WORLD ANTI-DOPING AGENCY
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WADA Technical Letter – TL16

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Written by: Reviewed by:	*WADA* Science *WADA* Laboratory Expert Group	Approved by:	*WADA* Executive Committee
Date:	21 December 2020	Effective Date:	1 January 2021

TRETOQUINOL

1.0 Introduction

WADA wishes to draw the attention of the Laboratories to the detection and reporting of **Tretoquinol** [Trimetoquinol; 1-(3',4',5'-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline] in urine *Samples*.

Tretoquinol is a non-selective beta-2 agonist, which is listed as an example of prohibited beta-2 agonists under class S3 of the *Prohibited List*. Tretoquinol is used therapeutically for the treatment of asthma (sold as Inolin® in some Asian countries) and is also used as an ingredient of over-the-counter (OTC) cold and flu medications.

Studies on tretoquinol metabolism [1,2] have shown that it is excreted in urine either as free form (minor) or phase-II conjugates (glucuronide and sulfate); in addition, tretoquinol is metabolized by catechol-O-methyl transferase (COMT) into **6-** and **7-Methoxytetroquinol**, which are also excreted in urine either unchanged or after phase-II conjugation (Figure 1). However, not much has been published about the kinetics of urinary excretion of tretoquinol or its *Metabolites* and, therefore, there has been no information available about the expected urinary concentrations after administration.

A recent study performed by the Tokyo Laboratory, in which volunteers were administered 6 mg of oral tretoquinol hydrochloride hydrate (as per manufacturer's recommendations) has helped shed light on the excretion kinetics and provides the basis for a conservative *Minimum Reporting Level* (*MRL*) for tretoquinol (free plus glucuronide conjugate) as outlined below [2]. This *MRL* is established to avoid the reporting of an *Adverse Analytical Finding* for Tretoquinol, which may have resulted from the inadvertent use of tretoquinol-containing OTC medications.

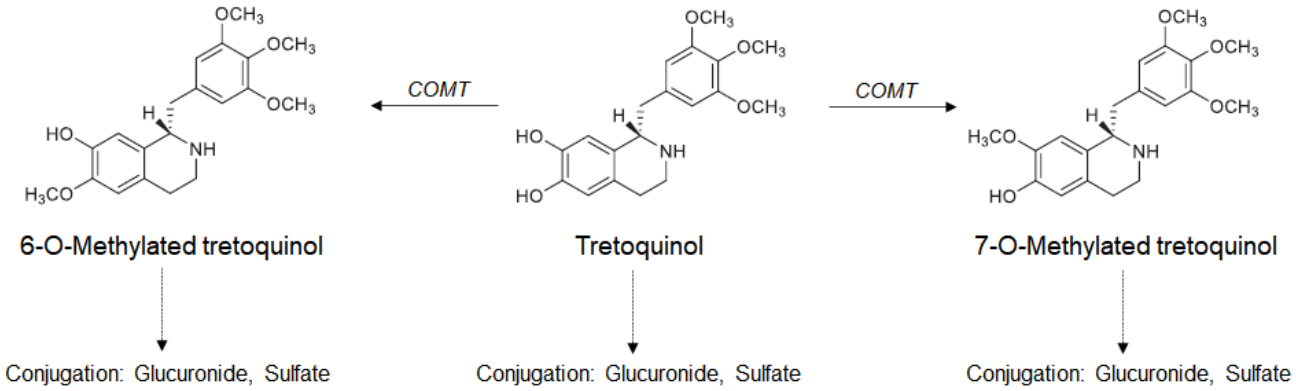

Figure 1. Metabolic pathway of Tretoquinol (adapted from Okano *et al*. [2])

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2.0 Analysis and Reporting Requirements

- Laboratories shall target the analysis of the tretoquinol **parent compound** and its **glucuronoconjugated *Metabolite*** only, following urine enzymatic hydrolysis with β-glucuronidase (from *E. Coli*);
- Report findings for tretoquinol as an *AAF* in *ADAMS* only when the total estimated concentration of tretoquinol (free + glucuronidated conjugate) is higher than (>) 20 ng/mL.

3.0 References

[1] Camargo F.C., *et al*. Chromatographic detection of trimetoquinol (Inolin®) and its major urinary metabolites in the horse: A preliminary report. *Chromatographia*. **60**(7-8): 371-378, 2004.

[2] Okano M., *et al*. Analysis of tretoquinol and its metabolites in human urine by liquid chromatography–tandem mass spectrometry. *Drug Test Anal*. **11**(11-12): 1724-1730, 2019.