WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[CV024 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nirmatrelvir 150-mg film coated tablets

Each film coated tablet contains 150 mg nirmatrelvir.

Ritonavir 100-mg film coated tablets

Each film coated tablet contains 100 mg ritonavir

Excipients with potential clinical effect

Each nirmatrelvir 150mg film-coated tablet contains 185mg of lactose monohydrate and 2.8mg (0.12mmol) of sodium.

Each ritonavir 100mg film-coated tablet contains 87.76mg (3.82mmol) of sodium. To be taken into consideration by patients on a controlled sodium diet.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

[CV024 trade name] consists of nirmatrelvir 150-mg tablets co-packed together with ritonavir 100-mg tablets.

Nirmatrelvir 150-mg film-coated tablets

[CV024 trade name] is pink, oval, film-coated tablets. They are biconvex (rounded on top and bottom) with a beveled edge. The tablets have ‘T5’ debossed (stamped into) on one side and are plain on the other side.

No score line.

Ritonavir 100mg film-coated tablets

[CV024 trade name] is yellow, capsule-shaped, film-coated tablets. They are biconvex (rounded on top and bottom) with a beveled edge. The tablets have ‘M163’ debossed (stamped into) on one side and are plain on the other side.

No score line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[CV024 trade name] is indicated for the treatment of coronavirus disease 2019 (COVID-19) in patients with non-severe disease (i.e without pneumonia or signs of respiratory distress or sepsis, and with blood oxygen saturation of at least 90%) whose disease is at higher risk for progressing to severe COVID-19.

A higher risk of progressing to severe COVID-19 may be associated with any of the following patient factors:

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency’s responsibility.

immunosuppressive disease or immunosuppressive treatment (this carries the highest risk of hospitalisation)

age of 65 years or older

obesity

chronic cardiopulmonary disease

chronic kidney or liver disease

diabetes

active cancer

disabilities

comorbidities of other chronic diseases

Lack of vaccination against SARS-CoV-2 is an additional risk factor.

The management of COVID-19 should follow the most recent authoritative guidelines, including those issued by WHO.

4.2 Posology and method of administration

Posology

Treatment with [CV024 trade name] should be started as soon as possible after diagnosing COVID-19 and within 5 days of the onset of COVID-19 symptoms.

Adults

The recommended dosage for adults is 300 mg nirmatrelvir (two 150-mg tablets) together with 100 mg ritonavir (one 100-mg tablet) every 12 hours for 5 days.

It is recommended that the 5-day treatment course is completed even if the patient is hospitalised for severe or critical COVID-19 after starting treatment with [CV024 trade name].

Children and adolescents

[CV024 trade name] may be used in children 6 years of age and older. The recommended dose depends on body weight as follows:

Patient's weight	**Recommended dose**
Less than 20 kg	Use alternative treatment
20 to less than 40 kg	150 mg nirmatrelvir (one 150-mg tablet) together with 100 mg ritonavir (one 100-mg tablet) every 12 hours for 5 days
40 kg or more	As for adults

The medicine is not recommended for use in children less than 6 years of age or those weighing less than 20 kg.

Renal impairment

No dose adjustment is needed in patients with **mild** renal impairment (eGFR between 60 and 90 mL/minute).

In patients weighing at least 40 kg who have **moderate** or **severe** renal impairment (eGFR between 30 and 60 mL/minute and less than 30 mL minute respectively), the dose of nirmatrelvir should be reduced as follows:

Renal function (eGFR)	**Dosage**	
Moderate impairment (30 to less than 60 mL/minute)	Days 1–5	150 mg nirmatrelvir (one 150-mg tablet) with 100 mg ritonavir (one 100-mg tablet) **every 12 hours**
Severe impairment (less than 30 mL/minute)	Day 1	300 mg nirmatrelvir (two 150-mg tablets) with 100 mg ritonavir (one 100-mg tablet) **once**
	Days 2–5	150 mg nirmatrelvir (one 150-mg tablet) with 100 mg ritonavir (one 100-mg tablet) **once daily**

On days patients with severe renal impairment undergo haemodialysis, the dose should be administered after haemodialysis (see section 5.2).

Dose in paediatric patients with renal impairment weighing less than 40 kg has not been determined.

Dosing advice for patients with moderate or severe renal impairment

The patient should be carefully advised on the correct number of tablets to be taken and the fact that some tablets will remain in the pack by the end of the 5-day course.

Hepatic impairment

No dose adjustment of [CV024 trade name] is needed for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). [CV024 trade name] should not be used in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Severely immunocompromised patients

Data are limited in severely immunocompromised individuals. A treatment duration of 10 days may help to mitigate the risk of virological rebound in patients with severe immunodepression (e.g. active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) (see section 5.1).

Missed dose

If the patient misses a dose of [CV024 trade name] and

- the next scheduled dose is not due for 4 hours or more, the patient should take the dose right away and take the next dose at the usual time.
- if the next scheduled dose is due in less than 4 hours, the patient should not take the missed dose but instead just take the next dose at the usual scheduled time.

The patient should not double the dose to make up for a missed dose.

Method of administration

Nirmatrelvir must be taken as the same time as ritonavir to achieve effective plasma levels of the active substance.

[CV024 trade name] can be taken with food or between meals. The tablets should be swallowed whole and not chewed, broken or crushed.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

[CV024 trade name] is contraindicated with

- medicines that are highly dependent on CYP3A for clearance and are associated with serious or life-threatening reactions if their concentrations are raised
- medicines that are potent CYP3A inducers and so can significantly reduce plasma concentrations of nirmatrelvir or ritonavir, potentially causing loss of virologic response and possible resistance.

For further information on contraindicated medicine combinations see section 4.5.

4.4 Special warnings and precautions for use

Risk of reactions due to interactions

See section 4.5 for details of interactions that may lead to adverse reactions when [CV024 trade name] is used with medicines that are affected by CYP3A activity.

The management of interactions in patients receiving multiple medicines can be complex and requires thorough understanding of the nature and magnitude of each interaction. For certain patients, specialists (e.g. in clinical pharmacology) should be consulted for managing interactions especially if medicines need to be stopped, their dosage reduced, or if increased monitoring of side effects is necessary.

Hypersensitivity reactions

Anaphylaxis and other hypersensitivity reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported with nirmatrelvir/ritonavir (see section 4.8). If a clinically significant hypersensitivity reaction or anaphylaxis occurs, [CV024 trade name] should be stopped immediately and treatment started to manage the reaction.

Severe hepatic impairment

No pharmacokinetic and clinical data are available in patients with severe hepatic impairment. Therefore, [CV024 trade name] should not be used in patients with severe hepatic impairment.

Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, [CV024 trade name] should be used with caution in patients with liver disease, liver enzyme abnormalities or hepatitis.

Hypertension

Hypertension – generally transient and not serious – has been reported with nirmatrelvir/ritonavir treatment. Blood pressure may need to be closely monitored in some patients, especially the elderly since they are at higher risk of serious complications of hypertension.

Risk of HIV resistance

In individuals with uncontrolled or undiagnosed HIV infection, exposure to ritonavir in [CV024 trade name] may allow the virus to develop resistance to HIV protease inhibitors.

Excipients

Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

Patients who are allergic to cow’s milk proteins must not be given this medicine unless strictly necessary.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicines on [CV024 trade name]

Nirmatrelvir and ritonavir are CYP3A substrates.

Therefore, medicines that **induce** CYP3A may decrease nirmatrelvir and ritonavir plasma-concentrations and reduce [CV024 trade name] therapeutic effect.

Medicines that **inhibit** CYP3A4 may increase nirmatrelvir and ritonavir plasma-concentrations, and thus may increase the risk of [CV024 trade name] adverse reactions.

Effects of [CV024 trade name] on other medicinal products

[CV024 trade name] (nirmatrelvir/ritonavir) is also a strong inhibitor of CYP3A and may increase plasma concentrations of medicines that are primarily metabolised by CYP3A. Thus, co-administration of nirmatrelvir/ritonavir with medicines highly dependent on CYP3A for clearance is contraindicated if raised plasma concentrations of these medicines can cause serious or life-threatening events (see the first table, below, under contraindicated combinations). Co-administration of other CYP3A substrates with potential for significant interaction (see table 2, below, under other interactions to be considered) should be considered only if the benefits outweigh the risks.

Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and, as well as CYP3A, it may to a lesser degree inhibit oxidation with CYP2D6. Co-administration of [CV024 trade name] with substrates of CYP2D6 may therefore increase the CYP2D6 substrate concentration.

[CV024 trade name] also has a high affinity for P-glycoprotein (P-gp) and may inhibit this transporter. Concomitant administration should therefore be accompanied by close monitoring for efficacy and side effects and, if necessary, the dose should be adjusted or concomitant use avoided.

[CV024 trade name] may induce glucuronidation and oxidation by CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19, thereby increasing the biotransformation of some medicines metabolised by these pathways, which could reduce or shorten their therapeutic effect.

In vitro studies suggest a potential for nirmatrelvir to inhibit MDR1 and OATP1B1 at clinically relevant concentrations.

Interactions studies on [CV024 trade name] indicate that the drug interactions are primarily due to ritonavir. Hence, drug interactions pertaining to ritonavir apply to [CV024 trade name].

Contraindicated combinations

Interactions which have serious clinical consequences, and which therefore mean that the combination of [CV024 trade name] and the interacting medicines **must be avoided** are shown in the first table below. This list is a guide only and not a comprehensive list of all medicines that are contraindicated.

Drugs	**Comment**
Antiarrhythmics	
Dronedarone Propafenone Quinidine	Ritonavir co-administration is likely to increase plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and co-administration with [CV024 trade name] is therefore contraindicated.
Antiepileptics	

Drugs	Comment
Carbamazepine Phenobarbital Phenytoin Primidone	Carbamazepine decreases nirmatrelvir AUC by 55% and C_{max} by 43%. Phenobarbital, phenytoin and primidone are strong CYP3A4 inducers, and this may similarly decrease nirmatrelvir and ritonavir concentrations with potential loss of antiviral effect. [CV024 trade name] induces oxidation by CYP2C9 and glucuronidation and, as a result, is expected to decrease the plasma concentrations of phenytoin. Concomitant use of carbamazepine, phenobarbital, phenytoin or primidone with [CV024 trade name] is contraindicated.*
Antihistamines	
Terfenadine	Increased plasma concentrations of terfenadine with increased risk of serious arrhythmias. Concomitant use with [CV024 trade name] is contraindicated.
Anti-infectives	
Antibacterials (including TB medicines)	
Rifampicin Rifapentine	Rifampicin and rifapentine are strong CYP3A4 inducers, and this may reduce concentrations of nirmatrelvir/ritonavir with potential loss of antiviral effect. Concomitant use of rifampicin or rifapentine with [CV024 trade name] is contraindicated.*
Antipsychotics	
Cariprazine	Co-administration is contraindicated due to increased plasma exposure of cariprazine and its active metabolites.
Lurasidone	CYP3A inhibition by ritonavir is expected to increase lurasidone concentrations. Concomitant administration of [CV024 trade name] with lurasidone is contraindicated due to the increased risk of toxicity.
Pimozide	[CV024 trade name] co-administration is likely to increase plasma concentrations of pimozide and is therefore contraindicated due to the increased risk of toxicity.
Quetiapine	CYP3A inhibition by ritonavir is expected to increase, quetiapine concentrations. Concomitant administration of [CV024 trade name] and quetiapine is contraindicated due to the increased risk of toxicity.
Benign prostatic hyperplasia medicines (alpha1-adrenoreceptor antagonist)	
Alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated.
Silodosin	Co-administration is contraindicated due to potential for postural hypotension.
Cancer medicines	
Apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may decrease concentration of nirmatrelvir/ritonavir with potential loss of antiviral effect. In addition, serum concentrations of apalutamide may be increased when co-administered with ritonavir, potentially resulting in serious adverse events including seizure. Concomitant use of [CV024 trade name] with apalutamide is contraindicated.*

Drugs	Comment
Enzalutamide	Enzalutamide is a strong CYP3A4 inducer, and this may decrease concentration of nirmatrelvir/ritonavir with potential loss of antiviral effect and development of resistance, Concomitant use of [CV024 trade name] with enzalutamide is contraindicated.*
Neratinib	Serum concentrations may increase due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with [CV024 trade name] is contraindicated due to serious or life-threatening potential reactions including hepatotoxicity.
Venetoclax	Serum concentrations may increase due to CYP3A inhibition by ritonavir, increasing the risk of tumour lysis syndrome **at the start of treatment and during the ramp-up phase**. Co-administration with [CV024 trade name] is therefore contraindicated. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors such as [CV024 trade name] (the venetoclax product information should be consulted for dosing instructions).
Cardiovascular medicines	
Eplerenone	Co-administration with eplerenone is contraindicated due to potential for hyperkalaemia.
Ivabradine	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances.
Ranolazine	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration of ranolazine with [CV024 trade name] is contraindicated.
Cystic fibrosis medicines	
Lumacaftor/ivacaftor	Co-administration contraindicated due to potential loss of virologic response and possible resistance.*
Ergot derivatives	
Dihydroergotamine Ergometrine Ergotamine Methylergometrine	Ritonavir co-administration is likely to increase plasma concentrations of ergot derivatives and co-administration with [CV024 trade name] is therefore contraindicated.
Immunosuppressants	
Voclosporin	Co-administration is contraindicated due to potential for acute or chronic nephrotoxicity.
Lipid regulating medicines	

Drugs	Comment
Lovastatin Simvastatin	Concentrations of HMG-CoA reductase inhibitors that are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to increase markedly when co-administered with ritonavir. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, co-administration of these medicines with ritonavir is contraindicated.
Lomitapide	CYP3A4 inhibitors increase lomitapide concentrations, with strong inhibitors increasing concentrations about 27-fold. CYP3A inhibition by ritonavir is expected to increase lomitapide concentrations. Concomitant use of [CV024 trade name] with lomitapide is contraindicated).
Phosphodiesterase (PDE5) inhibitors	
Avanafil Sildenafil Tadalafil Vardenafil	Concomitant use of avanafil, sildenafil, tadalafil and vardenafil with [CV024 trade name] is contraindicated.
Sedatives/hypnotics	
Clorazepate Diazepam Estazolam Flurazepam	Ritonavir co-administration is likely to increase plasma concentrations of clorazepate, diazepam, estazolam, and flurazepam and use of these medicines with [CV024 trade name] is therefore contraindicated.
Midazolam	Midazolam is extensively metabolised by CYP3A4. Co-administration with [CV024 trade name] may cause a large increase in the concentration of midazolam. Plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, co-administration of [CV024 trade name] with oral midazolam is contraindicated. For advice on parenteral midazolam, see the table below.
Triazolam	Ritonavir co-administration is likely to increase triazolam plasma concentrations and use of triazolam with [CV024 trade name] is therefore contraindicated.
Other medicines	
Colchicine (gout medicine)	Concentrations of colchicine are expected to increase when co-administered with ritonavir. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (CYP3A4 and P-gp inhibition). Concomitant use of colchicine with [CV024 trade name] is contraindicated.
Eletriptan (migraine medicine)	Co-administration of eletriptan within 72 hours of [CV024 trade name] is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events.
Naloxegol	Coadministration of [CV024 trade name] with naloxegol is contraindicated due to the potential for increased naloxegol plasma concentrations leading to opioid withdrawal symptoms.

Drugs	Comment
St John's Wort	Herbal preparations containing St John's wort (*Hypericum perforatum*) may decrease plasma concentrations of nirmatrelvir and ritonavir and reduce antiviral effect, so concomitant use with [CV024 trade name] is contraindicated.*
Tolvaptan (vasopressin receptor antagonist)	Co-administration is contraindicated due to potential for dehydration, hypovolaemia and hyperkalaemia.

*Note. [CV024 trade name] cannot be started immediately after discontinuing a CYP3A inducer because the CYP3A-inducing effect may persist and reduce the antiviral effect of [CV024 trade name]. Specialists (e.g. in clinical pharmacology) may need to be consulted to determine when [CV024 trade name] can be started, taking into account the persisting enzyme-inducing effect of the recently discontinued CYP3A inducer and the need to start [CV024 trade name] within 5 days of the onset of disease symptoms.

Other interactions to be considered

The following table includes medicines that can interact with [CV024 trade name] but the listing is not considered comprehensive.

Medicines are grouped by their therapeutic use or pharmacological categories, followed by a listing of other medicines.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Analgesics		
Buprenorphine	Buprenorphine AUC ↑ 57%, C_{max} ↑ 77%	The increased plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in opioid-tolerant patients. No adjustment to the dose of buprenorphine may therefore be necessary when the two are co-administered.
Fentanyl Oxycodone	Fentanyl ↑ Oxycodone ↑	Ritonavir inhibits CYP3A4 and [CV024 trade name] is expected to increase plasma concentrations of fentanyl and oxycodone. If concomitant use is necessary, consider a dose reduction of these analgesics, Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended.
Methadone	Methadone AUC ↓ 36%, C_{max} ↓ 38%	Increased methadone dose may be necessary when co-administered with [CV024 trade name] due to induction of glucuronidation. Dose adjustment should be considered, based on the patient's clinical response to methadone therapy. Monitor patients maintained on methadone for evidence of withdrawal effects.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Morphine	Morphine ↓	Morphine levels may be decreased due to induction of glucuronidation by co-administered [CV024 trade name].
Pethidine	Pethidine ↑	Co-administration could result in increased or prolonged opioid effects. If concomitant use is necessary, consider reducing pethidine dose. Monitor for respiratory depression and sedation.
Piroxicam	Piroxicam ↓	Decreased piroxicam exposure due to CYP2C9 induction by [CV024 trade name].
Antiarrhythmics		
Amiodarone Flecainide	Amiodarone ↑ Flecainide ↑	Ritonavir co-administration is likely to increase plasma concentrations of amiodarone and flecainide. Given the risk of amiodarone- or flecainide-related adverse events, co-administration should be avoided unless a multidisciplinary consultation can be obtained to safely guide it.
Digoxin	Digoxin ↑	The interaction may be due to modification of P-gp mediated digoxin efflux by pharmacokinetic enhancing dose of ritonavir. Digoxin concentration is expected to increase. Digoxin levels and digoxin safety and efficacy should be monitored if possible.
Disopyramide	Disopyramide ↑	Ritonavir may increase plasma concentrations of disopyramide which could result in an increased risk of adverse events such as cardiac arrhythmias. Caution is warranted and therapeutic concentration monitoring is recommended for disopyramide if available.
Anticoagulants		
Apixaban	Apixaban ↑	Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban and increase the risk of bleeding. Dosing recommendations for coadministration of [CV024 trade name] with apixaban depend on the apixaban dose. For apixaban doses of 5 or 10 mg twice daily, reduce the apixaban dose by 50%. In patients already taking apixaban 2.5 mg twice daily, coadministration with [CV024 trade name] should be avoided.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Dabigatran	Dabigatran AUC ↑ 94%, C_{max} ↑ 133%	Concomitant administration of [CV024 trade name] is expected to increase dabigatran concentrations and increase the risk of bleeding. The dose of dabigatran should be reduced, or concomitant use avoided. The dabigatran product information should be consulted for further information.
Rivaroxaban	Rivaroxaban AUC ↑ 153%, C_{max} ↑ 53%	Inhibition of CYP3A and P-gp lead to increased plasma concentrations and effects of rivaroxaban which may increase the risk of bleeding. The use of [CV024 trade name] is not recommended in patients receiving rivaroxaban.
Warfarin	S-Warfarin AUC ↑ 9%, C_{max} ↓ 9%, R-Warfarin AUC ↓ 33% C_{max} ↔	Induction of CYP1A2 and CYP2C9 may reduce R-warfarin concentrations but there is little pharmacokinetic effect on S-warfarin when co-administered with ritonavir. Decreased R-warfarin levels may reduce anticoagulation; therefore, it is recommended that anticoagulation parameters are monitored when warfarin is co-administered with [CV024 trade name].
Antidepressants		
Amitriptyline Fluoxetine Imipramine Nortriptyline Paroxetine Sertraline	Amitriptyline ↑ Fluoxetine ↑ Imipramine ↑ Nortriptyline ↑ Paroxetine ↑ Sertraline ↑	Ritonavir dosed as an antiretroviral agent can inhibit CYP2D6 and increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. However, any increase in concentrations with the lower doses of ritonavir in standard courses of [CV024 trade name] is expected to be small, and not clinically significant. Closer monitoring of therapeutic and adverse effects of these antidepressants may be considered when co-administered with [CV024 trade name].
Antiepileptics		
Clonazepam	Clonazepam ↑	A decrease in clonazepam dose may be needed if co-administered with [CV024 trade name] and clinical monitoring is recommended.
Divalproex (sodium valproate and valproic acid) Lamotrigine	Divalproex ↓ Lamotrigine ↓	[CV024 trade name] induces oxidation by CYP2C9 and glucuronidation and, as a result, is expected to decrease the plasma concentrations of the antiepileptics. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are co-administered with ritonavir.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Antihistamines		
Fexofenadine	Fexofenadine ↑	[CV024 trade name] may modify P-gp mediated fexofenadine efflux and increase concentrations of fexofenadine. The patient should be monitored for therapeutic and adverse effects when fexofenadine is co-administered with [CV024 trade name].
Loratadine	Loratadine ↑	[CV024 trade name] inhibits CYP3A and is expected to increase plasma concentrations of loratadine. The patient should be monitored for therapeutic and adverse effects when loratadine is co-administered with [CV024 trade name].
Anti-infectives		
Anthelmintics		
Albendazole	Albendazole ↓	Significant decreases in plasma concentrations of albendazole and its active metabolite may occur due to induction by ritonavir, with a risk of decreased albendazole efficacy. Clinical monitoring of therapeutic response and possible adjustment of albendazole dosage during treatment with [CV024 trade name] and following discontinuation is recommended.
Antibacterials (including TB medicines)		
Bedaquiline	Bedaquiline ↑	No interaction study is available with ritonavir only. Due to the risk of bedaquiline-related adverse events, co-administration should be avoided. If the benefit outweighs the risk, bedaquiline and [CV024 trade name] must be co-administered with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (the product information for bedaquiline should be consulted).
Clarithromycin	Clarithromycin AUC ↑ 77%, C_{max} ↑ 31%, 14-OH clarithromycin metabolite AUC ↓ 100%, C_{max} ↓ 99%)	Due to the large therapeutic window of clarithromycin, no dose reduction should be necessary in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co-administered with [CV024 trade name]. For patients with renal impairment, clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30–60 mL/minute the dose should be reduced by 50%. See also section 4.2.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Delamanid		No interaction study is available with ritonavir only. In a healthy volunteers given delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the delamanid metabolite DM-6705 increased by 30%. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with [CV024 trade name] is considered necessary, very frequent ECG monitoring throughout treatment is recommended (the product information for delamanid should be consulted).
Erythromycin	Erythromycin ↑	[CV024 trade name] inhibits CYP3A4 and is expected to increase the plasma concentrations of erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin is co-administered with [CV024 trade name].
Fusidic acid	Fusidic acid ↑	[CV024 trade name] co-administration is likely to increase plasma concentrations of both fusidic acid and ritonavir. Given the risk of substantial increase in fusidic acid (systemic route) exposure and thus of its related adverse events, co-administration should be avoided unless a multidisciplinary consultation can be obtained to safely guide it.
Rifabutin	Rifabutin AUC ↑ 4-fold, C_{max} ↑ 2.5-fold 25-O-desacetyl rifabutin metabolite AUC ↑ 38-fold, C_{max} ↑ 16-fold	Due to the large increase in rifabutin AUC, reduction of the rifabutin dose to 150 mg 3 times per week may be indicated when co-administered with [CV024 trade name].
Sulfamethoxazole/ trimethoprim		Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.
Antifungals		
Itraconazole	Itraconazole ↑	Itraconazole increases nirmatrelvir AUC by 39% and C_{max} by 19%. Pharmacokinetic enhancing dose of ritonavir inhibits CYP3A4 and is expected to increase the plasma concentrations of itraconazole. Careful monitoring of therapeutic and adverse effects is recommended when itraconazole is co-administered with [CV024 trade name].

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Ketoconazole	Ketoconazole AUC ↑ 3.4-fold, C_{max} ↑ 55%	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole and can increase the incidence of gastrointestinal and hepatic adverse reactions. A dose reduction of ketoconazole should be considered when co-administered with [CV024 trade name].
Voriconazole	Voriconazole AUC ↓ 39%, C_{max} ↓ 24%	Co-administration of voriconazole and [CV024 trade name] should be avoided unless the benefit to the patient of using voriconazole outweighs the risk.
Antiretrovirals		
Bictegravir/emtricitabine/tenofovir	Bictegravir ↑ Emtricitabine ↔ Tenofovir ↑	Ritonavir may significantly increase the plasma concentrations of bictegravir through CYP3A inhibition. Ritonavir is expected to increase the absorption of tenofovir alafenamide by inhibition of P-gp, thereby increasing the systemic concentration of tenofovir.
Efavirenz	Efavirenz AUC ↑ 21%	A higher frequency of adverse reactions (e.g. dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have occurred when efavirenz is co-administered with ritonavir.
Maraviroc	Maraviroc AUC ↑ 161%, C_{max} ↑ 28%	Ritonavir increases the serum levels of maraviroc because of CYP3A inhibition. Maraviroc may be given with ritonavir to increase maraviroc concentrations. For further information, the product information for maraviroc should be consulted.
Raltegravir	Raltegravir AUC ↓ 16%, C_{max} ↓ 1%)	Co-administration of ritonavir and raltegravir results in a minor reduction in raltegravir levels
Zidovudine	Zidovudine AUC ↓ 25%, C_{max} ND	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased zidovudine concentrations. Dose alterations should not be necessary.
Hepatitis C medicine		
Glecaprevir/pibrentasvir	Glecaprevir/pibrentasvir ↑	Serum concentrations may increase due to P-gp, BCRP, and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and [CV024 trade name] is not recommended due to increased risk of ALT elevations associated with increased glecaprevir concentrations. If treatment with nirmatrelvir/ritonavir is necessary, consult an HCV specialist and use with caution and monitor for liver toxicity

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Sofosbuvir/velpatasvir/voxilaprevir	Sofosbuvir/velpatasvir/ voxilaprevir ↑	Serum concentrations may be increased due to OATP1B inhibition by ritonavir. Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and [CV024 trade name] is not recommended. For further information the current sofosbuvir/velpatasvir/voxilaprevir product information should be consulted.
Pneumocystis pneumonia medicine		
Atovaquone	Atovaquone ↓	[CV024 trade name] induces glucuronidation and is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of serum levels or therapeutic effects is recommended when atovaquone is co-administered with [CV024 trade name].
Antipsychotics		
Aripiprazole Brexpiprazole	Aripiprazole ↑ Brexpiprazole ↑	Dose adjustment of aripiprazole and brexpiprazole is recommended. For further information the current product information for these medicines should be consulted.
Clozapine	Clozapine ↑	[CV024 trade name] co-administration is likely to increase plasma concentrations of clozapine. Given the risk of increase in clozapine exposure and thus of its related adverse events, co-administration should be avoided unless a multidisciplinary consultation can be obtained to safely guide it.
Haloperidol Risperidone Thioridazine	Haloperidol ↑ Risperidone ↑ Thioridazine ↑	Ritonavir is likely to inhibit CYP2D6 and is expected to increase concentrations of haloperidol, risperidone and thioridazine, though the effect is likely to be moderate. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are administered concomitantly with [CV024 trade name].

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Benign prostatic hyperplasia medicines (alpha1-adrenoreceptor antagonist)		
Tamsulosin	Tamsulosin ↑	Tamsulosin is extensively metabolised, mainly by CYP3A4 and CYP2D6, both of which are inhibited by ritonavir. Avoid concomitant use with [CV024 trade name].If tamsulosin is paused during COVID-19 treatment, it should only be restarted 3 days after completing nirmatrelvir/ritonavir as CYP3A4 inhibition takes several days to resolve. If co-administered, consider using a maximum of tamsulosin 0.4 mg/day or every other day, and monitor for hypotension.
Cancer medicines		
Abemaciclib	Abemaciclib ↑	Serum concentrations may increase due to CYP3A4 inhibition by ritonavir. Co-administration of abemaciclib and [CV024 trade name] should be avoided. If co-administration cannot be avoided, up to date product information for abemaciclib should be consulted for dosage adjustment recommendations. The patient should be monitored for adverse effects of abemaciclib.
Afatinib	Afatinib ↑	Serum concentrations may be increased due to breast cancer resistance protein and acute P-gp inhibition by ritonavir. The extent of increase in AUC and C_{max} depends on the timing of ritonavir administration. Afatinib and [CV024 trade name] should be co-administered cautiously. The patient should be monitored for afatinib adverse effects.
Ceritinib	Ceritinib ↑	Serum concentrations of ceritinib may increase due to CYP3A and P-gp inhibition by ritonavir. Ceritinib and [CV024 trade name] should be co-administered cautiously. Up to date ceritinib product information should be consulted for dosage adjustment recommendations. The patient should be monitored for adverse effects of ceritinib.
Dasatinib Nilotinib Vinblastine Vincristine	Dasatinib ↑ Nilotinib ↑ Vinblastine ↑ Vincristine ↑	Serum concentrations may be increased when co-administered with [CV024 trade name] resulting in the potential for increased incidence of adverse events.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Encorafenib Ivosidenib	Encorafenib ↑ Ivosidenib ↑	Serum concentrations of encorafenib or ivosidenib may be increased when co-administered with ritonavir, which may increase the risk of toxicity, including the risk of serious adverse events such as QT interval prolongation. Co-administration of encorafenib or ivosidenib and [CV024 trade name] should be avoided. If the benefit is considered to outweigh the risk patients must be carefully monitored for side effects.
Fostamatinib	Fostamatinib ↑	Co-administration of fostamatinib with ritonavir may increase the concentration of fostamatinib metabolite R406 resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. Up to date fostamatinib product information should be consulted for dose reduction recommendations if such events occur when used with [CV024 trade name].
Ibrutinib	Ibrutinib ↑	Serum concentrations of ibrutinib may increase due to CYP3A inhibition by ritonavir, increasing the risk for toxicity including tumour lysis syndrome. Co-administration of ibrutinib and [CV024 trade name] should be avoided. If the benefit is considered to outweigh the risk and [CV024 trade name] must be used, the dose of ibrutinib should be reduced to 140 mg and the patient monitored closely for toxicity.
Venetoclax	Venetoclax ↑	During the ramp-up phase. Co-administration with [CV024 trade name] is contraindicated at the start of treatment and during the ramp-up phase (see table above). For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used with strong CYP3A inhibitors such as [CV024 trade name] (the venetoclax product information should be consulted for dosing instructions).

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Cardiovascular medicines		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil	Amlodipine ↑ Diltiazem ↑ Felodipine ↑ Nicardipine ↑ Nifedipine ↑ Verapamil ↑	Ritonavir inhibits CYP3A4 and is expected to increase plasma concentrations of calcium channel antagonists. A multidisciplinary consultation is required to advise on the possibility of dose decrease or temporary discontinuation of calcium channel antagonists during treatment with [CV024 trade name]. If coadministration is undertaken, patients should be carefully monitored for therapeutic and adverse effects.
Bosentan	Bosentan ↑	Co-administration of bosentan and ritonavir may increase bosentan concentrations (C_{max}) and AUC. Co-administration of bosentan with [CV024 trade name] is not recommended (product information for bosentan should be consulted)
Cilostazol	Cilostazol ↑	Dose adjustment of cilostazol is recommended. Consult current product information for cilostazol for further information.
Lercanidipine	Lercanidipine ↑	[CV024 trade name] co-administration is likely to increase plasma concentrations of lercanidipine. Given the risk of increase in lercanidipine exposure and thus of its related adverse events, co-administration should be avoided unless a multidisciplinary consultation can be obtained to safely guide it. If lercanidipine is stopped temporarily during [CV024 trade name] treatment, it should not be restarted until 3 days after the last dose of nirmatrelvir/ritonavir
Riociguat	Riociguat ↑	Serum concentrations may increase due to CYP3A and P-gp inhibition by ritonavir. If co-administration of riociguat with [CV024 trade name] cannot be avoided, the dose of riociguat should be modified (product information for riociguat should be consulted)
Ticagrelor	Ticagrelor ↑	[CV024 trade name] co-administration is likely to increase plasma concentrations of ticagrelor. Given the risk of increase in ticagrelor exposure and thus of its related adverse events, co-administration should be avoided unless a multidisciplinary consultation can be obtained to safely guide it.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Corticosteroids		
Budesonide Fluticasone propionate (inhaled, injectable or intranasal) Triamcinolone		Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (86% decrease in plasma cortisol levels) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A e.g. budesonide and triamcinolone. Consequently, co-administration of [CV024 trade name] with these corticosteroids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. Consideration should be given either to dose reduction of the corticosteroid with close monitoring of local and systemic effects or a switch to a corticosteroid which is not a substrate for CYP3A4 (e.g. beclomethasone). Moreover, in case of withdrawal of the corticosteroid, progressive dose reduction may be required over a longer period
Dexamethasone	Dexamethasone ↑	Ritonavir inhibits CYP3A and is expected to increase dexamethasone plasma concentrations. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is co-administered with [CV024 trade name].
Prednisolone	Prednisolone AUC ↑ 28%, C_{max} ↑ 9%	The AUC of the predisone metabolite prednisolone increased by 37% after 4 days ritonavir and by 28% after 14 days. Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is co-administered with [CV024 trade name].
Cystic fibrosis medicines		
Elexacaftor/tezacaftor/ivacaftor Ivacaftor Tezacaftor/ivacaftor	Elexacaftor/tezacaftor/ivacaftor↑ Ivacaftor↑ Tezacaftor/ivacaftor↑	Dose of these transmembrane conductance regulator potentiators should be reduced when co-administered with [CV024 trade name]. For further information the current product information for the medicine should be consulted.
Diabetes medicines		
Saxagliptin	Saxagliptin ↑	Dose adjustment of saxagliptin to 2.5 mg once daily is recommended

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Immunosuppressants		
Ciclosporin Everolimus Sirolimus Tacrolimus	Ciclosporin ↑ Everolimus ↑ Sirolimus ↑ Tacrolimus ↑	Ritonavir inhibits CYP3A4 and is expected to increase plasma concentrations of ciclosporin, everolimus, sirolimus and tacrolimus. Co-administration of these immunosuppressants with [CV024 trade name] should only be considered with close and regular monitoring of immunosuppressant serum concentrations and reduction of the immunosuppressant dose to avoid over-exposure and subsequent increase of serious adverse reactions of the immunosuppressant. Monitoring must continue after treatment with [CV024 trade name] finishes. Specialist advice (e.g. clinical pharmacology) is required to handle the complexity of such co-administration.
Lipid regulating medicines		
Atorvastatin Rosuvastatin	Atorvastatin ↑ Rosuvastatin (31%, 112%) ↑	Atorvastatin is less dependent on CYP3A for metabolism than lovastatin or simvastatin but some increase in its concentration might be expected with ritonavir. Rosuvastatin elimination is not dependent on CYP3A, but raised rosuvastatin concentrations have been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but likely to result from transporter inhibition. When used with ritonavir, the lowest possible doses of atorvastatin or rosuvastatin should be administered.
Fluvastatin Pravastatin	Fluvastatin ↑ Pravastatin ↑	The metabolism of fluvastatin and pravastatin is not dependent on CYP3A, but some increase in exposure may occur due to transporter inhibition. Consider temporary discontinuation of pravastatin and fluvastatin during treatment with [CV024 trade name].
Respiratory medicines		
Theophylline	Theophylline AUC ↓ 43%, C_{max} ↓ 32%	An increased dose of theophylline may be required when co-administered with [CV024 trade name], due to induction of CYP1A2.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Salmeterol	Salmeterol ↑	Ritonavir inhibits CYP3A4 and a pronounced increase in the plasma concentrations of salmeterol is expected, resulting in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Therefore, concomitant use with [CV024 trade name] is not recommended.
Sedatives/hypnotics		
Alprazolam	Alprazolam AUC ↑ 2.5-fold, C_{max} ↔	Alprazolam metabolism is inhibited by the introduction of ritonavir. Alprazolam and [CV024 trade name] should be co-administered with caution during the first few days, before induction of alprazolam metabolism occurs.
Buspirone	Buspirone ↑	Ritonavir inhibits CYP3A and is expected to increase plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone is co-administered with [CV024 trade name].
Midazolam	Oral Midazolam AUC ↑ 1330%, C_{max} ↑ 268% ↑ Parenteral midazolam	Co-administration of [CV024 trade name] with oral midazolam is contraindicated (see table above). Data from concomitant use of parenteral midazolam with other protease inhibitors suggests a possible 3- to 4-fold increase in midazolam plasma concentrations. Co-administration of [CV024 trade name] with parenteral midazolam should occur in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and medical management in case of respiratory depression or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is given.
Zolpidem	Zolpidem AUC ↑ 28%, C_{max} ↑ 22%	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Other medicines		
Amphetamine derivatives (CNS stimulant)	Amphetamine ↑	Ritonavir at antiretroviral doses is likely to inhibit CYP2D6 and increase concentrations of amphetamine and its derivatives; some inhibition is possible at the lower doses present in [CV024 trade name]. Careful monitoring for adverse effects is recommended when amphetamine medicines are co-administered with [CV024 trade name].
Bupropion (smoking cessation aid)	Bupropion AUC ↓ 22%, C_{max} ↓ 21%	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion concentrations. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir also inhibits CYP2B6 in vitro, the recommended dose of bupropion should not be exceeded. In contrast to long-term administration of ritonavir, there was no significant interaction with bupropion after short-term administration of low doses of ritonavir (200 mg twice daily for 2 days), suggesting bupropion concentrations may only start decreasing several days after starting ritonavir co-administration
Darifenacin Solifenacin (antimuscarinic medicines for urinary problems)	Darifenacin ↑ Solifenacin ↑	[CV024 trade name] may increase exposure to the antimuscarinics darifenacin and solifenacin. Given the risk of substantial increase in exposure and thus of adverse effects, co-administration should be avoided unless a multidisciplinary consultation can be obtained to safely guide it.
Ethinylestradiol (hormonal contraceptive)	Ethinylestradiol AUC 40% C_{max} ↓ 32%	Due to reductions in ethinylestradiol concentrations, ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of ethinylestradiol-containing contraceptives. Alternatives such as barrier or other non-hormonal methods of contraception should be considered during use of [CV024 trade name].
Levothyroxine (thyroid replacement hormone)		Reported cases indicate a potential interaction between ritonavir and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine for at least 1 month after [CV024 trade name] treatment.

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Rimegepant	Rimegepant ↑	Avoid concomitant use with [CV024 trade name] Considering the short duration of nirmatrelvir/ritonavir treatment, rimegepant can be stopped temporarily if treatment with nirmatrelvir/ritonavir is deemed essential. Further rimegepant doses should not be taken until 3 days after the last dose of nirmatrelvir/ritonavir.
Tofacitinib	Tofacitinib ↑	Dose adjustment of tofacitinib is recommended. Current tofacitinib product information should be consulted for further information
Upadacitinib	Upadacitinib ↑	Dosing recommendations for co-administration of upadacitinib with [CV024 trade name] depend on the upadacitinib indication. Current upadacitinib product information should be consulted for further information

↓	Decreased	AUC	area under the curve (bioavailability)
↑	Increased	C_{max}	maximum (peak) concentration (in plasma or blood)
↔	No change	C_{min}	minimum (trough) concentration (in plasma or blood)
ND	Not determined		

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential

There are few data on the use of nirmatrelvir/ritonavir in pregnant women and drug-associated risk of adverse developmental outcomes. Women of childbearing potential should avoid becoming pregnant during treatment with [CV024 trade name] and, as a precaution, for 7 days after completing treatment with [CV024 trade name].

Ritonavir may reduce the efficacy of combined hormonal contraceptives. Women using combined hormonal contraceptives should be advised to use an additional barrier method of contraception or an effective alternative contraceptive method during treatment with [CV024 trade name] and for one menstrual cycle after stopping [CV024 trade name].

Pregnancy

There are limited data on the use of nirmatrelvir/ritonavir in pregnant women. As pregnancy represents a risk factor for progression to severe or critical COVID-19 disease, [CV024 trade name] may be considered for use during pregnancy following discussion of the benefits and risks with the patient.

A large number of women exposed to ritonavir during pregnancy indicate no increase in the rate of birth defects compared to rates in population-based birth defect surveillance systems.

Animal data on ritonavir have shown reproductive toxicity (see section 5.3). Animal data with nirmatrelvir have shown developmental toxicity in the rabbit (lower foetal body weights) but not in the rat (see section 5.3).

Breast-feeding

There are no data on whether the use of nirmatrelvir/ritonavir in breast-feeding women affects the breast-fed infant or milk production. Breast-feeding should be stopped during [CV024 trade name] treatment and, as a precaution, breast-feeding avoided for 48 hours after treatment is complete.

In a clinical pharmacokinetics study, 8 healthy lactating women who were at least 12 weeks postpartum were administered 3 doses (steady-state dosing) of 300 mg/100 mg nirmatrelvir/ritonavir. Nirmatrelvir and ritonavir were excreted in breast milk in small amounts, with a milk to plasma AUC ratio of 0.26 and 0.07, respectively. The mean (range) estimated daily infant dose (assuming average milk consumption of 150 mL/kg/day), was 1.8% (1.3-2.5%) and 0.2% (0.1-0.3%) of the maternal dose.

Fertility

There are no human data on the effect of nirmatrelvir together with ritonavir or ritonavir alone on fertility. Nirmatrelvir and ritonavir, tested separately, produced no effects on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

[CV024 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions during treatment with nirmatrelvir/ritonavir 300 mg/100 mg every 12 hours for 5 days were dysgeusia (4.6%), diarrhoea (3.0%), headache (1.2%) and vomiting (1.2%).

Tabulated list of adverse reactions

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000) or very rare (less than 1 in 10 000).

Immune system disorders

Uncommon	hypersensitivity
Rare	anaphylaxis

Nervous system disorders

Common	dysgeusia, headache

Vascular disorders

Uncommon	hypertension

Gastrointestinal disorders

Common	diarrhoea, vomiting, nausea
Uncommon	abdominal pain

Skin and subcutaneous tissue disorders

Uncommon	Rash (may be sign of hypersensitivity reaction)
Rare	Stevens-Johnson syndrome, pruritus (may be signs of hypersensitivity reaction)

Musculoskeletal and connective tissue disorders

Uncommon	myalgia

General disorders and administration site conditions

Rare	malaise

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Treatment of [CV024 trade name] overdose should consist of general supportive measures including monitoring the patient's clinical status. There is no specific antidote for [CV024 trade name] overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, protease inhibitors, ATC code: J05AE30

Mechanism of action

Nirmatrelvir inhibits the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibiting SARS-CoV-2 Mpro prevents the processing of polyprotein precursors which, in turn, prevents viral replication.

Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby increasing plasma concentrations of nirmatrelvir.

Antiviral activity

Nirmatrelvir was active against SARS-CoV-2 infection of dNHBE cells, a primary human lung alveolar epithelial cell line (EC_{50} of 61.8 nM and EC_{90} of 181 nM) after 3 days of drug exposure.

The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7 (P252L+F294L), BF.7 (T243I), BQ.1.11, BQ.1, XBB.1.5, EG.5 and JN.1 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} of 88 nM (range: 39–146 nM) against the Omicron sub-variants, reflecting EC_{50} fold-changes ≤ 1.8 relative to the USA-WA1/2020 isolate.

In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} of 25 nM (range: 16–141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} fold-changes ≤ 1.1 relative to USA-WA1/2020

Resistance

SARS-CoV-2 Mpro residues potentially associated with nirmatrelvir resistance have been identified using a variety of methods, including SARS-CoV-2 resistance selection, testing of recombinant SARS-CoV-2 viruses with Mpro substitutions, and biochemical assays with recombinant SARS-CoV-2 Mpro containing amino acid substitutions. The list below indicates Mpro substitutions and combinations of Mpro substitutions observed in nirmatrelvir-selected SARS-CoV-2 in cell culture. Individual Mpro substitutions are listed regardless of whether they occurred alone or in combination with other Mpro substitutions. Note that the Mpro S301P and T304I substitutions overlap the P6 and P3 positions of the nsp5/nsp6 cleavage site located at the C-terminus of Mpro. Substitutions at other Mpro cleavage sites have not been associated with nirmatrelvir resistance in cell culture. The clinical significance of these substitutions is unknown.

SARS-CoV-2 Mpro amino acid substitutions selected by nirmatrelvir in cell culture (with EC_{50} fold-change > 5)

S144A (2.2-5.3), E166V (25-288), P252L (5.9), T304I (1.4-5.5), T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1-8.9), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), F140L+A173V (10.1), A173V+T304I

(20.2), T21+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), L50F+F140L+L167F+T304I (54.7)

Most single and some double Mpro amino acid substitutions identified which reduced the susceptibility of SARS-CoV-2 to nirmatrelvir resulted in an EC_{50} shift of < 5-fold compared to wild type SARS-CoV-2. In general, triple and some double Mpro amino acid substitutions led to EC_{50} changes of > 5-fold to that of wild type. The clinical significance of these substitutions needs to be further understood.

Viral load rebound

Post-treatment viral nasal RNA rebounds were observed on Day 10 and/or Day 14 in a subset of nirmatrelvir/ritonavir and placebo recipients in EPIC-HR, irrespective of COVID-19 symptoms. The incidence of viral rebound in EPIC-HR occurred in both nirmatrelvir/ritonavir-treated participants and untreated (placebo) participants, but at a numerically higher incidence in the nirmatrelvir/ritonavir arm (6.3% vs. 4.2%). Viral rebound and recurrence of COVID-19 symptoms were not associated with progression to severe disease including hospitalisation, death or emergence of resistance.

Clinical efficacy and safety

The efficacy of [CV024 trade name] is based on the analysis of EPIC-HR, a Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised, symptomatic adults with laboratory-confirmed SARS-CoV-2 infection. Patients were 18 years of age and older with at least one of the following risk factors for progression to severe disease: diabetes, overweight (BMI more than 25 kg/m^2), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, technological dependence for medical reasons, or 60 years of age and older. The study included participants with COVID-19 symptom onset of up to 5 days; it excluded vaccinated individuals or those who had a previous COVID-19 infection.

Study patients received either nirmatrelvir 300 mg/ritonavir 100 mg or placebo every 12 hours for 5 days. The primary efficacy endpoint was the proportion of patients with COVID-19 related hospitalisation or death from any cause within 28 days. The analysis was in:

- modified intent-to-treat (mITT) set—all treated patients with onset of symptoms within 3 days who had not received nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment
- mITT-1 analysis set—all treated patients with onset of symptoms within 5 days who had not received nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and
- mITT-2 analysis set—all treated patients with onset of symptoms within 5 days.

In the mITT-1 population (analysis of 1966 patients), 9 out of 977 (0.9%) patients who received nirmatrelvir/ritonavir had COVID-19 related hospitalisation (none died) within 28 days compared with 64 out of 989 (6.5%) patients who received placebo (12 patients died). The estimated risk reduction was – 6.1% (95% CI – 8.2, – 4.1) in patients receiving nirmatrelvir/ritonavir within 3 days of the onset of symptoms; in patients receiving nirmatrelvir/ritonavir after 3 days of the onset of symptoms, the risk reduction was – 4.6% (95% CI – 7.4, – 1.8).

Results from the final mITT and mITT2 analysis populations were consistent. A total of 1,318 patients were included in the mITT analysis population. The event rates were 5/671 (0.75%) in the nirmatrelvir/ritonavir group, and 44/647 (6.80%) in the placebo group.

Post-hoc subgroup analysis in severely immunocompromised participants

A post-hoc subgroup analysis in severely immunocompromised participants (e.g., active haematologic malignancies, haematopoietic stem cell transplantation, CAR T-cell therapy or B-cell depleting therapies) has been performed and was derived from EPIC-IC (C4671034) study in immunocompromised participants.

In participants who were severely immunocompromised, the median time to achieving NP swab SARS-CoV-2 RNA <LLOQ was numerically longer in the 5-day treatment group (28 days) compared with the 10-day (13 days) and 15-day (15 days) treatment groups.

The proportion of participants with both a positive SARS-CoV-2 rapid antigen test and any self-reported targeted symptom of COVID 19 from Day 15 through Day 44 was 33.3% (6 of 18 participants), 6.3% (1 of 16 participants), and 0% (0 of 16 participants) in the 5-, 10- and 15-day nirmatrelvir/ritonavir treatment groups, respectively. The incidence of viral RNA rebound observed in the severely immunocompromised participants was 25% (5 of 20 participants), 0% (0 of 17 participants) and 5% (1 of 20 participants) in the 5-, 10-, and 15-day treatment groups, respectively.

Paediatric population

Efficacy in paediatric patients is based on matching exposure to adult COVID-19 patients.

5.2 Pharmacokinetic properties

Absorption of [CV024 trade name]

The absorption characteristics of [CV024 trade name] have been determined after administration of two nirmatrelvir 150 mg tablet and one ritonavir 100 mg tablets in healthy volunteers in the fasting state as follows:

Nirmatrelvir

Pharmacokinetic variable'	**Mean value* (± standard deviation)**
	Nirmatrelvir
Maximum concentration (C_{max})	3466 ± 923 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	34198 ± 9237 ng·h/mL
Time to attain maximum concentration (t_{max})	2.25 ± 1.10 h

* arithmetic mean

Ritonavir

Pharmacokinetic variable'	**Mean value* (± standard deviation)**
	Ritonavir
Maximum concentration (C_{max})	859 ± 382 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	7367 ± 3614 ng·h/mL
Time to attain maximum concentration (t_{max})	4.50 h (2.00-7.00)

* arithmetic mean

Pharmacokinetics of nirmatrelvir/ritonavir

	Nirmatrelvir	**Ritonavir**
General	Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations of nirmatrelvir. Steady-state achieved after 2 days with about 2-fold accumulation.	
Absorption	After a single 300 mg/100 mg dose: geometric mean C_{max} and AUC_{∞} was 2.21 µg/mL and 23.01 µg·hour/mL, respectively.	After a single 300 mg/100 mg dose: geometric mean ritonavir C_{max} and AUC_{∞} was 0.36 µg/mL and 3.6 µg·hour/mL, respectively.
Effect of food on oral absorption	C_{max}: 15% ↑ AUC: 1.6% ↑	Not investigated, but small decrease in C_{max} and AUC expected in line with known food effect of ritonavir.
T_{max}	3 hours	4 hours
Distribution		
Plasma protein binding in vitro	About 69%.	About 98-99%.
Metabolism	Primarily metabolised by CYP3A4. Co-administration with ritonavir, in plasma, the only nirmatrelvir-related entity detected was unchanged nirmatrelvir. Minor oxidative metabolites were detected in the faeces and urine.	Primarily metabolised by CYP3A, although CYP2D6 also contributes to the formation of oxidation metabolite M–2.
Elimination		
Terminal half life	6.1 hours	6.1 hours
Proportion of dose excreted in urine	About 50% (co-administered with ritonavir)	–
Proportion of dose excreted in faeces	About 35% (co-administered with ritonavir)	About 86%
Pharmacokinetic linearity	After 75 mg/100 mg, 250 mg/100 mg, and 500 mg/100 mg twice daily, steady state exposure increases less in proportion to dose increase.	–

Drug interactions	Nirmatrelvir is not an inducer or substrate of other CYP enzymes other than CYP3A of which nirmatrelvir/ritonavir is an inhibitor. CYP3A4 was the major contributor to the oxidative metabolism of nirmatrelvir, when nirmatrelvir was tested alone in human liver microsomes, hence administration with ritonavir to increase plasma concentrations.. Despite being co-administered with ritonavir as a pharmacokinetic enhancer, there is potential for strong inhibitors and inducers to alter the pharmacokinetics of nirmatrelvir. Nirmatrelvir does not reversibly inhibit CYP2D6, CYP2C9, CYP2C19, CYP2C8, or CYP1A2 in vitro at clinically relevant concentrations. In vitro study results showed nirmatrelvir may be inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9. The clinical relevance is unknown. Based on in vitro data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.	In vitro studies using human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of oxidation metabolite M–2. Co-administration with other medicines that induce or inhibit CYP3A4 may decrease or increase ritonavir plasma concentrations respectively.

Paediatric population

The pharmacokinetics of nirmatrelvir following nirmatrelvir/ritonavir 150 mg/100 mg or 300 mg/100 mg given twice daily have been evaluated in 68 paediatric participants 6 years of age and older and weighing at least 20 kg.

Population pharmacokinetic analyses and model-based simulation demonstrated that the pharmacokinetics of nirmatrelvir/ritonavir in these participants were similar to those in adults after accounting for weight differences, with C_{max}, AUC_{tau}, and C_{min} values that were 1.2, 1.4, and 1.7-fold higher, respectively.

Estimated[a] pharmacokinetic parameters of nirmatrelvir on day 5 in paediatric patients 6 or more years of age using population PK modelling

Body weight	**Dose regimen**	**C_{max} (µg/mL)[b]**	**AUC_{tau} (µg*hr/mL)[b,c]**	**C_{min} (µg/mL)[b]**
40 kg or more	300 mg nirmatrelvir/ 100 mg ritonavir twice daily for 5 days	4.31 (2.88, 6.40)	36.3 (22.5, 58.3)	1.62 (0.71, 3.48)
20 to less than 40 kg	150 mg nirmatrelvir/ 100 mg ritonavir twice daily for 5 days	4.11 (2.76, 6.15)	34.1 (21.0, 55.3)	1.47 (0.61, 3.19)

a. Data presented were generated using a population PK analysis model (adult Phase 1 + paediatric) simulation of 10,000 virtual subjects in each group
b. Data presented as geometric mean (10th and 90th percentile); C_{max}=predicted maximal concentration; C_{min}=predicted minimal (trough) concentration.
c. AUC_{tau}=predicted area under the plasma concentration-time profile from time 0 to 12 hours for twice daily dosing.

The recommended paediatric dosing regimens in participants 6 years of age and older weighing at least 20 kg result in no clinically relevant differences in systemic exposure to those in adults receiving nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days

Renal impairment

The C_{max} and AUC of nirmatrelvir in patients with mild renal impairment were 30% and 24% higher than in healthy controls with no renal impairment; in moderate renal impairment they were 38% and 87% higher, and in severe renal impairment they were 48% and 204% higher, respectively.

Severe renal impairment including those requiring haemodialysis

The pharmacokinetics of nirmatrelvir in adult participants with mild-to-moderate COVID-19 and severe renal impairment (eGFR< 30 mL/min) either requiring haemodialysis (n=12) or not requiring haemodialysis (n=2) were evaluated after administration of 300 mg/100 mg nirmatrelvir/ritonavir once on Day 1 followed by 150 mg/100 mg nirmatrelvir/ritonavir once daily on Days 2–5 for a total of 5 doses.

During a 4-hour haemodialysis session, approximately 6.9% of nirmatrelvir dose was cleared through dialysis. Haemodialysis clearance was 1.83 L/h.

Population pharmacokinetic model-based simulations showed that this dose regimen in adult participants with severe renal impairment resulted in comparable exposures on Day 1 and at steady-state (AUC_{0-24} and C_{max}) to those observed in adult participants with normal renal function receiving 300 mg/100 mg nirmatrelvir/ritonavir twice daily for 5 days.

Based on the results of population PK analysis model-based simulation, dose reduction in paediatric patients 6 years of age and older weighing at least 40 kg with renal impairment should parallel that recommended for adults with the same degree of renal impairment.

Dose in paediatric patients with renal impairment weighing less than 40 kg has not been determined.

Hepatic impairment

The pharmacokinetics of nirmatrelvir in subjects with moderate hepatic impairment were not significantly different to those in healthy controls with no hepatic impairment. Adjusted geometric mean ratio (90% CI) of AUC_{∞} and C_{max} of nirmatrelvir comparing moderate hepatic impairment (test) to normal hepatic function (reference) was 98.8% (70.6%, 138.1%) and 102% (74.2%, 140.1%), respectively.

Nirmatrelvir/ritonavir has not been studied in patients with severe hepatic impairment.

Breast-feeding mothers

Following 3 doses of nirmatrelvir/ritonavir 300 mg/100 mg given twice daily to 8 healthy lactating women, under high-fat high-calorie fed conditions, both nirmatrelvir and ritonavir were excreted into breast milk. The estimated milk to plasma ratios for C_{max} and AUC were 0.27 and 0.26, respectively for nirmatrelvir and 0.06 and 0.07, respectively for ritonavir

5.3 Preclinical safety data

No nonclinical safety studies have been conducted with nirmatrelvir in combination with ritonavir.

Nirmatrelvir

Studies of repeated dose toxicity and genotoxicity revealed no risk due to nirmatrelvir. No adverse effects were observed in fertility, embryo-fetal development, or pre- and postnatal development studies in rats. A study in pregnant rabbits showed an adverse decrease in fetal body weight, in the absence of significant maternal toxicity. Systemic exposure (AUC_{24}) in rabbits at the maximum dose without adverse effect in fetal body weight was estimated to be about 3 times higher than exposure in humans at recommended therapeutic dose of [CV024 trade name].

No carcinogenicity studies have been conducted with nirmatrelvir.

Ritonavir

Repeat-dose toxicity studies of ritonavir in animals identified major target organs as the liver, retina, thyroid gland and kidney. Hepatic changes involved hepatocellular, biliary and phagocytic elements and were accompanied by increases in hepatic enzymes. Hyperplasia of the retinal pigment epithelium and retinal

degeneration occurred in all the rodent studies conducted with ritonavir, but have not been seen in dogs. Ultrastructural evidence suggests that these retinal changes may be secondary to phospholipidosis. However, clinical trials revealed no evidence of ritonavir-induced ocular changes in humans. All thyroid changes were reversible on discontinuation of ritonavir. Clinical investigation in humans has revealed no clinically significant alteration in thyroid function tests.

Renal changes including tubular degeneration, chronic inflammation and proteinuria occurred in rats and are considered to be attributable to species-specific spontaneous disease. Furthermore, clinical trials did not reveal clinically significant renal abnormalities.

Genotoxicity studies revealed no risk due to ritonavir. Long-term carcinogenicity studies of ritonavir in mice and rats revealed tumorigenic potential specific for these species, but are regarded as of no relevance for humans.

Ritonavir produced no effects on fertility in rats. Developmental toxicity in rats (embryo-lethality, decreased fetal body weight and ossification delays and visceral changes, including delayed testicular descent) occurred mainly at maternally toxic dosage. Developmental toxicity in rabbits (embryo-lethality, decreased litter size and decreased fetal weights) occurred at a maternally toxic dosage.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nirmatrelvir 150mg film-coated tablets

Core tablet: Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Colloidal silicon dioxide
Sodium stearyl fumarate

Film coat: Titanium dioxide
Hypromellose
Macrogol/PEG
Iron oxide red

Ritonavir100mg film-coated tablets

Core tablet: Sorbitan monolaurate
Copovidone
Colloidal silicon dioxide
Sodium chloride
Sodium stearyl fumarate

Film coat: Colloidal anhydrous silica
Hypromellose
Hydroxypropyl cellulose
Iron oxide yellow
Macrogol/PEG
Polysorbate 80
Talc
Titanium dioxide

Nirmatrelvir 150-mg film-coated tablets
This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

Ritonavir 100mg film-coated tablets

Each tablet contains 3.82 mmol (87.76 mg) sodium, equivalent to about 4% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Alu/PA/Alu/PVC blister

[CV024 trade name] consists of Nirmatrelvir 150-mg tablets co-packed together with Ritonavir 100-mg tablets.

[CV024 trade name] is provided in aluminium-aluminium foil blister cards each containing 4 nirmatrelvir 150 mg film-coated tablets and 2 ritonavir 100 mg film-coated tablets. There are 5 such blister cards packed in a carton.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Mylan Laboratories Limited,
Plot No.564/A/22, Road No.92,
Jubilee Hills
Hyderabad - 500096,
Telangana, India.
Email: ProductSafety@viatris.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

CV024

9. DATE OF PREQUALIFICATION

19 December 2024

10. DATE OF REVISION OF THE TEXT

March 2026

References

General

WHO. Therapeutics and COVID-19: living guideline, August 2025. Geneva: World Health Organization; 2025 (https://www.who.int/publications/i/item/B09540, accessed 27 Jan 2026)

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Covid-19 drug interactions [online database]. Liverpool Drug Interactions Group, University of Liverpool; 2023 (https://www.covid19-druginteractions.org/, accessed 27 Jan 2026).

Drug-drug interactions between ritonavir-boosted nirmatrelvir (Paxlovid) and concomitant medications. NIH COVID-19 treatment guidelines. Bethesda: National Institutes of Health; 2023 (https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions, accessed 19 Nov 2023).

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Hammond J, Leister-Tebbe H, Gardner A, et al; EPIC-HR Investigators. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med* 2022; 386:1397–1408. doi: 10.1056/NEJMoa2118542.

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products