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].

![Proposed metabolic pathway of lomerizine](image)

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.
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;]

<table>
<thead>
<tr>
<th>Transition (m/z) [3,4]</th>
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<tbody>
<tr>
<td>Trimetazidine</td>
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<tr>
<td>267&gt;181</td>
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<tr>
<td>267&gt;166</td>
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<tr>
<td>267&gt;136</td>
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</tbody>
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   [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


