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

[CV016 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of nirmatrelvir contains 150 mg nirmatrelvir and each tablet of ritonavir contains 100 mg ritonavir.

Excipients with potential clinical effect

Each nirmatrelvir 150 mg film-coated tablet contains 176 mg of lactose monohydrate and 3.6 mg (0.15mmol) of sodium.

Each ritonavir 100 mg tablet contains 0.2 mg (0.01mmol) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Nirmatrelvir 150 mg film-coated tablets

Yellow, oval, film- coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have '150' debossed (stamped into) one side and are plain on the other side.

Ritonavir 100 mg film-coated tablets

White, oval, film- coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have "54" debossed (stamped into) on one side and "247" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[CV016 trade name] is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and 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:

age of 60 years or older

BMI greater than 25 kg/m^2

chronic lung disease (including asthma) or being a current smoker

chronic kidney disease

immunosuppressive disease or immunosuppressive treatment

cardiovascular disease or hypertension

sickle cell disease

neurodevelopmental disorders

active cancer

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

dependence on a medical technology device to manage a clinical condition

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

Treatment with [CV016 trade name] should be started as soon as possible after diagnosing COVID-19 and within 5 days of the onset of COVID-19 symptoms.

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

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 [CV016 trade name].

Missed dose

If the patient misses a dose of [CV016 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.

Children and adolescents

[CV016 trade name] is not indicated for patients younger than 18 years of age because its safety and efficacy have not been established.

Renal impairment

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

In patients with **moderate** renal impairment (eGFR between 30 and 60 mL/minute), the dose of nirmatrelvir should be halved and the patient should receive nirmatrelvir 150 mg (one 150-mg tablet) and ritonavir 100 mg (one 100-mg tablet) every 12 hours for 5 days; this recommended dose adjustment has not been clinically tested.

Dosing advice for patients with moderate renal impairment

The patient should be carefully advised that only one nirmatrelvir (150-mg) tablet should be taken with the (100-mg) ritonavir tablet every 12 hours. This means that only half of the nirmatrelvir tablets in the pack are used by the end of the 5-day course.

[CV016 trade name] **should not be used in patients with severe renal impairment** (eGFR less than 30 mL/minute, including patients with end-stage renal disease on haemodialysis) (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment of [CV016 trade name] is needed for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). [CV016 trade name] should not be used in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Method of administration

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

[CV016 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.

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 (see also list below) can significantly reduce plasma concentrations of nirmatrelvir or ritonavir, potentially causing loss of virologic response and possible resistance.

The medicines listed below are contraindicated with [CV016 trade name]; the list is a guide only and not a comprehensive list of all medicines that are contraindicated.

- Antianginal: ranolazine
- Antiarrhythmics: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Antibacterial: fusidic acid
- Anti-gout: colchicine
- Antihistamines: terfenadine
- Antipsychotics: clozapine, lurasidone, pimozide, quetiapine
- Benign prostatic hyperplasia medicines (alpha1-adrenoreceptor antagonists): alfuzosin, silodosin
- Cancer medicines: neratinib, venetoclax
- Cardiovascular medicines: eplerenone, ivabradine
- Ergot derivatives: dihydroergotamine, ergometrine, ergotamine, methylergometrine
- Immunosuppressant: voclosporin
- Lipid-modifying agents:
    - HMG Co-A reductase inhibitors: lovastatin, simvastatin
    - Microsomal triglyceride transfer protein (MTTP) inhibitor: lomitapide
- Migraine medicine: eletriptan
- PDE5 inhibitors: avanafil, sildenafil, tadalafil, vardenafil
- Sedatives/hypnotics: clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam
- Vasopressin receptor antagonist: tolvaptan

Potent CYP3A inducers, which significantly reduce nirmatrelvir/ritonavir plasma concentrations may be associated with loss of antiviral effect of [CV016 trade name] and possible resistance, include:

- Antibacterial: rifampicin
- Antiepileptics: carbamazepine, phenobarbital, phenytoin
- Cancer medicine: apalutamide
- Herbal products: St John's wort (*Hypericum perforatum*)

[CV016 trade name] cannot be started immediately after discontinuing a CYP3A inducer because the CYP3A-inducing effect may persist and reduce the antiviral effect of [CV016 trade name]. Specialists (e.g. in clinical pharmacology) may need to be consulted to determine when [CV016 trade name] can be started, taking into account the persisting enzyme-inducing effect of the recently discontinued CYP3A inducer and the need to start [CV016 trade name] within 5 days of the onset of disease symptoms.

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 [CV016 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 have been reported with [CV016 trade name] (see section 4.8). Toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported with ritonavir, a component of [CV016 trade name]. If a clinically significant hypersensitivity reaction or anaphylaxis occurs, [CV016 trade name] should be discontinued immediately and treatment started to manage the reaction.

Severe renal impairment

No clinical data are available in patients with severe renal impairment (including patients with end-stage renal disease). Pharmacokinetic data (see section 5.2) indicate that the use of [CV016 trade name] in patients with severe renal impairment could lead to excessive concentrations and potential toxicity. Therefore, [CV016 trade name] should not be used in patients with severe renal impairment (eGFR less than 30 mL/minute, including patients with end-stage renal disease on haemodialysis).

Severe hepatic impairment

No pharmacokinetic and clinical data are available in patients with severe hepatic impairment. Therefore, [CV016 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, [CV016 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 [CV016 trade name] 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-1 resistance development

In individuals with uncontrolled or undiagnosed HIV-1 infection, ritonavir in [CV016 trade name] may lead to HIV-1 developing resistance to HIV protease inhibitors.

Excipients

[CV016 trade name] contains lactose. 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.

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 [CV016 trade name]

Nirmatrelvir and ritonavir are CYP3A substrates. Therefore, medicines that **induce** CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce [CV016 trade name] therapeutic effect.

Medicines that **inhibit** CYP3A4 may increase nirmatrelvir and ritonavir plasma concentrations, and thus may increase the risk of [CV016 trade name] adverse reactions.

Effects of [CV016 trade name] on other medicinal products

[CV016 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 table, below). Co-administration of other CYP3A substrates with potential for significant interaction (see table, below) 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 [CV016 trade name] with substrates of CYP2D6 may therefore increase the CYP2D6 substrate concentration.

[CV016 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.

[CV016 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 [CV016 trade name] indicate that the drug interactions are primarily due to ritonavir. Hence, drug interactions pertaining to ritonavir apply to [CV016 trade name].

The following table includes medicines that can interact with [CV016 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.

[CV016 trade name] interactions

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	Fentanyl ↑	Ritonavir inhibits CYP3A4 and [CV016 trade name] is expected to increase plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when these medicines are co-administered.
Methadone	Methadone AUC ↓ 36%, C_{max} ↓ 38%	Increased methadone dose may be necessary when co-administered with [CV016 trade name] due to induction of glucuronidation. Dose adjustment should be considered, based on the patient's clinical response to methadone therapy.
Morphine	Morphine ↓	Morphine levels may be decreased due to induction of glucuronidation by co-administered [CV016 trade name].

Drugs	**Change in AUC and C_{max}**	**Recommendation on co-administration**
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 [CV016 trade name].
Antiarrhythmics		
Amiodarone Dronedarone Flecainide Propafenone Quinidine	Amiodarone ↑ Dronedarone ↑ Flecainide ↑ Propafenone ↑ Quinidine ↑	Ritonavir co-administration is likely to increase plasma concentrations of amiodarone, dronedarone, flecainide, propafenone and quinidine and co-administration with [CV016 trade name] is therefore contraindicated.
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.
Anticoagulants		
Dabigatran	Dabigatran AUC ↑ 94%, C_{max} ↑ 133%	Concomitant administration of [CV016 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 [CV016 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 [CV016 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 [CV016 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 [CV016 trade name].

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Antiepileptics		
Carbamazepine Phenobarbital Phenytoin		Carbamazepine decreases nirmatrelvir AUC by 55% and C_{max} by 43%. Phenobarbital and phenytoin are strong CYP3A4 inducers, and this may decrease nirmatrelvir and ritonavir concentrations with potential loss of antiviral effect. [CV016 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 and phenytoin with [CV016 trade name] is contraindicated.
Divalproex (sodium valproate and valproic acid) Lamotrigine	Divalproex ↓ Lamotrigine ↓	[CV016 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.
Antihistamines		
Fexofenadine	Fexofenadine ↑	[CV016 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 [CV016 trade name].
Loratadine	Loratadine ↑	[CV016 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 [CV016 trade name].
Terfenadine	Terfenadine ↑	Increased plasma concentrations of terfenadine with increased risk of serious arrhythmias. Concomitant use with [CV016 trade name] is contraindicated.
Anti-infectives		
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 [CV016 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 [CV016 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%. [CV016 trade name] should not be used for patients with creatinine clearance less than 30 mL/minute (see 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 [CV016 trade name] is considered necessary, very frequent ECG monitoring throughout treatment is recommended (the product information for delamanid should be consulted).
Erythromycin	Erythromycin ↑	[CV016 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 [CV016 trade name].
Fusidic acid	Fusidic acid ↑	[CV016 trade name] co-administration is likely to increase plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated.
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 [CV016 trade name].
Rifampicin		Rifampicin is a strong CYP3A4 inducer, and this may reduce concentrations of nirmatrelvir/ritonavir with potential loss of antiviral effect. Concomitant use of rifampicin with [CV016 trade name] is contraindicated.
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 [CV016 trade name].
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 [CV016 trade name].
Voriconazole	Voriconazole AUC ↓ 39%, C_{max} ↓ 24%	Co-administration of voriconazole and [CV016 trade name] should be avoided unless the benefit to the patient of using voriconazole outweighs the risk.
Antiretrovirals		
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.

Drugs	**Change in AUC and C_{max}**	**Recommendation on co-administration**
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 [CV016 trade name] is not recommended due to increased risk of ALT elevations associated with increased glecaprevir concentrations.
Pneumocystis pneumonia medicine		
Atovaquone	Atovaquone ↓	[CV016 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 [CV016 trade name].
Antipsychotics		
Clozapine Pimozide	Clozapine ↑ Pimozide ↑	[CV016 trade name] co-administration is likely to increase plasma concentrations of clozapine or pimozide and is therefore contraindicated.
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 [CV016 trade name].
Lurasidone	Lurasidone ↑	CYP3A inhibition by ritonavir is expected to increase lurasidone concentrations. Concomitant administration of [CV016 trade name] with lurasidone is contraindicated.
Quetiapine	Quetiapine ↑	CYP3A inhibition by ritonavir is expected to increase, quetiapine concentrations. Concomitant administration of [CV016 trade name] and quetiapine is contraindicated as it may increase quetiapine-related toxicity.
Benign prostatic hyperplasia medicines (alpha1-adrenoreceptor antagonist)		
Alfuzosin	Alfuzosin ↑	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated.
Silodosin	Silodosin ↑	Co-administration is contraindicated due to potential for postural hypotension

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Cancer medicines		
Abemaciclib	Abemaciclib ↑	Serum concentrations may increase due to CYP3A4 inhibition by ritonavir. Co-administration of abemaciclib and [CV016 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 [CV016 trade name] should be co-administered cautiously. The patient should be monitored for afatinib adverse effects.
Apalutamide	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 [CV016 trade name] with apalutamide is contraindicated.
Ceritinib	Ceritinib ↑	Serum concentrations of ceritinib may increase due to CYP3A and P-gp inhibition by ritonavir. Ceritinib and [CV016 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 [CV016 trade name] resulting in the potential for increased incidence of adverse events.
Encorafenib	Encorafenib ↑	Serum concentrations of encorafenib may increase 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 and [CV016 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 [CV016 trade name].

Drugs	**Change in AUC and C_{max}**	**Recommendation on co-administration**
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 [CV016 trade name] should be avoided. If the benefit is considered to outweigh the risk and [CV016 trade name] must be used, the dose of ibrutinib should be reduced to 140 mg and the patient monitored closely for toxicity.
Neratinib	Neratinib ↑	Serum concentrations may increase due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with [CV016 trade name] is contraindicated due to serious or life-threatening potential reactions including hepatotoxicity.
Venetoclax	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 [CV016 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 [CV016 trade name] (the venetoclax product information should be consulted for dosing instructions).
Cardiovascular medicines		
Amlodipine Diltiazem Nifedipine	Amlodipine ↑ Diltiazem ↑ Nifedipine ↑	Ritonavir inhibits CYP3A4 and is expected to increase plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when amlodipine, diltiazem or nifedipine are co-administered with [CV016 trade name].
Bosentan	Bosentan ↑	Co-administration of bosentan and ritonavir may increase bosentan concentrations (C_{max}) and AUC.
Eplerenone	Eplerenone ↑	Co-administration with eplerenone is contraindicated due to potential for hyperkalaemia
Ivabradine	Ivabradine ↑	Co-administration with ivabradine is contraindicated due to potential for bradycardia or conduction disturbances
Lercanidipine	Lercanidipine ↑	Co-administration of lercanidipine with [CV016 trade name] should be avoided.
Ranolazine	Ranolazine ↑	Due to CYP3A inhibition by ritonavir, concentrations of ranolazine are expected to increase. The concomitant administration of ranolazine with [CV016 trade name] is contraindicated.
Riociguat	Riociguat ↑	Serum concentrations may increase due to CYP3A and P-gp inhibition by ritonavir. Co-administration of riociguat with [CV016 trade name] is not recommended (product information for riociguat should be consulted)

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 [CV016 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 [CV016 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 [CV016 trade name].
Ergot derivatives		
Dihydroergotamine Ergometrine Ergotamine Methylergometrine	Dihydroergotamine ↑ Ergometrine ↑ Ergotamine ↑ Methylergometrine ↑	Ritonavir co-administration is likely to increase plasma concentrations of ergot derivatives and co-administration with [CV016 trade name] is therefore contraindicated
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 [CV016 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 [CV016 trade name] finishes. Specialist advice (e.g. clinical pharmacology) is required to handle the complexity of such co-administration.
Voclosporin	Voclosporin ↑	Co-administration is contraindicated due to potential for acute or chronic nephrotoxicity

Drugs	Change in AUC and C_{max}	Recommendation on co-administration
Lipid regulating medicines		
Lovastatin Simvastatin	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. If treatment with an HMG-CoA reductase inhibitor is indicated, either pravastatin or fluvastatin is recommended (see below).
Atorvastatin Rosuvastatin	Atorvastatin ↑ Rosuvastatin ↑	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. However, if treatment with an HMG-CoA reductase inhibitor is indicated, either pravastatin or fluvastatin is recommended (see below).
Fluvastatin Pravastatin		The metabolism of fluvastatin and pravastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If concomitant treatment with an HMG-CoA reductase inhibitor is indicated, either pravastatin or fluvastatin is recommended.
Lomitapide	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 [CV016 trade name] with lomitapide is contraindicated (the product information for lomitapide should be consulted)
Phosphodiesterase (PDE5) inhibitors		
Avanafil Sildenafil Tadalafil Vardenafil	Avanafil AUC ↑ 13-fold, C_{max} ↑ 2.4-fold Sildenafil AUC ↑ 11-fold, C_{max} ↑ 4-fold Tadalafil AUC ↑ 124%, C_{max} ↔ Vardenafil AUC ↑ 49-fold, C_{max} ↑ 13-fold)	Concomitant use of avanafil, sildenafil, tadalafil and vardenafil with [CV016 trade name] is contraindicated
Respiratory medicines		
Theophylline	Theophylline AUC ↓ 43%, C_{max} ↓ 32%	An increased dose of theophylline may be required when co-administered with [CV016 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. Therefore, concomitant use with [CV016 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 [CV016 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 [CV016 trade name].
Clorazepate Diazepam Estazolam Flurazepam	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 [CV016 trade name] is therefore contraindicated
Midazolam	Oral Midazolam AUC ↑ 1330%, C_{max} ↑ 268% ↑ Parenteral midazolam	Midazolam is extensively metabolised by CYP3A4. Co-administration with [CV016 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 [CV016 trade name] with oral midazolam is contraindicated. 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 [CV016 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.
Triazolam	Triazolam AUC ↑ more than 20-fold, C_{max} ↑ 87%	Ritonavir co-administration is likely to increase triazolam plasma concentrations and use of triazolam with [CV016 trade name] is therefore contraindicated
Zolpidem	Zolpidem AUC ↑ 28%, C_{max} ↑ 22%	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.
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 [CV016 trade name]. Careful monitoring for adverse effects is recommended when amphetamine medicines are co-administered with [CV016 trade name].

Drugs	**Change in AUC and C_{max}**	**Recommendation on co-administration**
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
Colchicine (gout medicine)	Colchicine ↑	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 [CV016 trade name] is contraindicated.
Eletriptan (migraine medicine)	Eletriptan ↑	Co-administration of eletriptan within 72 hours of [CV016 trade name] is contraindicated due to potential for serious adverse reactions including cardiovascular and cerebrovascular events
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 [CV016 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 [CV016 trade name] treatment.
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 [CV016 trade name] is contraindicated.
Tolvaptan (vasopressin receptor antagonist)	Tolvaptan ↑	Co-administration is contraindicated due to potential for dehydration, hypovolaemia and hyperkalaemia

Drugs		Change in AUC and C_{max}		Recommendation on co-administration
↓	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 no data on the use of [CV016 trade name] in pregnant women and drug-associated risk of adverse developmental outcomes. Women of childbearing potential should avoid becoming pregnant during treatment with [CV016 trade name] and, as a precaution, for 7 days after completing [CV016 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 [CV016 trade name] and for one menstrual cycle after stopping [CV016 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, [CV016 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 the use of [CV016 trade name] in breast-feeding women. Breast-feeding should be stopped during [CV016 trade name] treatment and, as a precaution, breast-feeding avoided for 7 days after treatment is complete.

It is not known if nirmatrelvir passes into human or animal milk, nor if it affects the breast-fed infant or milk production. Limited published data indicate that ritonavir is present in human milk although there is no information on ritonavir's effects on the breast-fed infant or on milk production. Thus there is the possibility that nirmatrelvir/ritonavir may have effects in the breast-fed infant.

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

[CV016 trade name] is not expected to affect the ability to drive and use machines.

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 including pruritus and rash
Rare	anaphylaxis

Nervous system disorders

Common	dysgeusia, headache

Vascular disorders

Uncommon	hypertension

Gastrointestinal disorders

Common	diarrhoea, vomiting, nausea
Uncommon	abdominal pain

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 [CV016 trade name] overdose should consist of general supportive measures including monitoring the patient's clinical status. There is no specific antidote for [CV016 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, and XBB.1.5 was assessed in Vero E6-

TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} of 83 nM (range: 39–146 nM) against the Omicron sub-variants, reflecting EC_{50} fold-changes ≤ 1.5 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+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 [CV016 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.

5.2 Pharmacokinetic properties

Absorption of [CV016 trade name]

The absorption characteristics of [CV016 trade name] have been determined after administration of two nirmatrelvir 150 mg tablet and one ritonavir 100 mg tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**
	Nirmatrelvir
Maximum concentration (C_{max})	3007 ± 834 ng /mL
Area under the curve (AUC_{0-inf}), a measure of the extent of absorption	29582 ± 8820 ng·h/mL
Time to attain maximum concentration (tmax)	2.92 ± 1.22 hour

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. Ritonavir is an inhibitor of CYP3A and increases plasma concentrations of nirmatrelvir and other drugs that are primarily metabolised by CYP3A. 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.

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.

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.

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 [CV016 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 foetal 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:	hypromellose
	titanium dioxide
	macrogol/PEG

iron oxide yellow

Ritonavir100mg film-coated tablets

Core tablet: colloidal silicon dioxide
anhydrous dibasic calcium phosphate
copovidone
sorbitan monolaurate
sodium stearyl fumarate

Film coat: titanium dioxide
hypromellose
macrogol/PEG
polysorbate 80

These medicines are essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Silvery white Plastic and aluminium (PA/Alu/PVC) on aluminium foil blister cards, each containing 4 nirmatrelvir 150 mg tablets and 2 ritonavir 100 mg tablets. Available in cartons of 5 × 6 tablets.

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

Zhejiang Huahai Pharmaceutical Co., Ltd.
Xunqiao Linhai
Zhejiang 317 024
P.R.China
Tel.: 86-576-85010288
Fax: 86-576-85016013
Email: http://www.huahaipharm.com

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

CV016

9. DATE OF PREQUALIFICATION

18 December 2023

10. DATE OF REVISION OF THE TEXT

March 2024

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