

SUMMARY OF MAJOR MODIFICATIONS AND EXPLANATORY NOTES

2022 Prohibited List

SUBSTANCES AND METHODS PROHIBITED AT ALL TIMES (IN- AND OUT-OF-COMPETITION)

PROHIBITED SUBSTANCES

S0. Non-approved Substances

- BPC-157 is now prohibited under S0 following a recent re-evaluation and added as an example.

S1. Anabolic Agents

- Tibolone is transferred from S1.2 to S1.1 because it has clinical effects as a synthetic oral androgen mediated by effects on the androgen receptor, largely due to its conversion to the delta-4 tibolone metabolite, which is a potent androgen.
- Osilodrostat, a CYP11B1 inhibitor, is added to S1.2 due to its off-target increase in circulating testosterone.

S2. Peptide hormones, growth factors, related substances and mimetics

- Lonapegsomatropin, somapacitan and somatrogon are added as examples of growth hormone analogues, which led to the reorganization and splitting of S2.2.3.

S3. Beta-2 Agonists

- The daily dosing time intervals for salbutamol are modified to 600 micrograms over 8 hours starting from the time any dose is taken (previously 800 micrograms over 12 hours). This is to reduce the risk of any potential *Adverse Analytical Finding* arising after high doses are taken at once.
- The total permitted daily dose remains at 1600 micrograms over 24 hours. A *Therapeutic Use Exemption* (TUE) should be sought for doses in excess of these limits.
- For example, an athlete could take 600 micrograms in the first 8 hours, 600 micrograms in the following 8 hours, and 400 micrograms in the remaining 8 hours of the day, without the need for a TUE.

PROHIBITED SUBSTANCES

S6. Stimulants

- S.6 Exceptions: *Imidazole derivatives* was changed to *imidazoline derivatives* to distinguish between generic imidazole derivatives and sympathomimetic imidazolines.
- Cathine footnote: It was clarified that the urinary threshold of 5 µg/mL cathine refers to both isomers of norpseudoephedrine, i.e. the d- and the l-isomer (also referred to as 1S,2S- and 1R,2R-norpseudoephedrine, respectively).
- Ethylphenidate, methylnaphthidate ((±)-methyl-2-(naphthalen-2-yl)-2-(piperidin-2-yl)acetate) and 4-fluoromethylphenidate are added to S6.b as examples of methylphenidate analogues. These substances have been prevalent in a number of countries over the past decade as they are often presented as alternatives to methylphenidate.
- Hydrafenil (fluorenol) is added to S6.b as an example of modafinil and adrafinil analogue.

S9. Glucocorticoids

- Flucortolone is updated to its International Non-proprietary Name (INN), fluocortolone.
- All injectable routes of administration are now prohibited for glucocorticoids during the *In-Competition* period. As proposed in the draft 2021 Prohibited List circulated for consultation to stakeholders in May 2020, WADA's Executive Committee approved at its 14-15 September 2020 meeting prohibition of all injectable routes of administration of glucocorticoids during the In-Competition period. Examples of injectable routes of administration include: intravenous, intramuscular, periarticular, intra-articular, peritendinous, intratendinous, epidural, intrathecal, intrabursal, intralesional (e.g. intrakeloid), intradermal, and subcutaneous. However, in order to thoroughly and widely communicate the rule changes and to allow sufficient time for information and education, the Executive Committee decided to introduce the prohibition of all injectable glucocorticoid routes and the implementation of the new rules on 1 January 2022. This allows, for example, *Athletes* and medical personnel to get a better understanding of the practical implementation of the washout periods, Laboratories to update their procedures to incorporate the revised and substance-specific new minimum reporting levels (MRL), and sports authorities to develop educational tools for *Athletes*, medical and support personnel to address the safe use of glucocorticoids for clinical purposes and prevent doping.
- For clarification, oral administration of glucocorticoids also includes oromucosal, buccal, gingival and sublingual routes. Dental-intracanal application is not prohibited.

Addition of local injections as prohibited routes

- Oral, intramuscular, rectal and intravenous routes were prohibited because there is clear evidence of systemic effects which could potentially enhance performance and be harmful to health. There are now also sufficient data available to show that the same systemic concentrations as existing prohibited routes can be achieved after administration by local injection (including periarticular, intra-articular, peritendinous and intratendinous) at licensed therapeutic doses.
- The systemic plasma and hence urinary concentrations of glucocorticoids that are reached after administration by local injection using normal licensed therapeutic doses were demonstrated to reach levels consistent with doses that were shown to have the potential to improve performance in clinical studies. These levels are similar to, and even higher than, those obtained after other existing prohibited routes of administration of the same drug. The systemic effect of glucocorticoids following local injectable routes of administration may therefore present a significant potential to both improve performance and cause harm to health.

Explanation of the approach taken

- Glucocorticoids include naturally occurring hormones and synthetic analogues and possess a wide range of potencies and pharmacokinetic properties. The body naturally produces a daily output of the endogenous glucocorticoid (cortisol). However, administering glucocorticoid drugs can result in a total glucocorticoid exposure to the body that is much greater than the highest levels of normal physiological cortisol production, which could potentially be performance enhancing.
- The administration of glucocorticoid medications by inhaled, or topical routes (including dental-intracanal, dermal, intranasal, ophthalmological and perianal), in accordance with the manufacturer's approved dosing regimen, are unlikely to reach systemic concentrations which may be performance enhancing.
- However, for other routes of administration (for example, oral), studies involving commonly used glucocorticoids at the normal therapeutic dose range indicated a performance-enhancing effect. These doses can be expressed in terms of cortisol-equivalents and thereby the dose which may be potentially performance enhancing for any glucocorticoid and route of administration can be determined using this approach.
- This systematic approach was applied to determine the glucocorticoid routes of administration that are either prohibited or not prohibited in sport. Consequently, revised and substance-specific laboratory MRL based on excretion studies are introduced to better reflect the proposed approach. To note, the revised MRL are increased or remain unchanged for all glucocorticoids except triamcinolone acetonide, which was revised to a lower MRL. Overall, these changes should reduce the number of *Adverse Analytical Findings* reported by laboratories.

Washout periods following administration of glucocorticoids

- Any injection of glucocorticoids is prohibited In-Competition. Given the widespread availability and the common use of glucocorticoids in sports medicine, *Athletes* and their Support Personnel are advised of the following:
 1. Use of a glucocorticoid by injection during the In-Competition period requires a *Therapeutic Use Exemption*; otherwise, an alternative permitted medication in consultation with a physician shall be used.
 2. After administration of glucocorticoids, urinary MRL which would result in an *Adverse Analytical Finding* can be reached for different periods of time after administration (ranging from days to weeks), depending on the glucocorticoid administered and the dose. To reduce the risk of an *Adverse Analytical Finding*, *Athletes* should follow the minimum washout periods*, expressed from the time of administration to the start of the In-Competition period (i.e. beginning at 11:59 p.m. on the day before a Competition in which the *Athlete* is scheduled to participate, unless a different period was approved by WADA for a given sport). These washout periods are based on the use of these medications according to the maximum manufacturer's licensed doses:

Route	Glucocorticoid	Washout period*
Oral**	All glucocorticoids;	3 days
	Except: triamcinolone; triamcinolone acetonide	10 days
Intramuscular	Betamethasone; dexamethasone; methylprednisolone	5 days
	Prednisolone; prednisone	10 days
	Triamcinolone acetonide	60 days
Local injections (including periarticular, intra-articular, peritendinous and intratendinous)	All glucocorticoids;	3 days
	Except: prednisolone; prednisone; triamcinolone acetonide; triamcinolone hexacetonide	10 days

* **Washout period** refers to the time from the last administered dose to the time of the start of the In-Competition period (i.e. beginning at 11:59 p.m. on the day before a Competition in which the Athlete is scheduled to participate, unless a different period was approved by WADA for a given sport). This is to allow elimination of the glucocorticoid to below the reporting level.

** Oral routes also include e.g. oromucosal, buccal, gingival and sublingual.

3. If the glucocorticoid needs to be administered via a prohibited route within these washout time periods, a *Therapeutic Use Exemption* (TUE) may be required. Physicians administering local injections of glucocorticoids should be aware that periarticular or intra-articular injection may sometimes inadvertently result in intramuscular administration. If intramuscular administration is suspected, the washout periods for the intramuscular route should be observed, or a TUE application sought.

4. Please note that as per Article 4.1e of the International Standard for TUEs, an *Athlete* may apply retroactively for a TUE if the *Athlete Used Out-of-Competition*, for therapeutic reasons, a Prohibited Substance that is only prohibited *In-Competition*. *Athletes* are strongly advised to have a medical file prepared and ready to demonstrate their satisfaction of the TUE conditions set out at Article 4.2, in case an application for a retroactive TUE is necessary following Sample collection.
- For additional information including the revised MRL, please consult the recently published article with details of the process that lead to these changes: <https://bjism.bmj.com/content/early/2021/04/19/bjsports-2020-103512.full?ijkey=APWRPYVYjy69LOH&keytype=ref>

P1. Beta-blockers

- Underwater Sports (CMAS) subdisciplines were regrouped. This change does not affect the current subdisciplines where beta-blockers are prohibited.

MONITORING PROGRAM

- The monitoring of bemitil, and glucocorticoids is discontinued as the required prevalence data were obtained.

* For further information on previous modifications and clarifications, please consult the *Prohibited List Q & A* at www.wada-ama.org/en/questions-answers/prohibited-list-qa.