

Guidance Notes on Therapeutic Use Exemption (TUE) Applications

Beta-2 Agonists

This document is intended to provide physicians with guidance on how to complete the beta-2 agonist TUE application form and to assist in providing Athletes with medical evidence to confirm the diagnosis of asthma and/or its clinical variants. Asthma TUE applications for the **use of beta-2 agonists** require sections 1 and 2 set out below to be submitted in combination with the recommendations set out in either section 3 or 4 of this document.

Please note that TUE applications for glucocorticosteroid inhalers are no longer required but instead Athletes must declare to UK Sport when glucocorticosteroid use begins. For more information about how to declare glucocorticosteroid inhalers go to www.100percentme.co.uk.

It is important to note that:

- Forced Expiratory Volume (FEV₁) at rest, as well as changes in FEV₁ in response to either a bronchodilator or bronchoprovocation challenge, are essential measures when applying for Therapeutic Use Exemption.
- Challenge tests that have been performed more than 3 years prior to application will not be accepted.
- Peak flow and/or histamine challenge are no longer accepted as a measure of lung function for the purposes of TUE applications.
- Due to poor sensitivity and specificity a methacholine challenge is discouraged as a diagnostic tool.

Medical History

Physicians should consider the following points when completing the medical history section of the beta-2 agonist application form (page 3):

- Respiratory symptoms which suggest asthma in athletes. Symptoms may include recurrent breathlessness, cough, wheezing, chest tightness or excessive mucus production.
- Potential triggering factors of asthma.
- Seasonal/environmental asthma-like symptoms.
- History of asthma, atopic disorders and/or childhood asthma.
- Age of onset.
- Documented exploration of alternative causes of the symptoms being presented.
- Past history of acute exacerbations of asthma including hospital emergency department attendance/admission reports and/or previous treatment with oral corticosteroids.

Clinical Examination

Physicians should document the following points when completing the clinical examination section of the beta-2 Agonist application form (page 4):

- Clinical examination findings with specific focus on the respiratory system.
- Baseline measurement of resting spirometry noting FEV₁, Forced Vital Capacity (FVC), and FEV₁/FVC values. If preferred, these baseline measurements can be performed prior to either a bronchodilator (section 3) or bronchoprovocation challenge (section 4).

It is acknowledged that respiratory examination may be normal at rest however it remains important that this aspect of assessment is documented to confirm the completion of this component of clinical evaluation and to acknowledge due consideration for the differential diagnosis.

Baseline Spirometry

To accurately evaluate the test results, data for at least two flow loops must be provided to confirm that the best baseline FEV₁ is within 5% of the second best FEV₁. Further flow loops are required if the best baseline FEV₁ value is not within 5% of the second best FEV₁ value at baseline in accordance with ATS/ERS spirometry guidelines [4].

Bronchodilator Reversibility Challenge: short acting beta-2 agonist

To accurately evaluate this test, medication should be withheld prior to testing on the day of the test for salbutamol, 24 hours for long acting bronchodilators and 72 hours for corticosteroid medication. If any adverse symptoms occur the medication should be restarted immediately.

It is recommended that a bronchodilator challenge is the investigation of preference in athletes with abnormal resting lung function (FEV₁ < 80 % predicted, FEV₁/FVC < 0.7). It may also be chosen as an initial objective test in those with normal resting spirometry.

Evidence to be submitted in addition to the beta-2 agonist application form

- Key spirometry data (FEV₁, FVC, % difference from baseline FEV₁).
- Flow-volume loop tracing if available.

NB. Applications will not be reviewed unless duplicate FEV₁ measurements are taken at each time point following bronchodilator administration. Duplicate FEV₁ values must also agree within 5% & 150ml of each other to confirm reproducibility of the best FEV₁ value measured.

Positive test criteria

A bronchodilator test is deemed positive if FEV₁ increases by more than 12% from baseline value following short-acting beta-2 agonist administration.

NB. The absence of a bronchodilator response does not exclude a diagnosis of asthma. In such cases, athletes will require a bronchoprovocation challenge to provide objective evidence to support diagnosis.

Bronchoprovocation Challenge (EVH, Mannitol, Exercise Test)

To accurately evaluate this test, medication should be withheld prior to testing on the day of the test for salbutamol, 24 hours for long acting bronchodilators and 72 hours for corticosteroid medication. If any adverse symptoms occur the medication should be restarted immediately.

Bronchoprovocation testing is not recommended for those athletes with abnormal resting lung function values (FEV₁ < 80 % predicted, FEV₁/FVC < 0.7).

Evidence to be submitted in addition to the beta-2 agonist application form

- Electronic printout of spirometry results and flow volume loop tracing; or
- A data collection worksheet (**NB.** Worksheets can be found on the 100%ME website if the centre completing the bronchoprovocation challenge does not have their own).

Positive test criteria

EVH Challenge: A positive diagnosis is made with a fall in FEV₁ greater than 10% from baseline at two or more time points post-challenge.

Mannitol Challenge: A positive diagnosis is made with a fall in FEV₁ greater than 15% from baseline at any inhaled dose or a 10% incremental fall in FEV₁ between doses.

Exercise Challenge: A positive diagnosis is made with a fall in FEV₁ greater than 10% from baseline at two or more time points post-exercise.

Points to consider in the case of a 'negative' bronchoprovocation test:

- Further testing may be warranted and should be dictated by clinical suspicion.
- If clinical suspicion still exists, a detailed medical history including physician consultations, respiratory specialist reviews, exploration of alternative causes of symptoms and evidence of negative bronchoprovocation challenges should be submitted for review.
- Other disorders should also be considered such as vocal cord dysfunction, other chronic lung disorders, cardiac disorders, and poor breathing technique during exercise.

Physicians are guided to the references below for standardised protocols for bronchodilator [4], bronchoprovocation testing [1, 3], predicted value equations for spirometry [5] and guidelines for the diagnosis of asthma [2, 6]. For further information please contact Nick Wojek, Medical Coordinator at tue@uksport.gov.uk.

References

1. Anderson, S.D., and Brannan, J.B. (2003). Methods for "Indirect" Challenge Tests Including Exercise, Eucapnic Voluntary Hyperpnea, and Hypertonic Aerosols. *Clinical Reviews in Allergy and Immunology*, **24**, 27-54.
2. British Thoracic Society Scottish Intercollegiate Guidelines Network (2008). British Guideline on the Management of Asthma: A National Clinical Guideline. *Thorax*, **63 (4)**, iv1-121.
3. Diagnosis, Prevention and Treatment of Exercise Related Asthma, Respiratory and Allergic Disorders in Sport. Ed Carlsen et al. *European Respiratory Journal*, November 2005, Monograph **33**.
4. Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., van der Grinten, C.P., Gustafsson, P., Jensen, R., Johnson, D.C., MacIntyre, N., McKay, R., Navajas, D., Pedersen, O.F., Pellegrino, R., Viegi, G., Wanger, J.; ATS/ERS Task Force. (2005). Standardisation of spirometry. *Eur Respir J*, **26(2)**, 319-38.
5. Quanjer, P.H., Tammeling, G.J., Cotes, J.E., Pedersen, O.F., Peslin, R., and Yernault, J.C. (1993). Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl.*, **16**, 5-40.
6. Pauwels, R.A., Buist, A.S., Calverley, P.M.A., Jenkins, C.R., Hurd, S.S., and GOLD Scientific Committee. (2001). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *Am J Respir Crit Care Med.*, **163**, 1256-76.

NB. In case of any discrepancy between this guidance document and UK Sports Anti-Doping Rules and Procedures, the latter shall prevail.