I received a report that listed Chlorothiazide (CTZ)/Hydrochlorothiazide (HCTZ) as present. Why are these two medications reported together?

CTZ is a prescription medication and known pharmaceutical impurity of HCTZ. Furthermore, HCTZ can degrade into CTZ when exposed to certain environmental conditions. Therefore, if HCTZ and CTZ are both present in the absence of a known prescription for CTZ or HCTZ, both drugs will report together.

HCTZ is a thiazide diuretic and antihypertensive agent that has been in use since 1957. HCTZ produces a diuretic effect by blocking the reabsorption of sodium and chloride by the kidneys, increasing the volume of water being eliminated by the body. Antihypertensive effects are thought to be due initially to decreased blood volume and cardiac output, with more chronic effects related to reduced peripheral vascular resistance; however, the exact mechanism of action is unknown. HCTZ is FDA approved for the management of hypertension and edema (fluid retention by the body). It is also used off-label for calcium kidney stones.

CTZ, a less potent and pharmaceutically available thiazide diuretic, is a close structural relative of HCTZ. It is also a well-known pharmaceutical impurity that is formed during the synthesis of HCTZ. The US Pharmacopeia-National Formulary (USP-NF) lists the acceptable criteria of CTZ impurity in HCTZ as no more than 0.5%.

HCTZ is not known to be metabolized by the body. Within 48 hours of ingestion, 65-72% of the oral dose is eliminated unchanged. Up to 95% of a dose is eventually eliminated by the kidneys. Even though HCTZ is primarily excreted unchanged, it does undergo degradation other than metabolism; one of the degradation products is CTZ. Vojta et al. studied various forms of degradation for HCTZ. CTZ was noted as a degradation product of HCTZ when the parent drug was exposed to hydrolytic stress (1 mL of H2O at 65°C for 18h) and acidic stress (3mL of 0.5 M HCl at 50°C for 2h). Exposure to thermal (65°C for 18 h), alkaline (2mL of 0.2 M NaOH at 50°C for 2h), oxidative (3mL of 3% H2O2 at 50°C for 2h), and photolytic (daylight for 18h) stress did not noticeably increase the content of CTZ in the tested drug samples. Deventer et al. found CTZ present in samples of HCTZ solution at a temperature of 20°C and an acidic pH of 2 when exposed to light for 48h; CTZ was not detected at higher pH levels under the same conditions. Although CTZ was detected at a lower pH, HCTZ degraded faster at a high pH, however, converted to degradation products other than CTZ. In a study by Revelle et al., CTZ was formed in HCTZ solutions upon exposure to light for 21h.

CTZ is a prescription medication and has been found in urine specimens tested at Aegis from patients prescribed HCTZ due to being a pharmaceutical impurity and degradation product of HCTZ. When HCTZ is listed as a prescribed medication for a KardiAssure sample and both HCTZ and CTZ are detected, only HCTZ will be reported as present. The threshold for HCTZ (5 ng/mL) will show on the report (see Figure A). When neither HCTZ nor CTZ are indicated as prescribed but HCTZ and CTZ are detected, both HCTZ and CTZ will be reported in combination. The lowest threshold of the two (CTZ at 2 ng/mL) will show on the report (see Figure B). Given the reported degradation of HCTZ to CTZ and other degradation products, it is important to ship urine samples as soon as possible to the laboratory and to refrigerate and protect from light if delays in shipping occur.
FIGURE A:

**Medication(s) Prescribed**
Losartan, Pravastatin, Hydrochlorothiazide

**Test(s) Requested**
20400 - Cardiac Profile

**Results**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Result Interpretation</th>
<th>Comment</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>PRESENT</td>
<td>Test result is consistent and expected with prescribed drug.</td>
<td>5 ng/mL</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>PRESENT</td>
<td>Test result is consistent and expected with prescribed drug.</td>
<td>5 ng/mL</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>PRESENT</td>
<td>Test result is consistent and expected with prescribed drug.</td>
<td>10 ng/mL</td>
</tr>
</tbody>
</table>

FIGURE B:

**Medication(s) Prescribed**
Metoprolol

**Test(s) Requested**
20400 - Cardiac Profile

**Medication Compliance**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Result Interpretation</th>
<th>Comment</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>PRESENT</td>
<td>Test result is consistent and expected with prescribed drug.</td>
<td>1 ng/mL</td>
</tr>
<tr>
<td>Chlorothiazide/HCTZ</td>
<td>PRESENT</td>
<td>A prescription drug, not indicated as prescribed on the requisition form, was detected.</td>
<td>2 ng/mL</td>
</tr>
<tr>
<td>Aspirin</td>
<td>PRESENT</td>
<td>A prescription drug, not indicated as prescribed on the requisition form, was detected.</td>
<td>500 ng/mL</td>
</tr>
</tbody>
</table>

Please call our clinical scientists at 1-877-552-3232 if you require additional information.

**NOTICE:** The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

**REFERENCES:**