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# HPRA DRUG SAFETY NEWSLETTER

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## In this edition



## Paxlovid▼ – interactions between ritonavir component and other medicines leading to clinically significant reactions

Paxlovid is an oral antiviral medicine comprised of ritonavir and PF-07321332 which is recommended for the treatment of COVID-19 infection in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. A five-day treatment course is indicated as per the approved product information*.

### Drug-drug interactions

Ritonavir, a component of Paxlovid, is a well-known inhibitor of cytochrome P450 CYP3A and p-gylcoprotein (PgP), and may interact with other medicines and lead to clinically significant reactions, including potentially life-threatening or fatal reactions. Interactions may also lead to loss of therapeutic effect of Paxlovid and possible development of viral resistance. Healthcare professionals are therefore strongly advised to carefully review concomitant medicines before and during treatment with Paxlovid and to monitor for interactions and/or adverse reactions.

Information on medicines contraindicated with Paxlovid as well as others with potential significant interactions is available from sections 4.3 and 4.5 of the Summary of Product Characteristics (SmPC) and includes commonly prescribed medicines such as certain statins, anticonvulsants, diazepam, amiodarone and quetiapine. The information provided in the SmPC is a guide, and the potential for interactions with other medicines both prior to and during therapy should be carefully considered. A search tool for drug-drug interactions is available through COVID19oralRx.com, and via a QR code on the package leaflet and outer carton. This search tool has been made available by the marketing authorisation holder for Paxlovid.

### Hepatic and renal function

The standard recommended dose of Paxlovid is 300mg of PF-07321332 (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days. Paxlovid should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

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In patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min), a dose adjustment is recommended and such patients should be advised to take only one tablet of PF-07321332 with the one tablet of ritonavir every 12 hours. The patient should be advised of the adjustment from the standard dosing due to their renal impairment.

Paxlovid is contraindicated in patients with severe renal impairment (eGFR <30 mL/min, including patients with end stage renal failure under haemodialysis) or severe hepatic impairment as no pharmacokinetic and clinical data are available.

No dose adjustment of Paxlovid is advised for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. However, caution should be exercised when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis, as hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir.

### Women of childbearing potential

There are no human data on the use of Paxlovid in pregnancy to inform the drug-associated risk of adverse developmental outcomes. As such, women of childbearing potential should avoid becoming pregnant during treatment and as a precautionary measure for 7 days after completing treatment. As ritonavir may reduce the efficacy of combined hormonal contraceptives, patients using combined hormonal contraceptives should be advised to use an effective alternative contraception method or an additional barrier method of contraception during treatment, and until one menstrual cycle after stopping Paxlovid.

Breastfeeding should be interrupted during treatment and as a precautionary measure for 7 days after completing Paxlovid.

Treatment is not recommended during pregnancy or for women of childbearing potential not using contraception unless the clinical condition requires treatment with Paxlovid.

## Key Message

Ritonavir, a component of Paxlovid, is a well-known inhibitor of cytochrome P450 CYP3A (and PgP inhibitor), and may interact with other medicines leading to clinically significant reactions, including potentially life-threatening or fatal reactions or a loss of therapeutic effect of Paxlovid and possible development of viral resistance.

Refer to the Summary of Product Characteristics (SmPC) for guidance on medicines that are contraindicated or have potential significant interactions. A search tool for drug-drug interactions is available through COVID19oralRx.com

Paxlovid is contraindicated in patients with severe renal impairment. For patients with moderate renal impairment (eGFR ≥ 30 to < 60 mL/min) a dose adjustment is recommended i.e. one tablet of PF-07321332 with one tablet of ritonavir every 12 hours. The patient should be advised of the adjustment from the standard dosing.

Exercise caution when administering Paxlovid to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis, due to the risk of hepatotoxicity.

Advise women of childbearing potential to avoid becoming pregnant during treatment and as a precautionary measure for 7 days after completing treatment. Paxlovid should not be used in pregnant women or women of childbearing potential not using contraception unless the clinical condition requires treatment with Paxlovid.

Paxlovid is subject to additional monitoring▼ and suspected adverse associated with its use should be reported to the HPRA via the available methods.

* *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie or www.ema.europa.eu.*


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# Transmucosal fentanyl – labelling update to mitigate the risks of off-label use, accidental ingestion or unintentional exposure

Fentanyl is a potent opioid analgesic available in various forms (transdermal patches, solution for injection, nasal spray, buccal soluble film, sublingual tablets, and buccal tablets/lozenges). With respect to the transmucosal route of administration, the authorised indication for these medicines is the treatment of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

Transmucosal fentanyl use in those who are opioid naive, through off-label use, accidental ingestion or unintentional exposure, can cause serious harm and can be fatal, including in children. Following a review of available data, the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that warnings are strengthened on the labelling of transmucosal fentanyl products to further raise awareness and to mitigate this risk.

The strengthened warnings complement those already described in product information*. Educational materials to support healthcare professionals and patients in the safe use of these products, including guidance to mitigate the risk of accidental exposure, are available from the HPRA website, through the following links:

- Abstral sublingual tablets
- Actiq compressed lozenge
- Effentora buccal table
- Instanyl nasal spray

## Key Message

Transmucosal fentanyl is approved for use only in the treatment of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic cancer pain.

Use in an opioid naive patient, as either off label use, accidental ingestion or unintentional exposure can cause serious harm and can be fatal, including in children.

Healthcare professionals should ensure that patients are aware of the appropriate use of transmucosal fentanyl and the risks associated with accidental ingestion and unintentional exposure, including in children. Patients should be advised to keep their transmucosal fentanyl in a safe and secure place, out of the sight and reach of children.

Educational materials containing specific advice for each of these medicines, which complement product information, are available from the HPRA website for healthcare professionals and patients/carers. A copy of these should be provided to patients/carers when prescribing or dispensing one of these medicines.

* *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie or www.ema.europa.eu*


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# Product information updates recommended by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC)

The HPRA wishes to highlight a selection of recent recommendations, made by the the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), to update product information for medicines in clinical use. The PRAC, in which the HPRA participate, are responsible for assessing and monitoring the safety of medicines. Healthcare professionals (HCPs) are reminded to regularly check the HPRA or EMA websites for current product information concerning medicines they prescribe or dispense.

## Ibuprofen-containing medicines: Acute Generalised Exanthematous Pustulosis (AGEP)

*Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID), commonly used for the reduction of pain, inflammation and fever*

- Product information for ibuprofen-containing medicines already include a warning regarding very rare reports of serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. This warning will be updated to reflect that cases of AGEP have also been reported. HCPs are reminded that treatment with ibuprofen-containing medicines should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

## Aimovig▼ (erenumab): constipation and hypersensitivity

*Aimovig is an IgG2 monoclonal antibody which binds to the calcitonin gene-related peptide (CGRP) and is indicated for prophylaxis of migraine in adults who have at least four migraine days per month*

- Constipation, which is usually mild to moderate, is a known and common adverse reaction associated with Aimovig (erenumab). In the majority of reported cases, onset was after the first dose, however, patients have also experienced constipation later on in treatment. In most cases constipation resolved within three months. Product information has been updated to reflect that, in the post-marketing setting, constipation with serious complications has been reported with erenumab. In some cases hospitalisation was required, including cases where surgery was necessary. History of constipation or the concurrent use of medicines associated with decreased gastrointestinal motility may increase the risk for more severe constipation and the potential for constipation-related complications. Patients should be warned about the risk of constipation and advised to seek medical attention in case constipation does not resolve or worsens and immediately so if they develop severe constipation. Constipation should be managed promptly as clinically appropriate. For severe constipation, discontinuation of treatment should be considered.
- A warning in product information will reflect that serious hypersensitivity reactions, including rash, angioedema, and anaphylactic reactions, have been reported with erenumab in post-marketing experience. These reactions may occur within minutes, although some may occur more than one week after treatment. Patients should be warned about the symptoms associated with hypersensitivity reactions. HCPs are advised to discontinue erenumab immediately if serious hypersensitivity occurs.

## Emgality▼ (galcanezumab): hypersensitivity reactions

*Emgality is an IgG4 monoclonal antibody which binds to the calcitonin gene-related peptide (CGRP) and is indicated for prophylaxis of migraine in adults who have at least four migraine days per month.*

- A warning in product information will reflect that serious hypersensitivity reactions, including cases of anaphylaxis, angioedema and urticaria can occur rarely (may affect up to 1 in 1,000 people). Serious hypersensitivity reactions may occur within a day after galcanezumab administration, however cases with a delayed onset have also been reported. HCPs are advised to discontinue galcanezumab immediately if serious hypersensitivity occurs.


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## Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

| PRODUCT | SAFETY ISSUE |
|---|---|
| Mavenclad (cladribine) | Risk of serious liver injury and new recommendations about liver function monitoring |
| Xagrid (anagrelide hydrochloride) | Risk of thrombosis including cerebral infarction upon abrupt treatment discontinuation |
| Remicade, Flixabi, Inflectra, Remsima (infliximab) | Use of live vaccines in infants exposed in utero or during breastfeeding |

## Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at www.hpra.ie/report, which include an online report form.

All reports submitted to the HPRA are reviewed and stored on the HPRA's national adverse reaction database. They are subsequently submitted (anonymised) to the EMA's EudraVigilance database where they are available for analysis and to support early detection and monitoring of possible safety signals.

Reporting suspected adverse reactions, even those known to occur in association with a medicine, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.


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