NON-INTERVENTIONAL
STUDY REPORT ABSTRACT

Title: Safety of Paxlovid Among Patients With Moderate or Severe Hepatic or Renal Impairment

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Rationale and background:

Paxlovid (combination nirmatrelvir and ritonavir) was approved in the EU and UK in January 2022 for the treatment of COVID-19 in adults at high risk of progression to severe disease who do not require supplemental oxygen. Because Paxlovid use in patients with moderate or severe hepatic or renal impairment was missing information at authorisation, this non-interventional post-authorisation safety study (PASS) was conducted as a commitment to the European Medicines Agency to characterise its safety profile in these populations.

Research question and objectives:

To assess the safety of Paxlovid among patients with COVID-19 and moderate or severe hepatic or renal impairment who received Paxlovid compared with unexposed patients with COVID-19 who did not receive antiviral or who received other COVID-19 treatments. To assess side effects resulting from drug overexposure due to impaired liver function.

Following Interim Report 2, submitted to the EMA in December 2025 and reviewed by the PRAC, objectives and analyses related to the comparison with other COVID-19 treatments were not further pursued.

Study design: non-interventional population-based cohort study

Setting:

The study was a multinational study conducted using routinely collected healthcare data from 3 data sources in France, Spain, and the UK making use of secondary data collected primarily for healthcare purposes as follows: (1) SNDS (French Administrative Healthcare Database [Système National Des Données de Santé]) in France; (2) SIDIAP (Information System for the Development of Research in Primary Care) [Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària]) in Catalonia, Spain; and (3) Clinical Practice Research Datalink (CPRD) Aurum in the UK. The study period was from January 2022 until as late as possible in each data source: 31 December 2023 in SNDS, 30 June 2024 in SIDIAP, and 31 August 2024 in CPRD Aurum.

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Subjects and study size, including dropouts:

Two patient populations with documented COVID-19 were studied: those with moderate or severe hepatic impairment and those with moderate or severe renal impairment. Patients initiating Paxlovid within 7 days of COVID-19 diagnosis were matched to unexposed patients on age, sex, calendar time, COVID-19 timing and source of COVID-19 ascertainment, and linkage to hospital data in CPRD. Follow-up began at treatment initiation or matched index date and continued for up to 30 days.

Variables:

Exposure was identified from prescriptions and dispensings for Paxlovid. Safety outcomes for the primary objectives were from either outpatient or inpatient settings, as available, and included the following safety outcomes of special interest:

- Hepatic transaminase elevations, clinical hepatitis, or jaundice (only in the population with moderate to severe hepatic impairment)
- Severe vomiting, nausea, diarrhoea, or abdominal pain
- Dysgeusia
- Headache
- Hypertension
- Anaphylactic reactions
- Data-driven outcomes (identified based on events appearing in the study population within 30 days after exposure to Paxlovid).

Secondary outcomes were any of the primary outcomes resulting in emergency department visits or hospitalisations.

Results:

Across the 3 data sources, 866 Paxlovid users with hepatic impairment and 5127 with renal impairment were successfully matched to unexposed comparator cohorts of 4097 and 25,374 patients, respectively. Median follow-up was 30 days, with minimal censoring, primarily for administrative reasons. Death was a small proportion of censoring events and occurred mainly among Paxlovid-treated patients with renal impairment in France.

Matched cohorts were well balanced on key characteristics. Patients were predominantly older adults (≥ 60 years), with high COVID-19 vaccination coverage (≥ 3 doses). Paxlovid users less frequently had severe hepatic or renal impairment than unexposed patients, consistent with selective prescribing aligned with label restrictions. Also, Paxlovid users often had a high burden of comorbidities and risk factors for progression to severe COVID-19 (median of 4 to 5), including cancer, diabetes, cardiovascular disease, immunosuppression, and polypharmacy.

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Primary prespecified hepatic safety outcomes were uncommon among patients with hepatic impairment. In SNDS, adjusted comparative estimates for hepatic transaminase elevations, clinical hepatitis, and jaundice were close to or below unity, while estimates from SIDIAP and CPRD were largely non-estimable due to limited number of events. Among patients with renal impairment, gastrointestinal outcomes and headache occurred infrequently, with numerically higher but imprecise adjusted estimates among Paxlovid users in some settings; absolute risks remained low. Other primary prespecified outcomes, including anaphylaxis and hypertension, were rare across data sources. Secondary prespecified outcomes were almost entirely non-estimable, except in SNDS, and showed no indication of increased risk of any outcome, where calculable.

Analyses of data-driven outcomes showed no consistent pattern of increased risk for these outcomes among the hepatic or renal impaired populations. Observed variations, including for urinary tract infections, renal events, and selected cardiovascular outcomes, were heterogeneous across data sources and characterised by low event counts and wide confidence intervals.

Discussion:

Overall, Paxlovid was infrequently used in patients with moderate or severe hepatic or renal impairment, consistent with label restrictions across the 3 countries. Across all 3 data sources, no new or unexpected safety issues were identified. Observed findings were limited by sparse outcome data, and consistent with the established undesirable effects profile of Paxlovid in the SmPC, or compatible with known underlying patient vulnerability, and COVID-19–related complications.

Marketing Authorisation Holder(s): Pfizer Limited

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EMA = European Medicines Agency.

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