

## Overview

### Useful For

Monitoring for compliance of methadone treatment for analgesia or drug rehabilitation

Assessing compliance with rehabilitation programs by urine measurement of  
2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine

### Special Instructions

- [Clinical Toxicology CPT Code Client Guidance](#)

### Method Name

Gas Chromatography Mass Spectrometry (GC-MS) Confirmation with Quantitation

### NY State Available

Yes

## Specimen

### Specimen Type

Urine

### Ordering Guidance

1. For situations where chain of custody is required, a Chain-of-Custody Kit (T282) is available. For chain-of-custody testing, order MTDNX / Methadone Confirmation, Chain of Custody, Random, Urine.
2. Additional drug panels and specific requests are available. Call 800-533-1710 or 507-266-5700.
3. If urine creatinine is required or adulteration of the sample is suspected, order ADULT / Adulterants Survey, Random, Urine.

### Specimen Required

**Supplies:** Urine Tubes, 10 mL (T068)

**Collection Container/Tube:** Plastic urine container

**Submission Container/Tube:** Plastic, 10-mL urine tube

**Specimen Volume:** 10 mL

#### Collection Instructions:

1. Collect a random urine specimen.
2. No preservative.

### Forms

If not ordering electronically, complete, print, and send a [Therapeutics Test Request](#) (T831) with the specimen.

Specimen Minimum Volume

2.5 mL

Reject Due To

Gross hemolysis	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Urine	Refrigerated (preferred)	28 days	
	Ambient	14 days	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

Methadone (Dolophine) is a synthetic opioid, a compound that is structurally unrelated to natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin.(1) Methadone is used clinically to relieve pain, treat opioid abstinence syndrome, and treat heroin addiction in an attempt to wean patients from illicit drug use.

Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are cytochrome P450 (CYP) 3A4 and CYP2B6.(1-4) CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved.(1-5) Methadone is metabolized to a variety of metabolites with the primary metabolite being 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).(1-4) The efficiency of this process is prone to wide inter- and intraindividual variability, due to inherent differences in enzymatic activity as well as enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys.(1,4)

Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH.(5) EDDP levels, in contrast, are relatively unaffected by the influence of pH and are, therefore, preferable for assessing compliance with therapy.(5)

Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine.(6) This is commonly referred to as "spiking." In these situations, the specimen will contain large amounts of methadone and no or very small amounts of EDDP.(6) The absence of EDDP in the presence of

methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen.

**Reference Values**

Negative (Positive results are reported with a quantitative result.)

Cutoff concentrations by gas chromatography mass spectrometry:

METHADONE: 100 ng/mL

2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE (EDDP): 100 ng/mL

**Interpretation**

The absolute concentration of methadone and its metabolites found in patient urine specimens can be highly variable and does not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of greater than 0.60.(7)

An EDDP:methadone ratio less than 0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen.(6)

**Cautions**

Urine pH has a considerable effect on the ability to detect methadone, thus

2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine is preferable for urine measurements.

Urine concentrations of methadone show very poor correlation to serum levels or the amount of drug administered.

**Clinical Reference**

1. Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. 10th ed. McGraw-Hill; 2001:569-619
2. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002;41(14):1153-1193
3. Ferrari A, Coccia CP, Bertolini A, Sternieri E. Methadone-metabolism, pharmacokinetics and interactions. Pharmacol Res. 2004;50(6):551-559
4. Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 10th ed. Biomedical Publications; 2014
5. Levine B. Principles of Forensic Toxicology. 2nd ed. AACC Press; 2003:385
6. Galloway FR, Bellet NF. Methadone conversion to EDDP during GC-MS analysis of urine samples. J Anal Toxicol. 1999;23(7):615-619
7. George S, Braithwaite RA. A pilot study to determine the usefulness of the urinary excretion of methadone and its primary metabolite (EDDP) as potential markers of compliance in methadone detoxification programs. J Anal Toxicol. 1999;23(2):81-85
8. Langman LJ, Bechtel LK, Holstege CP. Clinical toxicology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2023:chap 43

**Performance**

Method Description

Confirmation testing is performed by gas chromatography mass spectrometry, solid phase extraction.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Tuesday, Thursday

Report Available

3 to 7 days

Specimen Retention Time

14 days

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

G0480  
80358 (if appropriate for select payers)  
[Clinical Toxicology CPT Code Client Guidance](#)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
MTDNU	Methadone Confirmation, U	104626-7

Result ID	Test Result Name	Result LOINC® Value
56028	EDDP-by GC-MS	104627-5
83129	Methadone-by GC-MS	104628-3
21107	Methadone Interpretation	69050-3
21110	Chain of Custody	77202-0