糖皮質素與治療用途豁免(TUE)指引

摘要

1. 糖皮質素、消炎劑/免疫抑制劑廣泛用於醫療用途，得於賽外經任何途徑施用。
2. 賽外施用糖皮質素仍可能於賽內檢測時造成不利檢測報告。
3. 賽內禁止經由注射、口服或經直腸施用糖皮質素。
4. 依治療用途豁免國際標準(ISTUE) 規定，因治療用途施用糖皮質素，可提出回溯性 TUE 申請。
5. 完整病歷資料有助於取得 TUE 核可，且可能被要求提供作為結果管理用途。

糖皮質素與運動禁藥禁用清單

1. 2022 年運動禁藥禁用清單，糖皮質素於賽內禁止以注射、口服、直腸施用。
2. 注射含靜脈、肌肉、關節周圍、關節注射、腱鞘周圍注射、肌腱內注射、硬膜外、鞘內、滑液囊、病灶內(如蟹足腫)、皮內、皮下等注射方式；
3. 口服含口腔粘膜、頰黏膜、牙齦、舌下等方式給藥
4. 其他施用途徑(除注射、口服、經直腸)未受禁止，無需申請治療用途豁免。如吸入、鼻內噴劑、眼科滴劑、肛圍、真皮、牙管、外用等任何時間均不在禁止之列。
5. 運動員因施用糖皮質素可能遭受處分之風險係於賽內採樣之檢體依藥檢實驗室提送代謝物或標示物濃度超過標準而定。
6. 依 2021 年世界運動禁藥管制規範所訂，賽內期起始自運動員參賽前一日 23:59 起迄競賽結束當日或採樣程序完成為止，惟不同運動種類有不同之賽內規定，運動員應詳洽所屬特定體育團體或國家運動禁藥管制組織。
7. 賽外施用糖皮質素，任何施用途徑均非禁止，惟賽內採樣之尿液檢體顯示糖皮質素係於賽外施用者，可能導致不利檢測報告，如運動員及主治醫師檢具相當之醫療證明，證明該糖皮質素係賽外施用者，則可提出回溯性 TUE 申請，經審查相關條件後取得核可；反之，若經審查後未核可者，將受到處分。

施用糖皮質素後之消除期

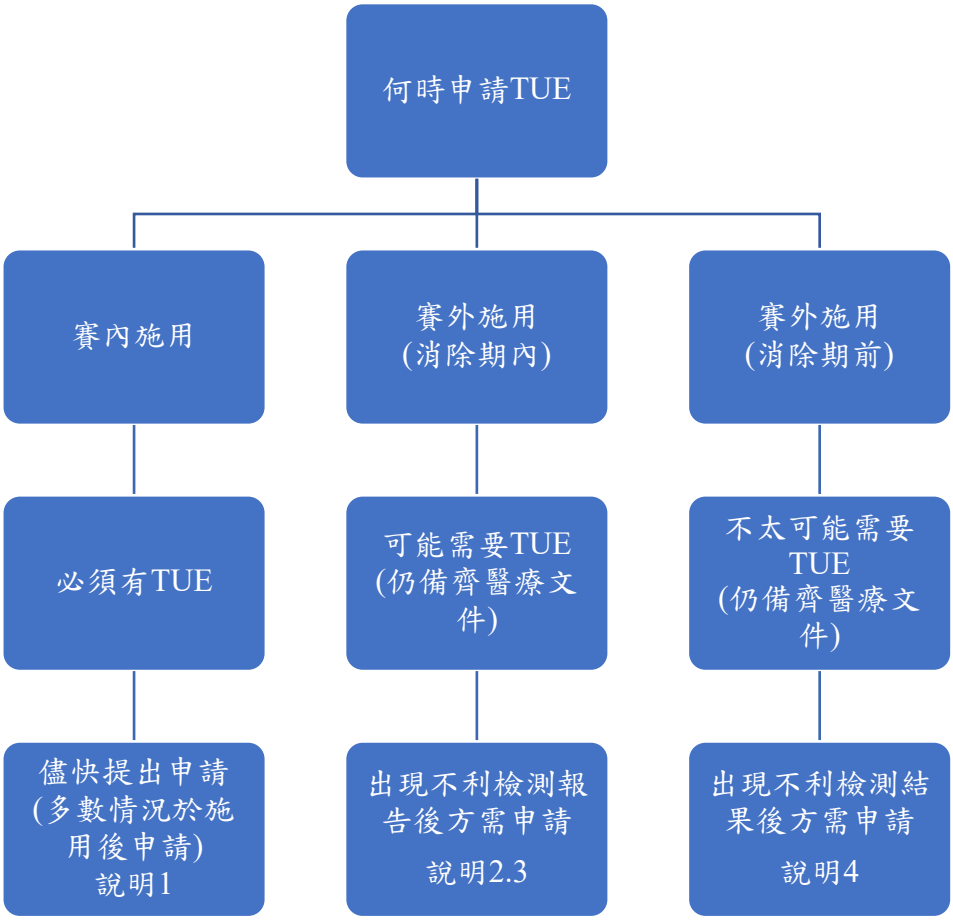
1. 施用糖皮質素後，尿液殘留濃度構成不利檢測報告依施用方式及劑量而有數日至數週不等。為避免此風險，應參照最低消除期，消除期自最後一劑施用迄賽內起始日止。
2. 經消除期後濃度將低於構成不利檢測報告之濃度。
3. 此消除期計算基於製藥商所訂之最高使用劑量。

施用方式	糖皮質素	消除期
口服	所有種類	3 天
	例外：Triamcinolone acetonide	30 天
肌肉注射	Betamethasone, Dexamethasone, Methylprednisonlone	5 天
	Prednisolone, Prednisone	10 天
	Triamcinolone acetonide	60 天
局部注射	所有種類	3 天
	例外：Triamcinolone acetonide, Prednisolone, Prednisone	10 天

糖皮質素與治療用途豁免申請

1. 如糖皮質素作為治療用途，該項核可得由 TUE 申請取得；目前已知糖皮質素經常用於治療不可預期之痼疾惡化、急性、經常性肌肉骨骼傷害，這些情況下 TUE 之申請將會是回溯性。
2. 賽外施用糖皮質素亦可能於賽內構成不利檢測報告，此情況特別列於 2021 年 ISTUE 允許提出回溯性申請。(ISTUE 4.1e 運動員基於治療用途於賽外施用限賽內禁用物質)
3. 惟 TUE 之核可係依提具之診療證明而定，建議主治醫師治療受運動禁藥管制規範之運動員時應保留完整且精確之診療紀錄，包含施用劑量及施用時間。即使於賽內期前即施用糖皮質素，建議醫師應熟悉糖皮質素之消除期(公告於 WADA 2022 Prohibited List Explanatory note)。

何時申請 TUE



說明：

1. 如運動員於賽內因緊急情況需施用糖皮質素，多數情況下於施用後提出回溯性申請。少數情況於施用前申請。
2. 如運動員於賽外之消除期內施用糖皮質素時，出現不利檢測報告後方須提出申請。
3. 因審核須一定工作時間，且審核於賽外施用限賽內禁用物質非必要。運動員於賽外之消除期內施用糖皮質素時，想確保 TUE 將被核可或涉及施用後是否可參賽，運動員仍可向本會詢問關於此情況之處理方式。
4. 如運動員於消除期前施用糖皮質素，於賽內出現不利檢測報告機率極低，運動員無須提出 TUE，如因此出現不利檢測報告者，可提出回溯性 TUE 申請。

TUE 審查委員會如何評估糖皮質素之申請案件

本會 TUE 審查委員會審查應符合 ISTUE 4.2 相關規定。

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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:

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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.