Direct Healthcare Professional Communication (DHPC) and communication plan

Paxlovid (nirmatrelvir; ritonavir): reminder of life-threatening and fatal drug-drug interactions with certain immunosuppressants, including tacrolimus

Dear Healthcare professional,

Pfizer in agreement with the European Medicines Agency and <National competent authority> would like to inform you of the following:

Summary

- **Co-administration of Paxlovid with certain immunosuppressants with narrow therapeutic index such as calcineurin inhibitors (ciclosporin, tacrolimus) and mTOR inhibitors (everolimus, sirolimus) can result in life-threatening and fatal reactions due to pharmacokinetic interactions.**
- **Due to the risk of serious interactions, co-administration with these immunosuppressants should only be considered if close and regular monitoring of immunosuppressant serum concentrations is possible.**
- **Monitoring should be performed not only during co-administration with Paxlovid but also after treatment.**
- **Paxlovid is contraindicated in patients using medicines with highly CYP3A dependent clearance and for which elevated plasma concentrations can lead to serious and/or life-threatening reactions, including the calcineurin inhibitor voclosporin.**
- **Consultation with a multidisciplinary group of specialists is required to manage the complexity of co-administration.**
- **The potential benefit of treatment with Paxlovid should be carefully weighed against the serious risks if the drug-drug interactions are not appropriately managed.**

Background on the safety concern:

Use of Paxlovid, a strong CYP3A inhibitor, in patients receiving concomitant medicines metabolised by CYP3A can increase the plasma concentrations of these medicines. Cases of serious adverse reactions, some of which were fatal, resulting from drug-drug interactions between Paxlovid and immunosuppressants including calcineurin inhibitors (voclosporin, ciclosporin and tacrolimus) and mTOR inhibitors (everolimus and sirolimus) have been reported. In several cases, immunosuppressant concentrations were observed to increase rapidly to toxic levels resulting in life-threatening conditions. For example, high tacrolimus levels can lead to acute kidney injury and increase susceptibility to severe infections due to excessive immunosuppression.

Paxlovid is contraindicated in patients taking the calcineurin inhibitor voclosporin. Consultation with a multidisciplinary group (e.g., involving physicians, specialists in immunosuppressive therapy, and/or specialists in clinical pharmacology) is required to manage the complexity of co-administration of Paxlovid with calcineurin inhibitors (ciclosporin and tacrolimus) and mTOR inhibitors (everolimus and sirolimus).

Calcineurin inhibitors and mTOR inhibitors are medicines with a narrow therapeutic index, therefore, co-administration of Paxlovid with these immunosuppressants should only be considered with close and regular monitoring of immunosuppressant serum concentrations, to adjust immunosuppressant dose in accordance with the latest guidelines, in order to avoid over-exposure to the immunosuppressant and

subsequent serious adverse reactions. It is important that monitoring is performed not only during co-administration with Paxlovid but is also pursued after the treatment.

To access further information regarding clinically significant drug-drug interactions, including medicinal products for which co-administration with Paxlovid is contraindicated due to serious interactions, consult the current SmPC or scan the QR code on the outer packaging of Paxlovid.

Call for reporting

Healthcare professionals are asked to report any suspected adverse drug reactions in accordance with the national spontaneous reporting system and include batch/Lot number if available. <include the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Communication plan for Direct Healthcare professional communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Paxlovid (nirmatrelvir, ritonavir)
Marketing authorisation holder(s)	Pfizer Europe MA EEIG
Safety concern and purpose of the communication	Reminder on the interactions associated with Paxlovid (nirmatrelvir tablets; ritonavir tablets)
DHPC recipients	General practitioners, specialists (infectiologists, transplantation physicians, specialists in immunosuppressive therapy, and/or specialists in clinical pharmacology), community pharmacists, hospital pharmacists, emergency units,professional societies, national associations. The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	All EU/EEA Member states

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	8/2/2024
Submission of translated DHPCs to the national competent authorities for review	1/3/2024
Agreement of translations by national competent authorities	8/3/2024
Dissemination of DHPC	21/3/2024