WADA Technical Letter – TL13

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Written by: Reviewed by:	*WADA* Science *WADA* Laboratory Expert Group	Approved by:	*WADA* Executive Committee
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TRIMETAZIDINE

1.0 Introduction

WADA wishes to draw the attention of the Laboratories to the following observations and instructions on the analysis and reporting of **Trimetazidine** (TMZ).

The detection of TMZ [1-(2,3,4-trimethoxybenzyl)piperazine] in urine may result from the metabolism of **Lomerizine** [1-[bis(4-fluorophenyl)methyl-4-(2,3,4-trimethoxybenzyl)piperazine], a permitted drug used for the treatment of migraine [1,2,3].

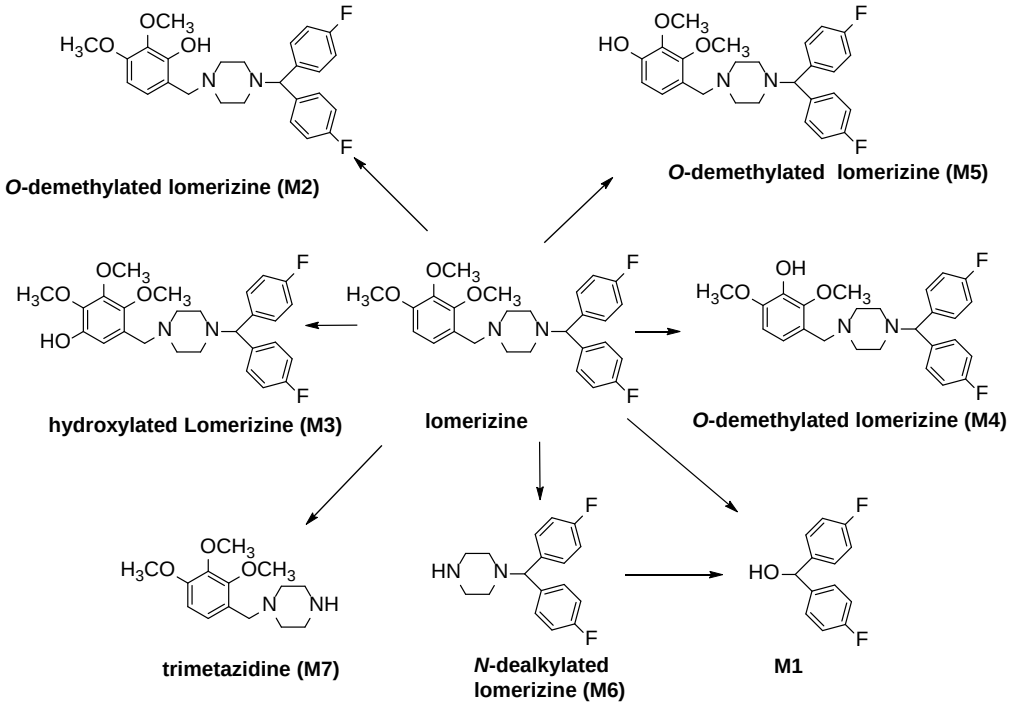

Figure 1. Proposed metabolic pathway of lomerizine (adapted from Okano *et al* [3]).

[Comment: Lomerizine (the parent compound), which has a short half-life, can be found in urine at concentrations much lower than that of TMZ (minor Metabolite), in a ratio of 1/20 or less. However, the concentration of the lomerizine M6-Metabolite is usually higher than that of TMZ.]

2.0 Analysis and Reporting Requirements

Before reporting a result as an *Adverse Analytical Finding* (*AAF*) for TMZ, Laboratories shall evaluate whether the finding is the result of the permitted administration of lomerizine.

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When detecting TMZ in a urine *Sample*, Laboratories shall:

1. Check the Sample *Doping Control* Form (DCF) for a declaration of use of lomerizine;

2. Whenever a Laboratory detects TMZ in an Initial *Testing* Procedure (ITP) of a urine *Sample*, an additional test for the presence of the non-prohibited lomerizine AND its specific *Metabolite*(s) [at least the N-dealkylated M6 *Metabolite*, 1-Bis-(4-fluorophenyl)-methylpiperazine] shall be included in the Confirmation Procedure (CP);

[Comment: The CP may include, for example, the use of LC-MS/MS targeting the diagnostic precursor/product ion pairs shown below, which are obtained from the protonated molecules of TMZ, lomerizine and lomerizine M6-Metabolite;

Transition (*m/z*) [3,4]		
Trimetazidine	**Lomerizine**	**Lomerizine M6-*Metabolite***
267>181	469>181	289>203
267>166	469>203	289>183
267>136	469>166	

[Comment: The Limit of Detection (LOD) of the Tests Method(s) used for the detection of lomerizine and its M6 Metabolite should be lower than (<) the corresponding LOD for TMZ.]

3. Report the result as a Negative Finding if it is considered that the presence of TMZ in the *Sample* could have resulted from the permitted administration of lomerizine;

4. Report the result as an *AAF* for TMZ when neither lomerizine nor its *Metabolite*(s) (at least M6) are detected in the *Sample*, or when otherwise the Laboratory concludes that the concentration of TMZ in the *Sample* is not consistent with the administration of lomerizine (*e.g.* concentration of TMZ higher than (>) that of lomerizine M6-*Metabolite*).

3.0 References

[1] Awata N., Kawashima T., and Sakai T. “Metabolism of lomerizine hydrochloride in humans” *Jpn Pharmacol Ther* **22**: 173-183, 1994.

[2] Sigmund G., *et al*. “Doping control analysis of trimetazidine and characterization of major metabolites using mass spectrometric approaches”. *Drug Test Anal*. **6**(11-12):1197-205, 2014.

[3] Okano M. *et al.*, “Analytical Detection of trimetazidine produced by metabolic conversion of lomerizine in doping control analysis”. *Drug Test Anal*. **8**(8):869-74, 2016.

[4] Ren Y., *et al*. “Determination of lomerizine in human plasma by liquid chromatography/tandem mass spectrometry and its application to a pharmacokinetic study”. *J Chromatogr B Analyt Technol Biomed Life Sci*. **947-948**: 96-102, 2014.