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# Key Updates in the WADA 2025 Prohibited List: Implications for Competitive Sports

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**Abstract**

The 2025 revision of the World Anti-Doping Agency (WADA) *Prohibited List* introduces significant updates grounded in recent pharmacological developments, emerging therapeutic compounds, and shifting patterns of misuse in sport. This scientific brief outlines key changes, including the addition of novel agents such as ryanodine receptor-1-calstabin complex stabilizers (e.g., S-107, ARM210) to the S0 category, the estrogen receptor degrader elacestrant to S4.2, and MOTS-c to the metabolic modulators section (S4.4). Other revisions include formal recognition of insulin mimetics (S519, S597), the naming of xipamide as a masking agent, and stricter dosing intervals for inhaled formoterol. Classification updates affect stimulants such as hydrafinil (reallocated to S6.A), and newly listed specified stimulants including midodrine and tesofensine. The revised policy also clarifies the permissibility of blood donation via apheresis procedure under strict oversight and introduces notable sport-specific changes, which is removal of β-blockers from the *Prohibited List* for selected skiing and snowboarding disciplines, following recommendations by the International Ski Federation (FIS). These changes underscore WADA's commitment to preemptive regulation based on emerging risks, ensuring fairness and athlete safety. Where applicable, clinical rationale, therapeutic use implications, and detection methodologies are discussed to support implementation and compliance across sports.

Keywords: WADA, World Anti-Doping Agency, Prohibited List, Prohibited List 2025, Doping, Olympics

Introduction:

The World Anti-Doping Agency (WADA) annually revises its *Prohibited List* to reflect advances in biomedical research, emerging trends in pharmacology, and evolving patterns of substance misuse in competitive sport. These updates are critical to ensuring both fair play and athlete safety, as well as maintaining the integrity of sport at all levels. The 2025 revision introduces several important modifications, many of which are not based on the addition of entirely new substances but rather on refined classifications and clarifications regarding existing compounds, especially those developed under or structurally related to already banned pharmacological classes. Such revisions are incredibly important, given the dynamic landscape of pharmaceutical innovation and the continued emergence of grey-zone compounds or procedures, that challenge regulatory definitions. This brief communication outlines the key updates to the 2025 WADA *Prohibited List*, with particular focus on changes in substance classification (e.g., the reclassification of certain stimulants), specification clarifications (e.g., inhaled β2-agonists), and sport-specific exemptions or adjustments (e.g., the removal of β-blockers for certain winter sports disciplines). Furthermore, this update highlights underlying scientific and clinical rationale where available, including efficacy data, potential for abuse, and impact on performance, as well as implications for therapeutic use exemptions (TUEs), athlete monitoring, and anti-doping enforcement policy [1,2].

Ryanodine receptor-1-calstabin complex stabilizers inclusion to the Prohibited at all times – in and out of competition substance (S0)

WADA prohibits any pharmacological substance that is not explicitly listed but lacks approval from regulatory health authorities for human therapeutic use. This includes investigational drugs, discontinued medications, designer substances, and compounds not intended for human use, such as veterinary medications. This class includes numerous substances, among which are: BPC-157, 2,4-Dinitrophenol (DNP), and troponin activators (e.g., Reldesemtiv and Tirasemtiv). Since 2025, additional substances have been named under this section: “ryanodine receptor-1-calstabin complex stabilizers [such as S-107, S48168 (ARM210)]”[1].

S-107 has been shown to stabilize calstabin1 binding to ryanodine receptor-1, the skeletal muscle sarcoplasmic reticulum calcium release channel required for muscle contraction. This interaction leads to a reduction in intracellular calcium leakage and oxidative stress (ROS). Additionally, it improves tetanic $Ca^{2+}$ release while limiting calcium channel leakage associated

with certain diseases and aging. Moreover, it has been observed to increase muscle-specific force production and elevate overall exercise capacity in mice, while simultaneously reducing fatigue [1-5],

Inclusion in the S0 category (substances prohibited at all times, both in- and out-of-competition) is likely intended to prevent potential misuse before it becomes widespread in the sporting community. Although the S-107 ryanodine receptor-1-calstabin complex stabilizer (RyR1) has been recognized for its potential risk of misuse [6], the specific classification of this substance under the S0 category coincides with the emergence of another novel RyR1 compound – S48168 (ARM210). The S48168/ARM210 compound has shown therapeutic potential for neuromuscular diseases such as dystrophinopathies in preclinical studies using animal models [7]. More recent reports suggest that daily administration of 200 mg of ARM210 leads to reduced fatigue and increased proximal muscle strength in patients with RYR1-related myopathies [8].

It is worth noting that while this update does not signal a radical shift in WADA's overall policy, it further reinforces its commitment to the principle of prohibiting substances "at all times." The theoretical risk of misuse, their unknown or poorly understood influence on physical performance, and unresolved safety concerns constitute sufficient justification for their explicit inclusion in the S0 category of WADA's 2025 *Prohibited List* [1].

Elacestrant naming to the Prohibited at all times (in- and out-of-competition) S4.2. Anti-estrogenic substances [Anti-Estrogens and Selective Estrogen Receptor Modulators (SERMs)]

Tamoxifen acts as an estrogen antagonist at the level of the hypothalamus and pituitary, stimulating the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In our experience, it mildly increases endogenous testosterone production and enhances spermatogenesis [9].Related elacestrant – a receptor degrader rather than modulator, approved by the FDA in 2023, has been shown to inhibit the expression of estrogen receptor alpha (ERα) in cultured breast tumor cell lines, leading to complete degradation of the receptor [10,11]. Given that estrogen receptors are also expressed in non-tumor tissues, there is a theoretical risk of misuse. In particular, reduction in estrogen receptor signaling within the hypothalamus may falsely signal a low-estrogen state, leading to reactivation of the hypothalamic-pituitary-gonadal (HPG) axis and the resumption of endogenous testosterone production. While this may promote muscle hypertrophy, the increase in serum testosterone concentrations remains modest

[12]. Suppression of spermatogenesis is a frequent consequence of androgen (AAS) use, due to negative feedback inhibition of the HPG axis. Recovery of this axis can take several months. Although no robust clinical evidence currently supports their use, anecdotal reports suggest that selective estrogen receptor modulators (SERMs) may facilitate faster restoration of gonadal function [9,12-14]. These properties position elacestran alongside other anti-estrogens and SERMs already included on the WADA *Prohibited List* [2], as a theoretical indirect anabolic agent and a potential masking substance following prior testosterone or AAS use.

Inclusion of *Mitochondrial Open Reading Frame of the 12S rRNA-c* (MOTS-c) to the Metabolic Modulators S4.4 subgroup

A novel member of the mitochondrial-derived peptide family, *mitochondrial open reading frame of the 12S rRNA-c* (MOTS-c), functions not only as a cell-autonomous peptide but also acts systemically as a "hormone," influencing numerous metabolic processes. Among its effects is the reduction of insulin resistance – MOTS-c systemically regulates in vivo glucose metabolism and enhances muscle insulin sensitivity [15]. Insulin enhances glucose uptake and maximizes glycogen storage prior to exercise, potentially improving performance. It also augments amino acid transport, thereby indirectly contributing to anabolic processes [16,17]. Improved insulin sensitivity of skeletal muscle cells supports enhanced glucose metabolism [15], while MOTS-c has also been associated with obesity prevention, improved muscle function, bone metabolism support, immune regulation, and delayed aging. In addition, MOTS-c contributes to nuclear–mitochondrial signaling and exerts cytoprotective properties within cells [18,19]. MOTS-c naturally targets skeletal muscle tissue, where it may accelerate energy-generating metabolic processes [18]. Moreover, it has been shown to increase glycolysis and ATP levels in dystrophic muscle cells, improving the absorption and activity of phosphorodiamidate morpholino oligomers [20]. MOTS-c is frequently advertised by wellness and anti-aging clinics as a "weight-loss peptide," despite its status as an experimental compound not approved for human therapeutic use [21]. Given its potential anabolic and performance-enhancing properties, alongside its uncertain safety profile, MOTS-c was added to the *World Anti-Doping Code International Standard Prohibited List 2025*, under the category of Metabolic Modulators [1].

**Insulin Mimetic example listing of S519, S597 analogues**

The influence of insulin and its synthetic analogues on carbohydrate metabolism and their anti-catabolic effects has led to their prohibition in sports at all times, according to the regulations of the World Anti-Doping Agency [1]. Insulin mimetics imitate the biological action of insulin by binding to the insulin receptor. [22]. Insulins and insulin mimetics have been included in Article S4.4.1 as non-specified substances since the year 2000. In the latest revision of *WADA Prohibited List 2025*, S519 and S597 are listed as examples of insulin analogues; however, the regulation also applies to all unnamed compounds that fall within this category.

S519 and S597 are the most extensively studied and well-characterized insulin mimetics. A validated method exists to detect these substances in plasma, utilizing advanced solid-phase extraction (SPE) and liquid chromatography coupled with high-resolution tandem mass spectrometry (LC-HRMS/MS). This method enables the detection of S519 and S597 at concentrations exceeding 0.5 ng/mL [22-24].

Inclusion of Xipamide as a diuretic example

Xipamide is a diuretic derived from salicylic acid which structure resemblance to chlorthalidone. Despite its similarity to thiazide diuretic, xipamide works mainly in the distal tubule and shows a diuretic efficacy compared to furosemide at doses up to 40mg [25,26]. The main factor that leaded to banning xipamide were its similarities to other diuretics which are described by WADA as masking agents, that potentially can be used to falsify the results of doping controls and to conceal doping [1,27].

In 2012 during Tour de France Frank Schleck sample A showed presence of xipamide and the cyclist was withdrawn by his team. At that time, the list of substances prohibited by WADA did not specifically include the name xipamide; however, the substance was indirectly banned due to its structural similarity to other classes of diuretics [28]. In the revised *Prohibited List*, xipamide was mentioned by name for the first time to emphasize the fact that it is a prohibited substance due to its structure and functions being analogous to other diuretics.

**Manipulation of Blood and Blood Components** - liberalisation for donation purposes

WADA strictly prohibits manipulation of Blood and Blood Components (BBC), including any form of intravascular manipulation of blood components by physical or chemical means, as well as artificially enhancing the uptake, transport, or delivery of oxygen. While plasmapheresis was exempted from this rule [2], as no signs of doping activity from the procedure were observed [29], the 2025 revision clarifies that donation of BBC by apheresis would not be prohibited when performed in an accredited collection center under strict regulatory oversight. The concern arises because red blood cell (RBC) collection and reinfusion – which is the basis of apheresis – can enhance oxygen delivery, potentially improving endurance performance; this practice is known as blood doping [30]. The M1.1category strictly prohibits blood component reinfusion. The donation of RBCs via apheresis is permitted under specific conditions, ensuring that the components are not reinfused [1]. The shift from permitting only plasmapheresis to allowing broader apheresis procedures reflects WADA's recognition of the importance of facilitating blood donations for medical and humanitarian purposes. By enabling athletes to donate various blood components under strict regulatory oversight, WADA balances the need to prevent doping with the ethical imperative to support blood donation initiatives. In conclusion, while apheresis includes the collection of components that could theoretically pose a threat of doping, the 2025 WADA *Prohibited List* maintains prohibitions on reinfusion practices that enhance performance, further reinforcing the need for strict supervision of the procedure at accredited centers. This policy change allows for ethical blood donations without compromising the integrity of competitive sports [1,21].

β2 Agonists - dosing intervals update for Formoterol

All selective and non-selective beta-2 agonists, including all optical isomers, are prohibited both in- and out-of-competition. Exemptions apply, including the use of Formoterol – a long-acting β2-agonist (LABA) with a duration of action of 12 hours [31] – when inhaled at a maximum delivered dose of 54 micrograms over 24 hours [2]. Administration of this medication within this regimen does not require a Therapeutic Use Exemption (TUE). Formoterol acts as a bronchodilator and, at supratherapeutic doses, may have performance-

enhancing effects such as increased endurance, bronchodilation beyond therapeutic need, and stimulation of muscle function [31,32]. Since 2025, the maximum inhaled dose of 54 μg over 24 hours must be divided into doses that do not exceed 36 micrograms over any 12-hour period [1]. The scientific basis for this change is grounded in studies showing dose-response relationships for β2-agonists. Supratherapeutic dosing – even within short timeframes – may yield systemic effects such as increased aerobic capacity or muscle strength, especially when doses are clustered [33]. It was shown that a single 54 μg dose of formoterol has performance-enhancing potential on sprint ability and short, intense performance [31]. With the 2025 revision of the *Prohibited List*, potential risks of misuse are minimized, limiting the possibility of β2-agonist exploitation [1].

**Hydrafinil reallocation to the stimulant group (S6)**

Hydrafinil (fluorenol, also known as 9-hydroxyfluorene) is structurally related to modafinil, which is an approved drug for the treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD), with cognitive enhancement activity [34].

After in vivo trials on rats, where it demonstrated wake-promoting properties surpassing those of modafinil, [35,36] the drug candidate was not further developed. Consequently, preclinical and clinical trial plans were abandoned. Hydrafinil has since appeared on some markets as a cheap and readily available substance [37].

The substance was included in the 2024 WADA *Prohibited List* in the S6.B section as a specified stimulant (prohibited in-competition). The revised List shifted the compound to the S6.A section as a non-specified stimulant [1,2]. A non-specified stimulant is a substance that is most likely used deliberately with the intention to dope, whereas a specified stimulant is recognized as more susceptible to inadvertent use [1]. The shift was largely based on WADA's notice that hydrafinil is more potent than modafinil and is not licensed for medical use; thus, there are no recognized therapeutic applications. These factors suggest that hydrafinil is more likely to be used for performance enhancement rather than for legitimate medical reasons [1,36].

Midodrine and Tesofensine inclusion in the Specified Stimulant (S6.B) section

Midodrine is a peripheral α-adrenergic agonist commonly used to reduce the effects of orthostatic hypotension. It is a prodrug that requires enzymatic hydrolysis to form its pharmacologically active metabolite, de-glymidodrine. Midodrine acts non-selectively on α1- and α2-adrenergic receptors, increasing standing blood pressure and decreasing venous capacity

[38]. In the latest edition of WADA *Prohibited List* [1], midodrine is named and classified as a specified stimulant (S6.B). Its inclusion was not particularly groundbreaking, as the ban mainly reflects the potential risk of hypertension and related complications, along with the theoretical possibility of enhancing sports performance.

Tesofensine is a triple monoamine reuptake inhibitor that inhibits the reuptake of dopamine, noradrenaline, and 5-HT. Tesofensine was originally developed and investigated for Alzheimer's and Parkinson's disease, but early results showed limited efficacy; however, weight loss was observed in those patients. The main mechanism leading to this effect is its appetite suppressant action. [39] The effectiveness of its impact on weight reduction is still being studied; however, the substance lacks documented clinical efficacy for WADA to consider allowing its use. Additionally, tesofensine may potentially enhance sporting performance, pose an actual or potential health risk, and violate "the spirit of sport." The combination of potential performance enhancement, health risks, and lack of documented clinical efficacy led WADA to include this substance by name in the newest list of prohibited substances [1].

Guanfacine status clarification as not prohibited

Guanfacine, an α2A-adrenergic receptor agonist, is primarily used to treat ADHD and certain anxiety disorders. The α2A-adrenoreceptors are highly concentrated in the *locus coeruleus* and prefrontal cortex – areas most heavily implicated in ADHD [40]. In the 2025 *Prohibited List*, it was explicitly included as an exemption in the S6 stimulant section. It does not possess stimulant properties and lacks evidence suggesting performance-enhancing effects. Additionally, it is not associated with significant health risks when used as prescribed. Therefore, it does not meet the necessary criteria for inclusion on the *Prohibited List* [1,41,42].

Adjustments to the regulations regarding β-blockers in certain disciplines following the International Ski and Snowboard Federation's endorsement

In the 2025 revision of the World Anti-Doping Agency *Prohibited List*, β-blockers were removed from the list of substances prohibited *in-competition* for specific skiing and snowboarding disciplines: ski jumping, freestyle aerials/halfpipe, and snowboard halfpipe/big air. This change was implemented based on information provided by the International Ski and Snowboard Federation (FIS) [1]. The rationale behind this decision likely stems from a reassessment of the actual performance-enhancing effects of β-blockers in these disciplines. β-blockers are known to reduce heart rate and tremors, which can be advantageous in sports

requiring precision and steadiness, such as shooting or archery [43]. However, in dynamic and acrobatic events like ski jumping and freestyle snowboarding, the benefits of β-blockers are less clear, and they may even impair performance due to their sedative and muscle-weakening effects. A few reports from the 20th century discussed a theoretical performance advantage of β-blockade in ski jumpers. However, these studies were limited by small sample sizes, subjective performance measures, inconsistent outcomes due to side effects, lack of long-term assessment, and overgeneralized conclusions [44,45].

The change, endorsed through FIS expertise, may lay the groundwork for a closer investigation into the effects of β-blockers in the aforementioned disciplines, as large-scale, carefully designed, and up-to-date trials are still lacking. An interesting opportunity for such research may arise during the Milano-Cortina 2026 XXV Olympic Winter Games, starting on the 6th of February. The potentially large sample size available for retrospective studies across multiple disciplines could provide a solid foundation for further evaluating the impact of β-blockers on performance in certain winter sports.

## Conclusions

The transition from the 2024 to the 2025 WADA *Prohibited List* marks a significant evolution in anti-doping regulations, reflecting advances in scientific understanding and emerging challenges in sports integrity. Notably, the 2025 list introduces several novel substances and revises existing frameworks to better address potential performance-enhancing methods.Among the most prominent additions is MOTS-c, a mitochondrial-derived peptide with promising anabolic and metabolic effects, now explicitly prohibited due to its unapproved status and theoretical performance-enhancing potential. Similarly, the inclusion of ARM210 and other next-generation metabolic modulators underscores WADA's commitment to monitoring cutting-edge compounds that may evade detection yet provide unfair advantages. Regulatory updates extend to blood manipulation controls, where the 2025 list broadens the scope of apheresis procedures, endorsing honorary blood donation in sportsmen. While WADA maintains a strict ban on reinfusion practices to prevent blood doping, it permits certain blood donations under tightly controlled conditions, balancing athlete health and ethical blood donation initiatives. Dosing adjustments in the realm of β2-agonists, with introduction of a 12-hour maximum dosing window aims to curb misuse while preserving therapeutic access, showcasing WADA's nuanced approach to substances with legitimate medical uses and reactive decision-making in response to the novel reports. Finally, the International Ski and Snowboard Federation's (FIS) endorsement of more permissive β-blocker regulations in selected

disciplines exemplifies an evolving attitude toward sport-specific doping risks. This liberalization acknowledges the differential impact of β-blockers across sports, offering a tailored regulatory framework that supports athlete safety and fairness. The competitors' performance is set to be under the close monitoring by the experts during upcoming Milano-Cortina 2026 XXV Olympic Winter Games.

In summary, the 2025 WADA *Prohibited List* demonstrates a proactive stance toward emerging doping strategies, incorporating novel compounds, refining dosage guidelines, and adjusting sport-specific policies. These changes collectively enhance the effectiveness of anti-doping efforts while striving to uphold the integrity and spirit of competitive sport.

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