Appendix 2- Paxlovid

Treatment Information

Paxlovid is an oral (i.e. taken by mouth) antiviral treatment that has been developed specifically for treatment of COVID-19. The drug works by inhibiting the replication of the virus that causes COVID-19 (SARS-CoV-2) and stops the virus from multiplying in the body. This keeps the virus level in the body low and helps the immune system to overcome the viral infection.

The treatment has been shown to have an acceptable safety profile. In several clinical trials, it has been shown to reduce the need to be admitted to hospital and may therefore be an effective treatment for COVID-19.

Paxlovid has a conditional license, which means that it has been licensed for use as a treatment based on less data than normally required. To receive this license, the data have shown that the treatment's benefits outweigh the risks. The aim of PANORAMIC is to collect more data to confirm whether Paxlovid is an effective COVID-19 treatment.

Paxlovid Dose and Administration

Paxlovid consists of 2 medicines: nirmatrelvir and ritonavir co-packaged together for oral use.

- Take 2 pink tablets of nirmatrelvir (150mg each) with 1 white tablet of ritonavir (100mg) 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.
- If you miss a dose of Paxlovid within 8 hours of the time you would usually take it, then take it as soon as you remember. If it is more than 8 hours from the time that you would usually take your medication, skip the missed dose, and take the next dose at your regular time. **Do not take 2 doses of Paxlovid at the same time.**
- **Please make sure that you complete a five-day course of this treatment**, even if symptoms improve and/or you feel better, to reduce the chances of a treatment-resistant version of the virus developing.
- If you are taking ritonavir or cobicistat-containing medicine to treat hepatitis C or Human Immunodeficiency Virus (HIV), you should continue to take your medication as prescribed

by your doctor.

- You can take the 1st dose as soon as the medication arrives as long as you can leave at least a 4 hour gap before the evening dose. For example, the 1st dose can be taken at 5pm and the second dose at 9 pm or later on day 1. If you cannot take the 1st dose before 5 pm or leave a 4 hour gap, take the 1st dose in the evening and the 2nd dose the next morning, 12 hours apart. Then the medication should be continued morning and evening from day 2 onwards.
- If you decide that you no longer wish to take the medication (or you are asked to stop taking it by the study team), you may be asked to dispose of it at a pharmacy or you will be asked to return your medication to the trial team in the pre-paid envelope (please see your medication card for full instructions on how to return medication)

Potential COVID-19 Treatment

Several small clinical studies have found that Paxlovid may help to treat COVID-19. However, we need more evidence from large clinical trials, which is why we have included the treatment in the PANORAMIC Trial. Paxlovid has been highly recommended by the Antivirals Taskforce (ATF) for the treatment of COVID-19.

The use of Paxlovid in PANORAMIC has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA regulates the use of all medicines in the UK.

Exclusion Criteria

Before you are enrolled, you will be asked if you meet any of the following reasons for NOT taking Paxlovid.

If you meet ANY of the following criteria, you will automatically be excluded from receiving Paxlovid:

- You are currently in hospital (inpatient)
- You have previously enrolled in the Paxlovid intervention arms of the PANORAMIC trial (those randomised in the molnupiravir intervention arms are eligible to re-register for the trial)
- You are currently taking part in a clinical trial which involves taking a new medication for COVID-19
- You have a known pregnancy (confirmed by a positive pregnancy test) or suspect you may be pregnant
- You are of childbearing potential and unwilling to take a pregnancy test.

- You are breastfeeding
- You are of childbearing potential and in a heterosexual relationship, and you are NOT willing to use a highly effective contraceptive
- You are currently taking Paxlovid
- You are allergic to nirmatrelvir, ritonavir, or any of the ingredients in Paxlovid
- You have a clinical need to take a medicine that affects how Paxlovid works or may cause serious side-effects or life-threatening side-effects when given with Paxlovid
- You have a level of kidney disease such that you are not suitable to take Paxlovid.
- You are galactose intolerant, have total lactose deficiency or glucose-galactose malabsorption
- You have severe liver disease characterised by severe ascites, encephalopathy, jaundice, or prolonged INR. Note that if you have liver disease without these features then you will be eligible

If you have previously taken part in the PANORAMIC trial in the Monlupiravir intervention and you are now interested in being enrolled in the Paxlovid intervention you will be asked to provide consent and enrolled on the study as if you were a new participant.

Participants of childbearing potential must agree to perform a pregnancy test provided by the trial to confirm a negative test result before taking Paxlovid and be willing to use a method of contraception acceptable for use with Paxlovid (see below). This negative test result is required regardless of your current contraception methods or relationship status.

A registered nurse prescriber, pharmacist or doctor will telephone you to go through a few questions with you and to check that you can take the treatment.

The registered nurse prescriber, pharmacist or doctor may access your medical records to make these assessments. Once confirmed and if you consent you will be enrolled into the trial.

Pregnancy and breastfeeding

There is no experience in treating pregnant women or breastfeeding mothers with Paxlovid. For a mother and an unborn baby, there could be significant risks associated with taking the drug that we are not yet aware of. Therefore, it is important that participants of childbearing potential and in a heterosexual relationship use effective contraceptives as described above.

Methods of contraception that are acceptable for use with Paxlovid include:

The implant, the coil, male or female sterilisation, the injection, or the progestogen only pill (“the mini-pill”) will be acceptable for use with Paxlovid and must be used for the duration of the treatment and 28 days of follow up. Paxlovid can stop combined hormonal contraceptives (e.g., “the pill”, patch,

vaginal ring) from working properly, so if you use a combined hormonal contraceptive, you must use an additional barrier method of contraception for the duration of treatment with Paxlovid and until one full menstrual cycle is completed after the last dose of Paxlovid. However, condoms alone won't be sufficient during the trial. Being abstinent for the 28 days before enrolling in the trial and continuing to be abstinent for the 28-day duration of follow-up will also be acceptable where this is in line with your preferred and usual lifestyle.

It is important to note that a barrier method on its own is not sufficient. If you were to become pregnant during the trial you must tell us immediately and you will be withdrawn from the trial, although we will ask to follow you up for safety reasons.

Other medications and Paxlovid

Paxlovid and taking other medicines:

Taking Paxlovid at the same time as some other medicines can cause serious side-effects or stop Paxlovid from working properly. Also, Paxlovid can stop some other medicines from working properly. You must let the nurse prescriber, pharmacist or doctor know about any other medicines that you are taking so that they can check whether it is safe for you to take Paxlovid. You may need to change the way you take some of your other medicines to safely take Paxlovid. A registered doctor from the trial will discuss this with you. If you are assigned to take Paxlovid in the trial, you will need to tell your own doctor or pharmacist that you are taking Paxlovid before starting a new medicine, stopping a medicine you are already taking or changing the dose of a medicine you are already taking.

Side-effects

Like all medicines, Paxlovid can cause side-effects. Most of these are mild and short-term and not everyone gets them.

Possible side effects of Paxlovid are:

- **Liver problems.** Please tell your doctor straight away if you have any of these signs and symptoms of liver problems: loss of appetite, yellowing of your skin and the whites of eyes (jaundice), dark-coloured urine, pale coloured stools and itchy skin, stomach ache (abdominal pain).
- **Resistance to HIV medicines.** If you have an untreated HIV infection, Paxlovid may lead to some HIV medicines not working as well in the future.

Common side effects include:

- altered sense of taste
- diarrhoea
- vomiting

A trial doctor or research nurse will call you the day after you start your medication (Day 2) to ask about these and any other side-effects you may have experienced. If you experience any side-effects which you're concerned about while taking Paxlovid, you will be given access to a 24-hour telephone line to speak to a member of the clinical team. Any symptoms reported in your daily diary are monitored by our clinical team who will call you if there any symptoms of concern.

Emergencies

If a medical emergency related to your treatment for this trial occurs while you are at home, you should initially try to contact the usual services that are open to you, such as 111, 999 or go to the accident and emergency (A&E) department at your local hospital. If you are unable to get to the hospital you should contact your GP who, with your consent, will already have been informed of your participation in the trial. You have been given a PANORAMIC participant card that you must show to the doctor you see.