Breastfeeding and Medication

Clinically extremely vulnerable, Covid 19 infection and breastfeeding

The clinically extremely vulnerable (CEV) are at particular risk of being admitted to hospital with symptoms of covid 19 and have been offered medication should they have a positive PCR. https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19. This factsheet provides the available information on the drugs for breastfeeding mothers. There are currently no published studies on any of them and this is not a recommendation but a digest of available data to discuss with clinicians.

Breastfeeding transfer of Covid 19

There is currently no evidence to suggest that the COVID-19 virus can transfer into breast milk. There is evidence that maternal antibodies generated in response to COVID-19 virus do pass into breast milk. The long-term well-established benefits of breastfeeding are highly likely to outweigh any potential risks of transmission of the virus through breastmilk (RCOG, Walker, UK Government, NHS & WHO June 2020). Breastmilk is the best source of nutrition for infants and provides protection against many illnesses.

Precautions against passing on Covid 19 to your baby

If you have confirmed COVID-19 or have symptoms you should take all possible precautions to avoid spreading the virus to your baby, including washing your hands for 20 seconds before touching your baby, sterilising any breast pump or bottles and washing your hands after changing nappies. Consider wearing a face covering or fluid-resistant face mask while feeding or caring for the baby. Babies should not wear a face covering or mask as they may risk suffocation.

If you are too unwell to breastfeed you may still be able to express milk for your baby. Pump equipment and bottles need to be sterilised according to manufacturer's instructions.

January 2023 *The information on this sheet is based upon my professional experience as a pharmacist with a specialised interest in the safety of drugs in breastmilk, supported by evidence from expert sources. However, I cannot take responsibility for the prescription of medication which remains with the healthcare professionals involved. I am happy to discuss the evidence by email wendy@breastfeeding-and-medication.co.uk*

Clinically Extremely Vulnerable (CEV)

The government published additional guidance on the treatment of the CEV population who have impaired immune responsehttps://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19 in December 2021.

Following a positive PCR test, most of these patients will be contacted by a local NHS coronavirus medicines team to assess whether they might benefit from treatments. Some of this population will be breastfeeding.

Update WHO Guidelines January 2023

https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.1

nirmatrelvir-ritonavir (Paxlovid)

- The GDG concluded that nirmatrelvir-ritonavir represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives; has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and the antibodies.
- Clinicians should review all medications and not consider nirmatrelvir-ritonavir in patients with possible dangerous drug interactions (note: many drugs interact with nirmatrelvir-ritonavir).
- Fully informed shared decision-making should determine whether nirmatrelvir-ritonavir should be used in pregnant or breast-feeding women, given possible benefit and residual uncertainty regarding potential undesirable effects.
- Nirmatrelvir-ritonavir should be administered as soon as possible after onset of symptoms, ideally within 5 days.

casirivimab-imdevimab strongly recommended against use

sotrovimab strong recommendation against use because neutralization of currently circulating variants of SARS-CoV-2 and their subvariants with sotrovimab is diminished.

2 types of COVID-19 treatment are available sotrovimab (Xevudy) and molnupiravir (Lagevrio). There is no experience to date of using these drugs during breastfeeding and there is currently limited information.

Nirmatrelvir-ritonavir (Paxlovid) and Breastfeeding

In this 13th iteration, an updated recommendation was made concerning the use of nirmatrelvir-ritonavir in breastfeeding and pregnant women with non-severe illness, based on data mainly available through the WHO VigiBase | UMC. While there were no reported serious adverse events linked to nirmatrelvir-ritonavir in pregnant or breastfeeding women - either in mother or child - there was residual uncertainty pertaining to the denominator to which this estimate of no undesirable effects applied. Therefore, given the likely benefits and residual uncertainty regarding

undesirable effects, the recommendation was updated to reflect the GDG's belief that shared, fully informed decision-making between mother and health care provider should determine the use or non-use of nirmatrelvir-ritonavir in pregnant or breastfeeding women with non-severe COVID-19.

Hale Medications and Mother's Milk (accessed January 2023) *:*

NIRMATRELVIR (DRUG LAST UPDATED: 03/16/2022)

Nirmatrelvir is an oral antiviral with activity against SARS-CoV-2 used in adults and children 12 years and older for mild to moderate COVID-19. It binds directly to the SARS-CoV-2 main protease, which prevents viral replication. No data is available on the transfer of nirmatrelvir into human milk. Due to modest protein binding and molecular weight, nirmatrelvir is only expected to transfer into milk transfer to a moderate degree. A transient small decrease in body weight (<10%) was observed in the nursing offspring of rats administered nirmatrelvir at doses 8 times higher than human equivalents. While it is not ideal for a breastfeeding mother, it is likely the benefit of treatment against COVID-19 may outweigh the infant risk of drug transfer with a short duration of therapy.

RITONAVIR is used to boost concentrations of nirmatrelvir. Ritonavir has been studied in breastfeeding mothers. It has moderate transfer into milk and low serum concentrations in some infants, but no reported adverse effects.

LactMed (accessed January 2023

Nirmatrelvir is given in combination with ritonavir, which enhances its bioavailability. No information is available on the use of nirmatrelvir during breastfeeding. Ritonavir is excreted into milk in measurable concentrations and low levels can be found in the blood of some breastfed infants. No reports of adverse reactions in breastfed infants have been reported. For more information, refer to the LactMed record on ritonavir. Because of the poor oral bioavailability of nirmatrelvir and small amounts of ritonavir in milk, this combination is unlikely to adversely affect the nursing infant. If nirmatrelvir is required by the mother, it is not a reason to discontinue breastfeeding, but until more data are available it should only be used with careful infant monitoring for adverse effects.

Elactancia (accessed January 2023)

Nirmatrelvir is an antiviral protease inhibitor with emergency use authorization for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen delivery and who are at high risk for progression to severe COVID-19, including hospitalization or death (EMA 2022, FDA 2022). It is given together with Ritonavir to increase its bioavailability, which is low. (Mikus 2022). At the date of the last update (may 2022) we did not find any published data on its excretion in breast milk. Its pharmacokinetic data (very wide volume of distribution and moderately high molecular weight) make it highly unlikely that significant quantities will pass into breast milk. Its low oral bioavailability minimizes the passage into plasma of the infant from ingested breast milk, except in the premature and in the immediate neonatal period in which there may be greater intestinal permeability. Possible side effects are neither frequent nor serious. (EMA 2022, FDA 2022). Expert authors consider the use of this medication possible during breastfeeding. (Anderson 2022)

Specialised Pharmacy Service (accessed January 2023 – last updated Feb 2022) https://www.sps.nhs.uk/medicines/nirmatrelvir-ritonavir/

Moderate amount of published evidence shows low amounts of ritonavir in breast milk resulting in variable infant serum levels, ranging from undetectable to low. No adverse effects reported in breastfed infants to date. No published evidence relating to use of nirmatrelvir in breastfeeding, but it is likely to pass into breast milk. Paxlovid is administered as a short course, and nirmatrelvir and ritonavir both have a short half-life, so risk of accumulation in the infant is low.

The manufacturer's advise that breastfeeding is not recommended during treatment with Paxlovid and for 7 days after the last dose. This is to ensure any infant exposure via breast milk is completely avoided.

As a precaution monitor infant for poor feeding, adequate weight gain, vomiting, diarrhoea, poor sleeping, and signs of jaundice.

Information written in previous factsheet April 2022

The current anti virals available in the UK are The treatments available are https://www.nhs.uk/conditions/coronavirus-covid-19/self-care-and-treatments-for-coronavirus/treatments-for-coronavirus/ last reviewed Oct 22) :

- nirmatrelvir and ritonavir (Paxlovid)
- remdesivir (Veklury)
- molnupiravir (Lagevrio)
- sotrovimab (Xevudy)

The UK government currently recommends sotrovimab as a third-line treatment for patients who test positive for COVID-19 following their admission to hospital, but first-line for eligible non-hospitalised patients.

Sotrovimab (Xevudy®)

- Sotrovimab is a monoclonal antibody directed against the SARS-CoV-2 virus that causes COVID-19. No information is available on the clinical use of sotrovimab during breastfeeding. Because sotrovimab is a large protein molecule, the amount in milk is likely to be very low. It is also likely to be partially destroyed in the infant's gastrointestinal tract and absorption by the infant is probably minimal. Until more data become available, sotrovimab should be used with caution during breastfeeding, especially while nursing a new-born or preterm infant. (LactMed database https://www.ncbi.nlm.nih.gov/books/NBK571318/)
- There is no published evidence for use in breastfeeding. However, **negligible levels are anticipated in milk, and very limited absorption from the infant's gastro-intestinal tract expected due to the drug's properties.** Therefore, infant side effects are unlikely. Theoretically, absorption may be increased slightly in the neonatal period due to increased

gastrointestinal permeability. Monitor the infant for adequate feeding and hypersensitivity reactions (https://www.sps.nhs.uk/medicines/Sotrovimab/)

- It is not known whether the ingredients of Xevudy can pass into breast milk. Tell your healthcare professional if you are breast-feeding before you receive Xevudy. (Patient Information Leaflet https://www.gov.uk/government/publications/regulatory-approval-of-xevudy-sotrovimab/patient-information-leaflet-for-xevudy)

However, in April 2022 the US Food and Drug Administration (FDA) revoked its authorisation of sotrovimab for treating COVID-19, owing to the increasing proportion of COVID-19 cases caused by the Omicron BA.2 sub-variant. In its decision, the FDA said clinical pharmacology data for sotrovimab suggested that the authorised dose of the drug was unlikely to be effective against the SARS-CoV-2 Omicron BA.2 variant. The Omicron BA.2 variant has been the dominant COVID-19 variant in the UK since the middle of February 2022, according to an update from the UK Health Security Agency (UKHSA) published on 25 March 2022, which added that BA.2 was estimated to account for approximately 93.7% of COVID-19 cases in England and continued to demonstrate a "substantial growth advantage". Prof Penny Ward, visiting professor in pharmaceutical medicine at King's College London commented that "Given the time taken to sequence, it is unlikely to be possible to sequence to confirm which strain the patient is affected by and only then administer the product to individuals affected by a sensitive strain, so I personally think it is inappropriate to continue to use sotrovimab at this point," she added (https://pharmaceutical-journal.com/article/news/thousands-receive-covid-19-monoclonal-antibody-despite-efficacy-concerns?fbclid=IwAR3JFlfOPPn6IbG9lqtNmuytqTmNy98Cj97KcIeDm3-kuzXTqZmoWpPzFmw)
In the UK Dr Laura Squire commented that "The MHRA is carefully reviewing emerging data for sotrovimab, including in response to new variants, and we continue to seek advice from the independent scientific advisory body, the Commission on Human Medicines, to determine if its benefit risk balance remains favourable," she added. "As part of this ongoing review, we are in contact with the FDA and are looking closely at the data supporting their decision. Patient safety is our top priority."

Molnupiravir (Lagevrio®)

- If you are breast-feeding or are planning to breastfeed, tell your doctor before taking this medicine**. Breast-feeding is not recommended during treatment and for 4 days after the last dose of Lagevrio**. This is because it is not known if Lagevrio gets into breast milk and will be passed to the baby. (Patient Information Leaflet https://www.medicines.org.uk/emc/product/13044/smpc#PREGNANCY)
- There is no published evidence relating to use in breastfeeding is available, but it is likely to pass into breast milk. Molnupiravir is administered as a short course and has a short half-life, so risk of accumulation in the infant is low. The manufacturer's state that breastfeeding is not recommended during treatment and for 4 days after the last dose. This is to ensure infant exposure via breast milk is completely avoided. Long term, high dose studies in infant animals showed toxicity in growing cartilage. Clinical significance of short-term exposure during breastfeeding is unknown. If exposed via breast milk, as a precaution, monitor infant for poor feeding, adequate weight gain, vomiting and diarrhoea. Individuals of childbearing potential, including breastfeeding women, should use effective contraception for the

duration of treatment and for 4 days after the last dose (https://www.sps.nhs.uk/medicines/molnupiravir/

Paxlovid® (Paxlovid PF-07321332 and ritonavir)

On December 31, 2021, the MHRA licensed Paxlovid in the treatment of covid-19 to keep patients out of hospital and prevent serious illness. https://www.gov.uk/government/news/oral-covid-19-antiviral-paxlovid-approved-by-uk-regulator Dec 31 2021

Based on the clinical trial data, Paxlovid is most effective when taken during the early stages of infection and so the MHRA recommends its use as soon as possible and within five days of the start of symptoms. It has been authorised for use in people aged 18 and above who have mild to moderate COVID-19 infection and at least one risk factor for developing severe illness. Such risk factors include obesity, older age (>60 years), diabetes mellitus, or heart disease.

Paxlovid consists of 2 medicines: nirmatrelvir and ritonavir.

Take 2 pink tablets of nirmatrelvir with 1 white tablet of ritonavir by mouth 2 times each day (in the morning and in the evening) for 5 days. For each dose, take all 3 tablets at the same time.

• Swallow the tablets whole. Do not chew, break, or crush the tablets.

• Take PAXLOVID with or without food. (FDA fact sheet for patients, parents, and caregivers emergency use authorization of paxlovid for coronavirus disease 2019 (covid-19) https://www.fda.gov/media/155051/download)

Paxlovid is not recommended during pregnancy and in people who can become pregnant and who are not using contraception. Breastfeeding should be interrupted during treatment. These recommendations are because laboratory studies in animals suggest that high doses of Paxlovid may impact the growth of the foetus. If you are breast-feeding or are planning to breastfeed, tell your healthcare provider before taking this medicine. **Breast-feeding is not recommended during treatment and for 7 days after the last dose of Paxlovid**. This is because it is not known if Paxlovid gets into breast milk and will be passed to the baby.
(SPC
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1044404/Paxlovid_PIL.pdf

Remdesevir (Veklury®)

Information from one patient indicates that milk levels of remdesivir and its active metabolite are very low in milk. Remdesivir is poorly absorbed orally, and the metabolite is only partially absorbed orally, so infants are not likely to absorb clinically important amounts of the drug from breastmilk. Newborn infants have received remdesivir therapy with no serious adverse drug reactions.[1-3] Given this limited information, it does not appear that mothers receiving remdesivir need to avoid nursing, but until more data are available, remdesivir should be used with careful infant monitoring during breastfeeding. The most common adverse effects reported after intravenous infusion include elevated aminotransferase and bilirubin levels and other liver enzyme elevations, diarrhoea, rash, renal impairment and hypotension (LatMed https://www.ncbi.nlm.nih.gov/books/NBK556881/).

In the published literature there is a study of one women who developed COVID-19 two days after giving birth. She was given 200mg remdesivir on the first day and then 100mg daily for a further 4 days (Wada YS, Saito J, Hashii Y, et al. Remdesivir and human milk: A case study. J Hum Lact. 2022). The authors estimated that the relative infant doses of remdesivir and its metabolite were 0.007% and 1.6%, well below the 10% level seen as compatible with breastfeeding. The half life of the metabolite was estimated to be 9.3 hours. The baby was not breastfed during treatment as this was not permitted in Japan despite the WHO recommendation. On discharge she resumed breastfeeding and continued for 6 months although with supplementation. The conclusion of the authors was that "Given the low amount of Remdesivir in the participant's milk, the inclusion of antibodies to Severe Acute Respiratory Syndrome Coronavirus 2, which can be expected to protect the infant from infection, and various other benefits of human milk, suggests that breastfeeding is safe during treatment with Remdesivir."

Evusheld® (tixagevimab co-packaged with cilgavimab)

Although Evusheld, an antibody which has shown both preventative and therapeutic activity against COVID-19 and is also still effective vs the Omicron variants, is approved for use to prevent COVID-19 among immunocompromised patients unable to respond to vaccination by the MHRA it seems currently unavailable. Evusheld is given as two injections of 150 mg tixagevimab and 150 mg cilgavimab at different sites, preferably in the gluteal muscles. There are no data on the excretion of tixagevimab and cilgavimab in human milk (https://www.gov.uk/government/publications/regulatory-approval-of-evusheld-tixagevimabcilgavimab/summary-of-product-characteristics-for-evusheld)

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