

## Glucocorticoids and Therapeutic Use Exemptions

This paper discusses glucocorticoid (GC) use in athletes and the general requirements of a Therapeutic Use Exemption (TUE), considering the changes to the S9 section of the 2022 WADA List of Prohibited Substances and Methods.

Note: The individual TUE Checklists or TUE Physician Guidelines should be consulted when considering the specific medical condition for which GCs may be used.

### Introduction

Glucocorticoids are a commonly used and very effective medication for a variety of medical conditions. They are administered primarily for their potent anti-inflammatory and immune-suppressive effects. They are readily available in various formulations and may be administered via different routes for local or systemic treatment.

GCs are catabolic agents and while sharing a common steroidal structure, display none of the physiological effects of androgenic anabolic steroids, agents with limited therapeutic use in sport. Since the term “steroid” only denotes chemical structure and not effect, use of the common collective “steroids” is confusing and should be avoided. GCs, like any medication, are not without some risks or side effects, particularly with long-term use. Given an associated risk profile, including secondary infection or adrenal suppression, all physicians should be judicious when choosing GCs in their management of athletes.

Athletes, as a subset of the general population, suffer the same general medical conditions and injuries for which GC treatment is frequently appropriate. What is less clear is whether athletes, with the increased stress of competition and training, receive treatment with GCs more frequently. In a study that involved 603 sports medicine doctors from 30 different countries, more than 85% of the respondents said that they routinely injected GCs and/or prescribed GCs.

### Glucocorticoids and the List of Prohibited Substances

As of the 2022 Prohibited List, GCs are prohibited in-competition when administered by all injectable, oral, or rectal routes. Examples of injectable routes of administration include intravenous, intramuscular, periarticular, intraarticular, peritendinous, intratendinous, epidural, intrathecal, intrabursal, intralesional (e.g., intrakeloid), intradermal, and subcutaneous. It should be noted that all oral routes of administration of GCs remain prohibited including oromucosal, buccal, gingival, and sublingual routes. All other routes of administration including inhalation, intranasal spray, ophthalmological drops, perianal, dermal, dental intracanal application and topical applications are permitted at all times and do not require a TUE.

An athlete risks being sanctioned when a GC, its metabolites or markers are found to exceed the laboratory reporting levels in a urine sample collected in-competition. As per the 2021 Code, an in-competition sample may be collected from 11:59 pm on the day before the competition to the end of such competition including the subsequent sample collection process. However, the definition of in-competition is defined differently in a few sports. Athletes are advised to confirm with their sport federation or national anti-doping organization.

Out-of-competition use of GCs, by any route, is not prohibited. However, an in-competition urine sample may contain evidence of GC use even though this took place out-of-competition, and an adverse analytical finding (AAF) may be reported. If the athlete and attending physician provide appropriate clinical justification for GC use, a retroactive TUE may be granted. However, if no TUE is granted, the AAF may lead to a sanction.

## Glucocorticoids and TUE Applications

If a GC is used therapeutically, exemption through the TUE pathway is appropriate. It is acknowledged that GC treatment is often in response to an unpredictable exacerbation of chronic disease or in acute or recurrent musculoskeletal injury. In these cases, the TUE application will, of necessity, be retroactive. GC use may often occur outside the competition period yet still result in an in-competition AAF. As of 2021, the International Standard for Therapeutic Use Exemption (ISTUE) specifically addresses this, permitting retroactive application where:

ISTUE 4.1e: The Athlete Used Out-of-Competition, for Therapeutic reasons, a Prohibited Substance that is only prohibited In-Competition.

The success of any TUE application rests upon the quality of the accompanying clinical justification. All treating physicians are strongly encouraged to keep full and accurate clinical records, including time and dose of administration when treating athletes liable to doping control, even when the administration of GC occurs prior to the in-competition period. Physicians are encouraged to familiarize themselves with the GC “wash-out periods” described in the WADA 2022 Prohibited List Explanatory notes.

### Washout periods following administration of glucocorticoids

After administration of GCs, urinary reporting levels which would result in an AAF can be reached for different periods of time after administration (ranging from days to weeks), depending on the GC administered, the route and the dose. To reduce the risk of an AAF athletes should follow the minimum washout periods.

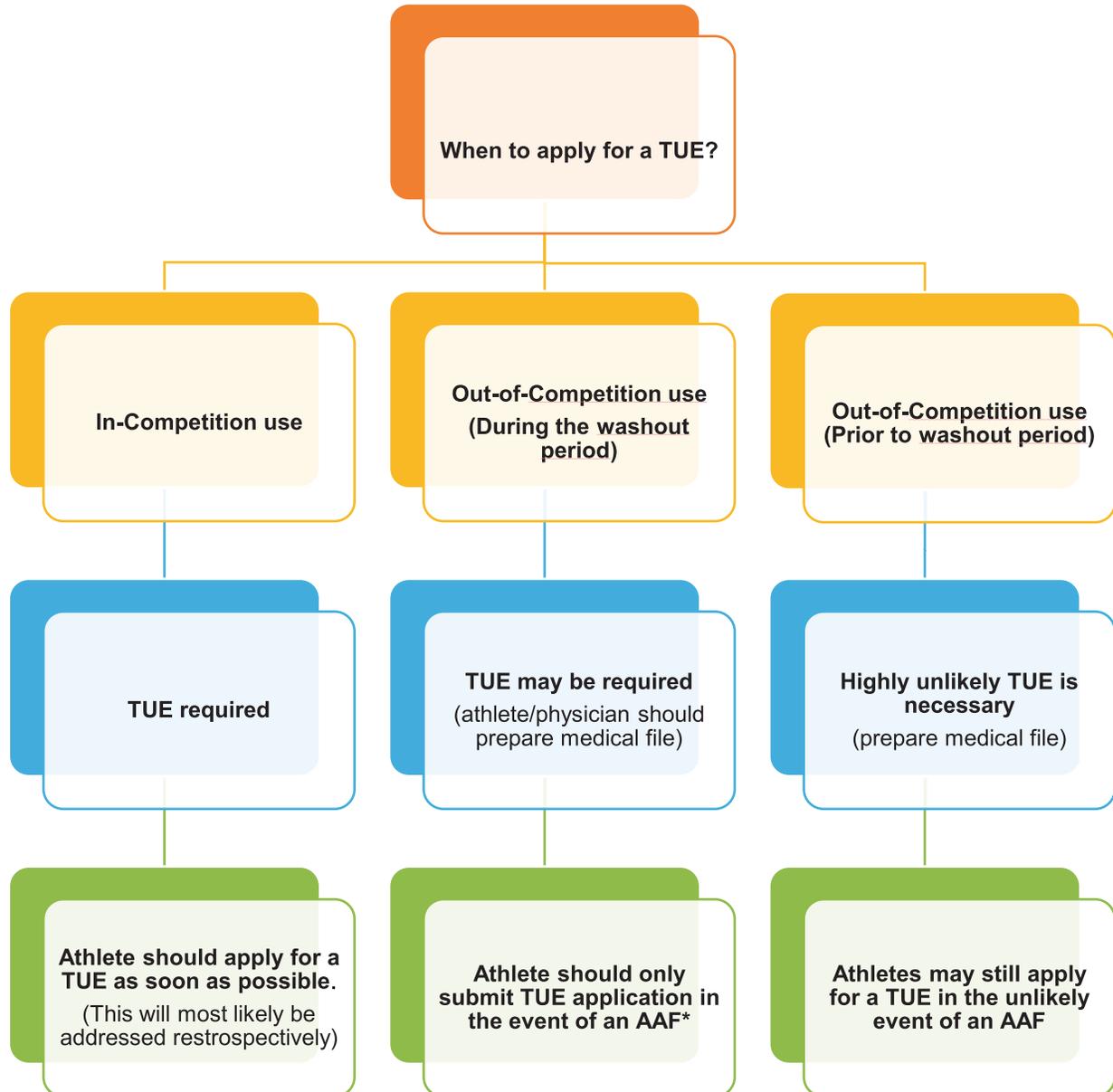
A washout period here refers to the time from the last administered dose to the time of the start of the in-competition period. This is to allow elimination of the GC to below the reporting level. These washout periods are based on the use of these medications according to the maximum manufacturer’s licensed doses:

**Figure 1: GC Washout Table**

Route	Glucocorticoid	Washout period
Oral	All glucocorticoids;	3 days
	Except: triamcinolone acetonide	30 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: triamcinolone acetonide; prednisolone; prednisone	10 days

**Figure 2: When to Apply for a TUE**

The chart below describes the three scenarios that may arise depending on whether the GC was administered in-competition or out-of-competition (in or prior to the washout period). Each pathway provides guidance on when athletes should apply and when ADOs would process the applications.



\*Some ADOs may evaluate TUEs in advance. This information should be clearly communicated to the athletes under their jurisdiction.

Below is a detailed description of the three scenarios described in Figure 2:

If an athlete has an urgent need for GC during the in-competition period, they should apply for a TUE as soon as possible. This situation would be quite rare for most sports and, as described earlier, this will most likely be addressed retroactively.

If an athlete uses a GC out-of-competition, but during the washout period, they do not need to apply for a retroactive TUE unless there is a sample collected from the athlete that results in an AAF.

Some athletes who use a GC during the washout period may desire assurance that their TUE will be granted prior to deciding on whether to take the medication, or if an injection was already received, prior to deciding on whether to enter the upcoming competition. ADOs are often not capable of providing a rapid evaluation and response, nor are they obliged to assess TUEs for substances taken out-of-competition that are only prohibited in-competition. Athletes and their physicians are encouraged to contact their ADO to seek advice on their specific policies and practices.

If an athlete uses a GC prior to the washout period, it is unlikely that an in-competition test would result in an AAF. Therefore, athletes should not apply for TUEs, nor should ADOs evaluate TUEs in these situations. If there is an AAF, a TUE could still be applied for retroactively, although the dates of usage and pharmacokinetics would need to be reviewed first by the ADO.

### **How would a TUE Committee evaluate a glucocorticoid TUE application?**

There are common principles underpinning the evaluation of any TUE application and a TUE Committee (TUEC) will consider, on a balance of probabilities, whether all four criteria described in Article 4.2 of the ISTUE are met.

4.2(a) Requires a diagnosis and need for the medication confirmed by a registered medical practitioner. It may not be a critical need nor even medical best practice but rather a reasonable and acceptable medical treatment. The TUEC must respect the doctor-patient relationship and not unduly interfere with medical practice. For certain conditions, such as ulcerative colitis, the diagnosis is usually well defined and, in such cases, may include biopsy reports, colonoscopy, etc. However, for a simple bursitis, there may be little diagnostic information beyond the physician's clinical and physical assessment. Nonetheless, it is important that the clinical circumstances and physician's clinical reasoning are clearly described, and the results of any investigations reported.

4.2(b) Requires affirmation that the treatment is not performance enhancing beyond a return to the athlete's previous state of health, which is considered the "norm" for that individual. In most cases, even after medication use, the athlete may not return to their full pre-injury or pre-illness status. Each application must be evaluated individually. There is no evidence suggesting that a single GC injection (intra-bursal, peri-tendinous or intra-articular) provides performance enhancement, despite the possibility of temporary systemic distribution.

4.2(c) There may not be any reasonable permitted alternatives to GCs, which are unique and potent anti-inflammatory agents, widely used across a range of medical conditions. However, if alternatives are available the applying/treating physician must explain why the GC was the most appropriate treatment.

4.2(d) Requires that the reason for the TUE is not a consequence of prior use of a prohibited substance. For example, in the unusual situation that adrenal insufficiency in an athlete was due to proven and prolonged doping, then criterion 4.2(d) would not be fulfilled.

### **SUMMARY POINTS**

1. Glucocorticoids, anti-inflammatory/immunosuppressive agents with wide clinical use, are permitted out-of-competition by any route of administration.
2. Out-of-competition administration of GCs may however result in an Adverse Analytical Finding during an in-competition test.
3. Glucocorticoids are prohibited in-competition only when administered by injectable, oral, or rectal routes.
4. Retroactive application for therapeutic use of a GC is permitted in accordance with the ISTUE criteria.
5. Complete clinical records will facilitate a successful TUE application and may be required for results management purposes.