

Date of report 31 Oct 2024

Reported case interaction between Cobicistat and Paroxetine

Drugs suspected to be involved in the DDI

Perpetrator	Daily Dose
Cobicistat	150 (mg)
Dose adjustment performed No	Administration Route Oral
Start date	End date
March 2, 2020	Ongoing
Victim	Daily Dose
Paroxetine	20 (mg)
Dose adjustment performed	Administration Route
Yes	Oral
Start date	End date
Nov. 6, 2023	Unknown

Complete list of drugs taken by the patient

Antiretroviral treatment

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir-AF

Complete list of all comedications taken by the patient, included that involved in the DDI

Paroxetine

Clinical case description	
Gender Female	Age 38
eGFR (mL/min) >60	Liver function impairment No

Description

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A 38-year-old woman diagnosed with HIV in 2020 has been well-controlled on a regimen of Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir alafenamide (EVG/c/F/TAF) for the past four years. She has a history of major depressive disorder with obsessive features, managed with paroxetine 20 mg once daily for the past six months.

She presents to the HIV clinic with complaints of increased fatigue, dizziness, and gastrointestinal discomfort, including nausea and occasional vomiting, over the past month. She also reports feeling more anxious and irritable, despite her depression being well-controlled until recently. Six weeks earlier, she decided to double the dose of paroxetine, believing the prescribed 20 mg was too low for her symptoms, and began taking 40 mg paroxetine daily. These symptoms were interpreted as an interaction between paroxetine and cobicistat. Her paroxetine dose was reduced back to the initial 20 mg, leading to improvement but not complete remission of symptoms.

The psychiatrist subsequently decided to switch her antidepressant to sertraline 50 mg daily, while her treatment with EVG/c/F/TAF was maintained.

Clinical Outcome

Toxicity

Drug Interaction Probability Scale (DIPS)

Score

6 - Probable

Editorial Comment

The maximum recommended dose of paroxetine for major depressive disorder is 50 mg/day (normal release) or 62.5 mg/ day (extended release), which are higher than the dose used in this clinical case.

Paroxetine is primarily metabolized by CYP2D6 (high affinity, saturable mechanism) and also by CYP3A4 (low affinity). Based on pharmacologic predictions, cobicistat could theoretically increase paroxetine's plasma concentration by inhibiting CYP2D6 and/or CYP3A. However, while cobicistat is a mild inhibitor of CYP2D6, paroxetine itself is a potent CYP2D6 inhibitor. Given the genetic variability in CYP2D6, there are four main metabolizing phenotypes: poor (PM), intermediate (IM), extensive (EM/normal), and ultrafast (UM). The use of paroxetine can induce a "phenoconversion," effectively creating an iatrogenic poor metabolizer (PM) phenotype by inhibiting CYP2D6. At a long-term dose of 20 mg/day, paroxetine has been shown to convert approximately 70% of EM to PM phenotypes. This shift can elevate paroxetine levels, increasing toxicity risks. The recent increase in paroxetine dosage from 20 mg to 40 mg in this case could have further contributed to toxicity due to paroxetine's nonlinear pharmacokinetics, although cobicistat's contribution cannot be ruled out. As a strong inhibitor of CYP3A4, cobicistat may also reduce the residual metabolism of paroxetine via CYP3A4, leading to further elevation in plasma concentrations of paroxetine.

Ref: Paxlil® FDA Revised:02/2024 <u>https://</u> www.accessdata.fda.gov/drugsatfda_docs/label/ 2024/020936Orig1s065lbl.pdf

Nassan M, Nicholson WT, Elliott MA, Rohrer Vitek CR, Black JL, Frye MA. Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine. Mayo Clin Proc. 2016 Jul;91(7):897-907. doi: 10.1016/j.mayocp.2016.02.023. Epub 2016 Jun 21. PMID: 27289413.

University of Liverpool Recommendation

Potential interaction - may require close monitoring, alteration of drug dosage or timing of administration

For more information <u>click here</u>

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