RATs can be enforced by surveillance, review of medical records, and drug testing.

Detection Time (DT) - Is the first time point after administration of a substance that all test horses in an administration study are at a concentration below the Limit if Detection or defined Screening Limit in a specific matrix (e.g., serum, plasma, urine, or hair). Note: Detection Times are not equivalent to Withdrawal Times

Withdrawal Time (WDT) – A recommendation as to the minimum interval between administration of a single medication, including specific dosage, route of administration, and treatment schedule, and a race or timed workout. Withdrawal time provides a margin of safety added to a Detection Time to help guide treatment decisions and avoid an adverse finding.

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Methodology:

The elimination half-life of a drug is a pharmacokinetic parameter that is defined as the time it takes for a concentration of the drug in the plasma or the total amount in the body to be reduced by 50%; (1) half-life = 50% of drug is eliminated from the body, (2) half-lives = 75% of drug is eliminated from the body, (3) half-lives = 87.5% of drug is eliminated from the body, and (4) half-lives = 93.75% of the drug is eliminated from the body.

Considering most administration studies used to determine detection times of these substances contain small numbers of horses, these sample sizes may not be an accurate representation of the entire population and the detection times do not account for all the variabilities that contribute to the elimination of a drug. The SAC has determined that four (4) half-lives, 94% (93.75% exactly) elimination of a drug from the body, accounts for the margin of safety the SAC has determined necessary to account for these variables and to provide this withdrawal guidance.

The **methodology** for providing this withdrawal guidance is based on determining the average terminal half-life (from published studies and/or RMTC administration study data) of each Controlled Therapeutic Substance (CTS) and applying the proposed Anti-Doping and Medication Control (ADMC) program screening limits to determine the detection times. Four (4) half-lives of a given substance are added to the calculated detection time; this number may be rounded up to the nearest whole number as agreed upon by the Scientific Advisory Committee (SAC). At four (4) half-lives, 94% (93.75 exactly) of the remaining medication in the horse's system, already at or below the agreed-upon screening limit, will be eliminated.

Note: This methodology may not apply to substances outside of the RMTC's schedule of Controlled Therapeutic Substances in consideration of available data or the number of horses in a particular study. There are different risk factors associated with applying this methodology to substances lacking administration data or smaller sample sizes.

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Substance	Dosage/Route	Detection Time[1] *Unless specified as a Restricted Administration Time (RAT) (#Horses[2])*	Withdrawal Time (WDT) *Unless specified as a Restricted Administration Time (RAT) or Stand Down Time*
Acepromazine (HEPS)	0.05 mg/kg single IV dose	48 hours (20)	WDT: 72 hours (IV)
Albuterol	5 x 100 µg actuations per dose for 2 days dosed every 4 hours Inhalation[3]	72 hours[3A]	
Butorphanol	0.1 mg/kg single IV dose	72 hours (6)	WDT: 96 hours
Cetirizine	0.4 mg/kg orally twice daily for 5 doses	48 hours (9)	WDT: 72 hours
Cimetidine	20 mg/kg orally twice daily for a total of 7 doses	RAT: 24 hours	WDT: 24 hours
Dantrolene	500 mg orally once daily for 3 days	48 hours (12)	WDT: 96 hours
Detomidine	0.02 mg/kg single IV dose	48 hours (10)	WDT: 48 hours[4]
Dexamethasone[8]	Single 20 mg IV, IM, or oral dose	72 hours (20)	WDT: 96 hours (IV) WDT: 96 hours (Oral)
Dexamethasone Sodium Phosphate[8]	0.06 mg/kg single IV dose	72 hours (6)	WDT: 96 hours (IV) WDT: 96 hours (Oral)[13]
Furosemide	1 mg/kg IV single IV dose (where permitted by exemption)	RAT: 4 hours	WDT: 4 hours Where permitted by HISA's furosemide exemption.
Furosemide		RAT: 48 hours (6)	WDT: 48 hours
Glycopyrrolate	1 mg single dose IV	48 hours (20)	WDT: 96 hours
Guaifenesin	2 grams total body dose, orally twice daily for 5 doses	48 hours (9)	WDT: 72 hours

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Substance	Dosage/Route	Detection Time[1] *Unless specified as a Restricted Administration Time (RAT) (#Horses[2])*	Withdrawal Time (WDT) *Unless specified as a Restricted Administration Time (RAT) or Stand Down Time*
Lidocaine (Lidocaine HCL 2%)	200 mg of Lidocaine, as Lidocaine Hydrochloride, administered subcutaneously	48 hours (6)	WDT: 72 hours
Lidocaine (Lidocaine HCL 2% and Epinephrine 1:100,000)			WDT: 72 hours
Mepivacaine	40 mg (2mL) single dose SQ distal limb	72 hours (6)	WDT: 120 hours[15]
Methocarbamol	15 mg/kg single IV dose	48 hours (20)	WDT: 72 hours (IV)[5]
Omeprazole	2.2 g orally once daily for 4 doses	RAT: 24 hours	WDT: 24 hours
Prednisolone[9]		No Detection Time[8]	
Ranitidine	8 mg/kg orally twice daily for 7 doses	RAT: 24 hours	WDT: 24 hours
Xylazine	200 mg single IV dose	72 hours (6)	WDT: 96 hours
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)			
Samples collected may contain one of the NSAIDs below detected at a concentration less than the Regulatory Screening Limit.			
Flunixin Meglumine[6, 7]	1.1 mg/kg single IV dose	RAT: 48 hours	WDT: 96 hours
Ketoprofen[6, 7]	2.2 mg/kg single IV dose	RAT: 48 hours	WDT: 72 hours
Phenylbutazone[6, 7]	4.4 mg/kg single IV dose	RAT: 48 hours	WDT: 96 hours (IV) WDT: 120 hours (Oral)[14]

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Substance	Dosage/Route	Detection Time[1] *Unless specified as a Restricted Administration Time (RAT) (#Horses[2])*	Withdrawal Time (WDT) *Unless specified as a Restricted Administration Time (RAT) or Stand Down Time*
Substances with Associated Stand Down Times			
14-day stand down following intra-articular injection			
Betamethasone[9,10,12]	**These substances are controlled by treatment reporting and a mandatory 14-day stand down following intra-articular injection.**		
Isoflupredone[9,10,12]			
Triamcinolone[9,10,12]			
Methylprednisolone[9,10,11,12]			
Other associated stand down times			
Clenbuterol	**Controlled by treatment reporting, veterinary list work, and clearance testing.**		

Table Endnotes:

[1]*Known Detection Times published by the Anti-Doping and Medication Control program (ADMC).*

[2]*Number of horses in an administration study to determine Detection Time.*

[3] *According to ADMC regulation, Albuterol administered by any route other than inhalation is a Banned Substance.*

[3A] *Based on currently available data, the RMTC is unable to provide withdrawal guidance for Albuterol. Out of an abundance of caution, it may be advisable to apply IFHA's Detection Time of 72 hours as a basis for determining a withdrawal interval. The 72-hour Detection Time strictly applies to an inhalation route of administration.*

[4]*Following the review of Detomidine administration study data, applying the ADMC screening limit, the RMTC Scientific Advisory Committee (SAC) recommends a Detection Time of 24 hours. Applying the four (4) half-life methodology, the SAC suggests a Withdrawal Time of 48 hours. ADMC's Detection Time for Detomidine is 48 hours which is the same as RMTC's suggested Withdrawal Time, this acknowledgement only applies for this substance unless specified otherwise.*

[5]*Oral treatments of Methocarbamol require additional time for clearance.*

[6]*The detection of more than one NSAID in a horse's Post-Race or Post-Work blood sample constitutes a Stacking Violation (detection of more than 1 NSAID in a blood sample).*

[7]*Three NSAIDs (Flunixin, Ketoprofen, and Phenylbutazone) are associated with Detection Times (DTs) of 48 hours. Only one of the three may be administered using a withdrawal guidance based on the 48-hour DT. See ADMC's secondary DTs to avoid Stacking Violation.*

[8] *Based on currently unavailable data, the RMTC is unable to provide withdrawal guidance for Prednisolone.*

[9]*The detection of more than one corticosteroid in a horse's post-race or post-work blood sample constitutes a stacking violation.*

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[10]*The RMTC 7-day withdrawal guidelines for corticosteroid intra-articular substances apply for testing associated post-work or out of competition samples, i.e., Betamethasone, Isoflupredone, and Triamcinolone.*

[11]*If methylprednisolone is administered by any route, clearance testing is advisable.*

[12]*Intramuscular administration will result in plasma or serum concentrations in excess of the Regulatory Screening Limits for an extended period.*

[13]*At a single 40 mg oral dose of Dexamethasone SP in the RMTC data*

[14]*At a single 2-gram oral dose of Phenylbutazone in the RMTC data*

[15]*This withdrawal guidance is limited to a 40 mg (2mL) single dose administered subcutaneously in a distal limb.*

Disclaimer:

The Withdrawal Guidance listed in this document is provided as a guide to horsemen and their veterinarians. It is neither endorsed nor reviewed by the Horseracing Integrity and Safety Agency (HISA). Moreover, the Withdrawal Guidance does not represent a guarantee or warranty by the RMTC that following the information will prevent a positive finding. Nor does this document relieve the trainer of the responsibility as the absolute insurer for medication overages. This document is solely meant to provide information to guide horsemen and their veterinarians as they perform an independent risk analysis.

The information contained herein is subject to change. As new research becomes available for each medication it may extend or decrease the time listed in the Withdrawal Guidance. Any subsequent change in this information based upon new research will be provided upon review by the Scientific Advisory Committee and approval by the RMTC Board.

The Detection Times listed in this document are based upon experimental data. That data is derived from as few as six (6) horses. The horses involved in these experiments were provided a single medication in a controlled environment and tested for only the presence of that medication at subsequent timepoints. The Withdrawal Guidance is derived from these Detection Times based upon a statistical analysis. Neither of these timepoints are intended to cover every situation in which a medication is administered.

Horses in these experiments are healthy. Sick horses may metabolize medications differently than healthy horses and this may result in prolonged Detection Times and make Withdrawal Guidelines irrelevant. Experimental horses may be subjected to different exercise plans, diets, and general husbandry which can potentially affect Detection Times and recommended Withdrawal Guidelines when compared to a horse in race training.

Use of a different formulation or concentration of the prescribed medication will likely change the elimination of the medication causing alterations to the Detection Times making the Withdrawal Guidelines inapplicable. The use of compounded medications represents another risk as these substances are produced absent regulatory oversight, and the concentration of drug, its stability and purity, have not been verified.

Furthermore, Detection Times and associated Withdrawal Guidelines are tied to the specified route of administration. In general, medications that are accidentally administered extravascular or outside of the joint space will have significantly different pharmacodynamics making the guidance in this document irrelevant. Additionally, oral administration of medication(s) or combining different medications or supplements may alter the Detection Time affecting the applicability of the Withdrawal Guidance. Extra caution must be taken to clean buckets, feed tubs, and stall environment after oral treatments have been administered.

The RMTC advises horsemen and veterinarians to use these findings as guidelines; they are not intended as guarantees of regulatory compliance. Though meant to be helpful, these are in no way intended to be strict principles that match all real-life situations. The RMTC cautions veterinarians and trainers that exact repetition of these medication dosages may still lead to unpermitted levels when an equine is tested. If horsemen or veterinarians have any concerns about a specific treatment or horse, they should request Clearance Testing from the Horseracing Integrity and Welfare Unit (HIWU).

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2. DiMaio Knych HK, Stanley SD. Pharmacokinetics and pharmacodynamics of detomidine following sublingual administration to horses. American Journal of Veterinary Research. 2011;72(10). doi:10.2460/ajvr.72.10.1378

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