HYDROMORPHONE

1.0 Introduction

WADA wishes to draw the attention of the Laboratories to the possible detection of the Prohibited Substance Hydromorphone in urine Samples resulting from the administration of the permitted drug Hydrocodone or from the administration of high doses of either the prohibited Threshold Substance Morphine or the permitted drug Codeine.

2.0 Detection of Hydromorphone as a Result of the Administration of Hydrocodone

It is indeed reported in the literature [1] that hydrocodone is metabolized by O-demethylation to hydromorphone and by N-demethylation to norhydrocodone (Figure 1).

[Comment: In single-dose administration studies [1,2] of hydrocodone, it was found that the levels of norhydrocodone in urine were always higher than or equal to (≥) the parent compound, whereas the levels of hydromorphone were lower (<). Additionally, norhydrocodone was detected in urine for a longer time than hydromorphone.

In a different study involving a population of 25,200 subjects treated with multiple doses of a hydrocodone/acetaminophen formulation, Barakat et al. [3] showed that the metabolic hydromorphone/hydrocodone ratio varied between 0.074 and 0.35.]

2.1 Analysis and Reporting Requirements

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

When detecting hydromorphone in a urine Sample, Laboratories shall:

- Check the Sample Doping Control Form (DCF) for a declaration of use of hydrocodone;
• Whenever a Laboratory detects hydromorphone in an Initial Testing Procedure (ITP) of a urine Sample, an additional test for the presence of hydrocodone and norhydrocodone shall be included in the Confirmation Procedure (CP);

• Report the result as a Negative Finding if the concentration of total* hydromorphone is lower than or equal to (≤) the concentration of total hydrocodone or total norhydrocodone;

• Report the result as an AAF for hydromorphone if the concentration of total hydromorphone is higher (> the concentrations of both total hydrocodone and total norhydrocodone.

[* In every case, total concentration refers to the sum of the concentrations of the respective free compound and its glucuroconjugated form(s).]

3.0 Detection of Hydromorphone as a Result of the Administration of Morphine

Additionally, it was reported in the literature [4,5] that hydromorphone might be found as a minor Metabolite of the prohibited Threshold Substance morphine, more specifically in urines of patients treated with high doses of morphine (Figure 2).

Therefore, it is important to evaluate hydromorphone findings in the presence of total morphine at concentrations below (< the Decision Limit (DL) for morphine of 1.3 µg/mL (or the adjusted DL if the SG is greater than (> 1.018) [6].

[Comment: Studies [5,7] involving patients undergoing treatment with daily high-doses of morphine have shown that the ratio of total hydromorphone (free + glucuronide forms) to total morphine (free + glucuronide forms) ranged between 0.002 to 0.022 [7] or had a mean ± SD value of 0.024 ± 0.017 [5], with urinary morphine concentrations in the range of 103-537 µg/mL or 21 ± 7.0 µg/mL, respectively. In both studies, the concentrations of morphine were higher (> the DL] [8].]

3.1 Reporting Requirements

If hydromorphone is detected in a urine Sample in the presence of morphine, Laboratories shall evaluate whether the finding is consistent with the formation of hydromorphone through the metabolism of morphine:
[Comment: These conditions do not apply to the reporting of hydromorphone findings in the absence of morphine. In such cases, the finding should be reported as an AAF for hydromorphone if the concentration is higher than the Minimum Reporting Level (MRL) for hydromorphone [8].]

- **Report the result as a Negative Finding for hydromorphone if:**

  - The ratio of total* hydromorphone to total morphine is less than or equal to (≤) 0.05, even if the concentration of hydromorphone is greater than (>) the MRL; and/or
  
  - The concentration of total hydromorphone is lower than (<) the MRL, even if the ratio of total hydromorphone to total morphine is greater than (> 0.05.

- **Report the result as an AAF for hydromorphone only if the estimated concentration of total hydromorphone is greater than (>) the MRL and the ratio of total hydromorphone to total morphine is greater than (> 0.05.

[* In every case, total concentration refers to the sum of the concentrations of the respective free compound and its glucuroconjugated form(s).]

### 4.0 References


[Current versions of WADA Technical Documents may be found at https://www.wada-ama.org/en/what-we-do/science-medical/laboratories ]