

Appendix 1

Inhaled Corticosteroid - Budesonide

Drug Information

Budesonide is a widely used inhaled corticosteroid used to treat asthma symptoms, but is not currently used to treat infections like COVID-19.

Side-effects

The common side effects are:

cough immediately after inhaling

mouth and throat pain

hoarse voice

oral candidiasis (thrush).

Appendix 2

Colchicine

Drug Information

Colchicine is a medicine which is licenced and widely used in the UK for the treatment of acute gout. Although is not currently used to treat infections like COVID-19, it has been investigated as a possible treatment for COVID-19.

Colchicine Dose and Administration

Colchicine is a new possible treatment for COVID-19, so the most effective dose is unknown. Studies like this are trying to find out how well the treatment works.

An oral dose (by mouth) of a tablet of 500 microgram (µg) each day for 14 days (14 tablets in total), will be used in the trial.

If you decide that you no longer wish to take the medication, you can stop at any time, and take your medication to your local pharmacy for disposal, when you are able to.

Potential COVID-19 Treatment

Several clinical studies have found that colchicine may help to treat COVID-19. However, we need more evidence from large clinical trials, about whether colchicine improves recovery from COVID-19 symptoms, which may reduce the number of people going into hospital with the disease. This is why we have included the treatment in the PRINCIPLE Trial. Colchicine has been recommended by the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP) for the treatment of COVID-19, and approved by the Chief Medical Officer.

The use of colchicine in PRINCIPLE has also been approved by the UK- Urgent Public Health Panel. The panel is formed by a group of independent experts including patient representatives and healthcare professionals from across the four UK nations.

Exclusion Criteria

Before you are enrolled, you will be asked if you have any of the following reasons for NOT taking Colchicine, and you will be excluded from receiving colchicine if you do.

Exclusions: If you have any of the following conditions you should not take Colchicine

- Allergy to colchicine or any of these inactive substances: lactose, Pregelatinised Maize Starch, Stearic Acid, Purified Talc, Purified Water or Ethanol 96%.

- Known or suspected pregnancy
- Breastfeeding
- Women of childbearing potential (premenopausal female that is anatomically and physiologically capable of becoming pregnant) not willing to use highly effective contraceptives for 28 day duration of the trial.
- Known blood dyscrasias (a blood disorder)
- Known severe kidney impairment or requiring dialysis
- Known severe liver impairment
- Currently taking any of the following drugs: colchicine, clarithromycin, erythromycin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors (e.g. ritonavir, atazanavir), cobicistat, verapamil, diltiazem, cyclosporin, quinidine, disulfiram.
- Inflammatory bowel disease or chronic diarrhoea or malabsorption

You will also be asked to agree not to drink any grapefruit juice while taking colchicine.

A registered nurse or doctor will review your answers to these screening questions against information obtained from your medical notes to check that you can take the treatment, once confirmed you will be enrolled into the trial.

Contraception

It is important that women of childbearing potential must use highly effective contraceptives from enrolment until day 28 of follow up.

Methods of contraception that are acceptable for the trial include the following:

The implant, the coil, and male or female sterilisation will be acceptable for participating in the trial. The injection and most forms of hormonal contraception will also be considered acceptable for the trial, if used in combination with condoms or other barrier methods. However, condoms alone won't be sufficient during the study. You can discuss any questions you have about contraception during the study period with the trial team. If you were to become pregnant during the trial you must tell us immediately and you will be withdrawn from the study, although we will ask to follow you up for safety reasons.

It is important to note that a barrier method on its own is not sufficient

Side-effects

Below, we have listed some possible side-effects of colchicine. We will ask you to record whether you experience any of these symptoms in your daily diary. You will also receive a call from the

study team on Day 3 to check that you have received your participant pack and to answer any questions you may have. We will also ask in your daily diary about how many colchicine tablets you have left.

Side effects that may be associated with Colchicine:

The common side effects are:

- Abdominal pain
- Diarrhoea*
- Nausea
- Vomiting

*side-effects also seen with COVID-19

Rare side effects that may be associated with colchicine:

Low white blood cell count; hair loss; bone marrow disorders; gastrointestinal bleeding; kidney injury; liver injury; menstrual cycle irregularities; disease of muscle tissue; nerve disorders; rash; sperm abnormalities; low blood platelet count.

Appendix 3 - Favipiravir

Drug Information

Favipiravir is an oral (i.e. taken by mouth) antiviral that is licensed in Japan for use as a treatment for flu, and has been used in clinical trials for Ebola. Although it is not currently licensed for use in the UK or routinely used, Favipiravir is proven to have a good safety profile and in a number of clinical trials the drug has been shown to improve recovery from COVID-19 symptoms and may therefore be an effective treatment for COVID-19.

Favipiravir Dose and Administration

Favipiravir is a new possible treatment for COVID-19, so the most effective dose is unknown. Studies like this are trying to find out how well the treatment works.

For this trial, nine tablets (1800mg) favipiravir to be taken orally twice a day on day one, and then four tablets (800mg) twice daily for four days (50 tablets in total).

You should avoid excessive exposure to sunlight or artificial ultraviolet light for the five days whilst taking favipiravir.

You must not take more than 6 paracetamol tablets in 24 hours whilst for the five days whilst taking favipiravir.

If you decide that you no longer wish to take the medication, you will be asked to return your medication to the trial team in the pre-paid envelope, via courier.

Potential COVID-19 Treatment

Several small clinical studies have found that favipiravir 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 PRINCIPLE Trial. Favipiravir has been highly recommended by the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP) for the treatment of COVID-19.

The use of favipiravir in PRINCIPLE has been approved by the UK- Urgent Public Health Panel. The panel is formed by a group of independent experts including patient representatives and healthcare professionals from across the four UK nations.

Exclusion Criteria

Before you are enrolled, you will be asked if you meet any of the following reasons for NOT taking favipiravir. If you meet ANY of the following criteria, you will automatically be excluded from

receiving favipiravir.

Exclusions: If you meet any of the following criteria you should not take Favipiravir

- Aged <50 years
- Known or suspected pregnancy
- Breastfeeding
- Women of childbearing potential (premenopausal female that is anatomically and physiologically capable of becoming pregnant), or male with a partner of childbearing potential, not willing to use highly effective contraceptive for 28 day duration of the trial.
- Known allergy to favipiravir
- Currently taking favipiravir
- Known history of gout
- Known severe liver disease

A registered nurse or doctor will review your answers to these screening questions against information obtained from your medical notes to check that you can take the treatment, once confirmed you will be enrolled into the trial.

Contraception

As there is currently no human research associated with the use of favipiravir among pregnant or lactating women, it is important that women of childbearing potential, or a male with a partner of childbearing potential, must use highly effective contraceptive from enrolment until day 28 of follow up.

Methods of contraception that are acceptable for the trial include the following:

The, implant, the coil and male or female sterilisation will be acceptable for the trial. The injection and most forms of hormonal contraception will also be deemed acceptable for the trial if used in combination with condoms or other barrier methods. However, condoms alone won't be sufficient during the study. You can discuss any questions you have about contraception during the study period with the trial team. If you were to become pregnant during the trial you must tell us immediately and you will be withdrawn from the study, although we will ask to follow you up for safety reasons.

It is important to note that a barrier method on its own is not sufficient

Side-effects

Below, we have listed some possible side-effects of the drug. We will ask you to record whether you experience diarrhoea, nausea, headaches, vomiting and urinary tract infections, in your daily diary

and the clinical team will monitor these and follow-up with you if required. If you are randomised to Favipiravir, you will receive a phone call from the study team within one day of being randomised, to reaffirm your consent to take part, and to explain what side-effects you may experience, and how to report and record them. This detail will also be in the participant pack that you will receive. You will also receive a call from the study team on Day 3.

In addition, if you experience any **major** side-effects at any time while taking Favipiravir (major side-effects are symptoms that cause considerable limitation in your usual activity. Medication or medical attention is required), please call the 24 hour telephone line to speak to a member of the clinical team: 0800 xxxxxx.

Side effects that may be associated with Favipiravir:

- Diarrhoea*
- Nausea
- Headache*
- Vomiting¹
- Urinary Tract Infections
- Raised liver enzymes
- Elevated uric acid concentrations

**side-effects also seen with COVID-19*

Emergencies

If a medical emergency related to your treatment for this study 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 study. You have been given a PRINCIPLE participant card that you must show to the Doctor you see.