Applicant/PHRC: Hetero Drugs South Africa (Pty) Ltd

Product proprietary name: NIRMACOM

Dosage form and strength: Film-coated tablets (Nirmatrelvir 150 mg and Ritonavir USP 100 mg Co-Pack)

APPROVED PROFESSIONAL INFORMATION FOR NIRMACOM

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

NIRMACOM 150/100 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each nirmatrelvir film-coated tablet contains 150 mg of nirmatrelvir.

Each ritonavir film-coated tablet contains 100 mg of ritonavir.

NIRMACOM contains sugar:

Each nirmatrelvir tablet contains 185 mg of lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nirmatrelvir film-coated tablet:

Yellow coloured, oval shaped, bevel edged, biconvex film coated tablets debossed with "N 15" on one side and "H" on the other side.

Ritonavir film-coated tablet:

White to off white, capsule shaped, film coated tablets debossed with 'H' on one side and 'R9' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NIRMACOM is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

4.2 Posology and method of administration

NIRMACOM is nirmatrelvir tablets co-packaged with ritonavir tablets.

Nirmatrelvir must be co-administered with ritonavir. Failure to correctly co-administer nirmatrelvir with ritonavir will result in plasma concentrations of nirmatrelvir that will be insufficient to achieve the desired therapeutic effect.

Posology

The recommended dosage for NIRMACOM is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), all taken together twice daily for five days. NIRMACOM should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within five days of onset of symptoms.

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with NIRMACOM, the patient should complete the full 5-day treatment course at the discretion of his/ her medical practitioner.

Special populations

Renal impairment

No dosage adjustment is needed in patients with mild renal impairment. In patients with moderate renal impairment, the dosage of NIRMACOM should be reduced to nirmatrelvir/ritonavir 150 mg/100 mg (1 tablet of each) twice daily for 5 days. The remaining tablet of nirmatrelvir should be disposed of in accordance with local requirements (see section 6.6). NIRMACOM is not recommended in patients with severe renal impairment or with renal failure as the

appropriate dose has not yet been determined (see section 5.2).

Hepatic impairment

No dosage adjustment of NIRMACOM is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in individuals with severe hepatic impairment (Child-Pugh Class C), therefore, NIRMACOM is contraindicated in patients with severe hepatic impairment.

Concomitant therapy with ritonavir- or cobicistat-containing regimen

No dose adjustment is needed, the dose of NIRMACOM is 300 mg/100 mg twice daily for five days. Patients diagnosed with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection who are receiving ritonavir- or cobicistat-containing regimen should continue their treatment as indicated.

Elderly

No dose adjustment is currently recommended for elderly patients.

Paediatric population

The safety and efficacy of NIRMACOM in patients below 18 years of age have not been established.

Method of administration

For oral use.

NIRMACOM can be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

4.3 Contraindications

NIRMACOM is contraindicated in patients:

- with hypersensitivity to nirmatrelvir, ritonavir or to any of the excipients listed in section 6.1.
- with severe hepatic impairment.
- with severe renal impairment.

NIRMACOM is contraindicated with medicines that are highly dependent on Cytochrome P4503A (CYP3A) for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions. It is also contraindicated in medicines that are potent CYP3A inducers where significantly reduced nirmatrelvir/ ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.

Table 1: Medicines that are contraindicated for concomitant use with NIRMACOM

Medicine class	**Medicines within class**	**Clinical comments**
Interactions that result in increased concentrations of concomitant medicine as NIRMACOM inhibits their CYP3A4 metabolic pathway		
Alpha 1-adrenoreceptor antagonist	alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension.
Analgesics	pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene may result in serious respiratory depression or haematologic abnormalities.
Antianginal	ranolazine	Potentially increased plasma concentrations of ranolazine may result in serious and/or life-threatening reactions.
Anticancer	neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions including hepatotoxicity. Increased plasma concentrations of venetoclax which may increase the risk of

	venetoclax	tumour lysis syndrome at the dose initiation and during the dose-titration phase.
Antidysrhythmics	amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine	Potentially increased plasma concentrations of amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone and quinidine may result in dysrhythmias or other serious adverse effects.
Antibiotic	fusidic acid	Increased plasma concentrations of fusidic acid and ritonavir.
Anti-gout	colchicine	Increased plasma concentrations of colchicine may result in serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antihistamines	astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine may result in serious dysrhythmias from these medicines.
Antipsychotics/ neuroleptics	lurasidone, pimozide, clozapine quetiapine	Increased plasma concentrations of lurasidone, pimozide and clozapine may result in serious and/or life-threatening reactions. Increased plasma concentrations of quetiapine may lead to coma.
Ergot derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia.
GI motility medicine	cisapride	Increased plasma concentrations of cisapride, thereby increasing the risk of

		serious dysrhythmias from this medicine.
Lipid-modifying medicines HMG-CoA reductase inhibitors Microsomal triglyceride transfer protein (MTTP) inhibitor	lovastatin, simvastatin lomitapide	Increased plasma concentrations of lovastatin and simvastatin resulting in increased risk of myopathy, including rhabdomyolysis. Increased plasma concentrations of lomitapide.
PDE5 inhibitors	avanafil, vardenafil sildenafil when used for pulmonary arterial hypertension (PAH)	Increased plasma concentrations of avanafil and vardenafil. Increased plasma concentrations of sildenafil can potentially result in visual abnormalities, hypotension, prolonged erection and syncope.
Sedative/hypnotics	clonazepam, diazepam, estazolam, flurazepam, triazolam, oral midazolam	Increased plasma concentrations of clonazepam, diazepam, estazolam, flurazepam, triazolam and oral midazolam can increase risk of extreme sedation and respiratory depression.
Interactions that result in decreased concentrations of nirmatrelvir/ritonavir as the concomitant medicines induce NIRMACOM'S CYP3A4 metabolic pathway		
Anticonvulsants	carbamazepine, phenobarbitone, phenytoin	Decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.

Antimycobacterials	rifampicin	Potentially decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.
Herbal medicines	St. John's Wort (*Hypericum perforatum*)	Potentially decreased plasma concentrations of nirmatrelvir/ritonavir may lead to loss of virologic response and possible resistance.

4.4 Special warnings and precautions for use

Risk of serious adverse reactions due to interactions with other medicines

Initiation of NIRMACOM, a CYP3A inhibitor, in patients receiving medicines metabolised by CYP3A or initiation of medicines metabolised by CYP3A in patients already receiving NIRMACOM, may increase plasma concentrations of medicines metabolised by CYP3A.

Initiation of medicines that inhibit or induce CYP3A may increase or decrease concentrations of NIRMACOM, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medicines.
- Clinically significant adverse reactions from greater exposures of NIRMACOM.
- Loss of therapeutic effect of NIRMACOM and possible development of viral resistance.

Potential for interactions should be considered with other medicines prior to and during NIRMACOM therapy; concomitant medicines should be reviewed during NIRMACOM therapy, and the patient should be monitored for the adverse reactions associated with the concomitant medicines. The risk of interactions with concomitant medications during the 5- day treatment period for NIRMACOM should be weighed against the risk of not receiving NIRMACOM.

Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir as contained in NIRMACOM. Therefore, caution should be exercised when administering NIRMACOM to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

Risk of HIV-1 resistance development

Because nirmatrelvir is co-administered with ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

NIRMACOM contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take NIRMACOM.

NIRMACOM contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Effect of NIRMACOM *on other medicines*

NIRMACOM inhibitor of CYP3A and may increase plasma concentrations of medicines that are primarily metabolised by CYP3A. Co-administration of NIRMACOM with medicines highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (see table 2).

Effects of other medicines on NIRMACOM

Nirmatrelvir and ritonavir as contained in NIRMACOM are CYP3A substrates; therefore, medicines that induce CYP3A may decrease nirmatrelvir and ritonavir plasma concentrations and reduce NIRMACOM therapeutic effect.

Significant interactions

Table 2 provides a list of clinically significant interactions. Medicines listed in Table 2 are a guide and not

considered a comprehensive list of all possible medicines that may interact with NIRMACOM. The medical practitioner should consult other appropriate resources for the interacting medicine for comprehensive information.

Table 2: Significant interactions

Medicine class	**Effect on concentration**	**Clinical advice**
Alpha 1-adrenoreceptor antagonist	↑ alfuzosin	Increased plasma concentrations of alfuzosin may lead to severe hypotension and is therefore contraindicated (see section 4.3).
Antianginal	↑ ranolazine	Co-administration contraindicated due to CYP3A inhibition by ritonavir leading increase in ranolazine concentrations.
Amphetamine derivatives	↑methylphenidate, ↑dexamfetamine	Ritonavir dosed as an antiretroviral medicines is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of adverse effects is recommended when these medicines are co-administered with NIRMACOM.
Antidysrhythmic	↑ amiodarone, ↑ dronedarone, ↑ flecainide, ↑ propafenone, ↑ quinidine ↑digoxin	Co-administration is contraindicated due to ritonavir likely to result in increased plasma concentrations of these medicines. This interaction may be due to modification of P-gp mediated digoxin efflux by ritonavir dosed as a pharmacokinetic enhancer.
Antiasthmatic	↓theophylline	An increased dose of theophylline may be required when co-

		administered with ritonavir, due to induction of CYP1A2.	
Anticancer medicines	↑ apalutamide	Apalutamide is a moderate to strong CYP3A4 inducer and this may lead to a decreased exposure of NIRMACOM and potential loss of virologic response by NIRMACOM. In addition, serum concentrations of apalutamide may be increased when co-administered with ritonavir resulting in the potential for serious adverse events including seizure. Co-administration of NIRMACOM with apalutamide is not recommended.	
	↑ abemaciclib	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Co-administration of abemaciclib and NIRMACOM should be avoided. If this co-administration is judged unavoidable, refer to the abemaciclib PI for dosage adjustment recommendations. Monitor for adverse drug reactions (ADRs) related to abemaciclib.	
	↑ ceritinib	Serum concentrations of ceritinib may be increased due to CYP3A and P-gp inhibition by ritonavir. Caution should be exercised in administering ceritinib with NIRMACOM. Refer to the ceritinib PI for dosage adjustment recommendations. Monitor for ADRs related to ceritinib.	

	↑ dasatinib, ↑ nilotinib, ↑ vinblastine, ↑ vincristine	Serum concentrations may be increased when co-administered with ritonavir resulting in the potential for increased incidence of adverse events.	
	↑ encorafenib,	Avoid co-administration of encorafenib due to potential risk of serious adverse events such as QT interval prolongation.	
	↑fostamatinib	Co-administration of fostamatinib with ritonavir may increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. Refer to the fostamatinib PI for dose reduction recommendations if such events occur.	
	↑ ibrutinib,	Serum concentrations of ibrutinib may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk for toxicity including risk of tumour lysis syndrome. Co-administration of ibrutinib and ritonavir should be avoided.	
	↑ neratinib,	Serum concentrations may be increased due to CYP3A4 inhibition by ritonavir. Concomitant use of neratinib with NIRMACOM is contraindicated due to serious and/or	

		life-threatening potential reactions including hepatotoxicity.	
	↑ venetoclax,	Serum concentrations may be increased due to CYP3A inhibition by ritonavir, resulting in increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase (see section 4.3 and refer to the venetoclax PI). 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 (refer to the venetoclax PI for dosing instructions).	
Anticoagulants	↑↓ warfarin	Induction of CYP1A2 and CYP2C9 lead to decreased levels of R-warfarin while little pharmacokinetic effect is noted on S-warfarin when co-administered with ritonavir. Decreased R-warfarin levels may lead to reduced anticoagulation. Therefore, it is recommended that anticoagulation parameters are monitored when warfarin is co-administered with NIRMACOM.	
	↑ rivaroxaban	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore,	

		the use of ritonavir is not recommended in patients receiving rivaroxaban.	
	↑ dabigatran ↑ apixaban	Increased bleeding risk with dabigatran and apixaban, avoid concomitant use. Refer to the dabigatran and apixaban professional information for further information.	
	↑ vorapaxar	Serum concentrations may be increased due to CYP3A inhibition by ritonavir. The co-administration of vorapaxar with NIRMACOM is not recommended (refer to the vorapaxar PI).	
Anticonvulsants	carbamazepine, ↓ phenytoin ↓divalproex, ↓lamotrigine	Co-administration contraindicated due to carbamazepine being a strong CYP3A4 inducer, and this may result in decreased exposure of nirmatrelvir and ritonavir which may lead to potential loss of virologic response. Phenytoin may decrease serum levels of NIRMACOM due to ritonavir. Ritonavir dosed as a pharmacokinetic enhancer induces oxidation by CYP2C9 and glucuronidation and as a result is expected to decrease the plasma concentrations of anticonvulsants. Careful monitoring of serum levels or therapeutic effects is recommended when these medicines are co-administered with ritonavir.	
Antidepressants	↑desipramine	Dosage reduction of desipramine is recommended when co-administered	

		with NIRMACOM.	
	↑amitriptyline, ↑fluoxetine, ↑imipramine, ↑nortriptyline, ↑paroxetine, ↑sertraline	Ritonavir dosed as an antiretroviral medicine is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.	
Antifungals	↓ voriconazole	Co-administration of voriconazole and ritonavir dosed as a pharmacokinetic enhancer should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.	
	↑ ketoconazole	Ritonavir inhibits CYP3A-mediated metabolism of ketoconazole. Due to an increased incidence of gastrointestinal and hepatic adverse reactions, a dose reduction of ketoconazole should be considered when co-administered with ritonavir.	
	↑ itraconazole	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of itraconazole. Careful monitoring of therapeutic and adverse effects is recommended when itraconazole is co-administered with ritonavir.	

Anti-gout	↑ 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 NIRMACOM is contraindicated.	
Antihistamines	↑fexofenadine	Ritonavir may modify P-gp mediated fexofenadine efflux when dosed as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine.	
	↑loratadine	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratadine is co-administered with ritonavir.	
Anti-HIV protease inhibitors	↑ atazanavir	Ritonavir increases the serum levels of atazanavir because of CYP3A4 inhibition. For further information, medical practitioners should refer to the PI for atazanavir.	
	↑ darunavir	Ritonavir increases the serum levels of darunavir as a result of CYP3A inhibition. Darunavir must be given with ritonavir to ensure its therapeutic effect. For further information, refer to the PI for darunavir.	

	↑ fosamprenavir ↑ amprenavir	Ritonavir increases the serum levels of amprenavir (from fosamprenavir) as a result of CYP3A4 inhibition. Fosamprenavir must be given with ritonavir to ensure its therapeutic effect. For further information, medical practitioners should refer to the PI for fosamprenavir.	
Anti-HIV	↑ efavirenz	A higher frequency of adverse reactions and laboratory abnormalities have been observed when efavirenz is co-administered with ritonavir.	
	↑ maraviroc	Ritonavir increases the serum levels of maraviroc as a result of CYP3A inhibition. Maraviroc may be given with ritonavir to increase the maraviroc exposure. For further information, refer to the PI for maraviroc.	
	↓raltegravir	Co-administration of ritonavir and raltegravir results in a minor reduction in raltegravir levels.	
	↓ zidovudine	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be required. For further information, refer to the respective anti-HIV medicines professional information.	
Antimycobacterial	↑ clarithromycin	Due to the large therapeutic window	

		of clarithromycin no dose reduction is required in patients with normal renal function. Clarithromycin doses greater than 1 g per day should not be co-administered with ritonavir dosed as a pharmacokinetic enhancer. For patients with renal impairment, a clarithromycin dose reduction should be considered: for patients with creatinine clearance of 30 to 60 ml/min the dose should be reduced by 50 %, for patients with creatinine clearance less than 30 ml/min the dose should be reduced by 75 %.	
	↑ erythromycin	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of erythromycin. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin is co-administered with ritonavir.	
	↑ 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, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see bedaquiline PI)	

	↑ rifabutin	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 ritonavir as a pharmacokinetic enhancer.	
	rifampicin	Rifampicin is strong CYP3A4 inducer, and this may lead to a decreased exposure of NIRMACOM and potential loss of virologic response. Concomitant use of rifampicin with NIRMACOM is contraindicated (see section 4.3).	
	↑fusidic acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore contraindicated (see section 4.3).	
	↓atovaquone	Ritonavir dosed as a pharmacokinetic enhancer induces glucuronidation and as a result 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 ritonavir.	
	delamanid	No interaction study is available with ritonavir only. In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, the exposure of the	

		delamanid metabolite DM-6705 was 30 % increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended (see section 4.4 and refer to the delamanid PI).	
	sulfamethoxazole/trimethoprim	Dose alteration of sulfamethoxazole/ trimethoprim during concomitant ritonavir therapy should not be necessary.	
Antipsychotics	↑ quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of NIRMACOM and quetiapine is contraindicated as it may increase quetiapine-related toxicity.	
	↑ clozapine ↑ pimozide	Ritonavir co-administration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore contraindicated.	
	↑ lurasidone	Due to CYP3A inhibition by ritonavir, concentrations of lurasidone are expected to increase. The concomitant administration with lurasidone is contraindicated.	

	↑haloperidol, ↑risperidone, ↑thioridazine	Ritonavir is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.	
Calcium channel blockers	↑amlodipine, ↑diltiazem, ↑nifedipine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral medicine inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.	
Corticosteroids primarily metabolised by CYP3A	↑prednisolone	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28 % after 4- and 14-days ritonavir, respectively.	
	↑ dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral medicine inhibits CYP3A and as a result is expected to increase the plasma concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone	

		is concomitantly administered with ritonavir.	
	Intranasal fluticasone, propionate, budesonide, triamcinolone	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86 %) 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, concomitant administration of ritonavir dosed as an antiretroviral medicines or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.	
Ergot derivatives	↑ dihydroergotamine ↑ ergotamine ↑ methylergonovine ↑ ergonovine	Co-administration contraindicated due to potential for acute ergot toxicity.	
Hepatitis C direct	↑glecaprevir/ pibrentasvir	Serum concentrations may be	

acting antivirals		increased due to P-gp, breast cancer resistance protein (BCRP) and OATP1B inhibition by ritonavir. Concomitant administration of glecaprevir/pibrentasvir and NIRMACOM is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure.	
Herbal products	St. John's Wort (*hypericum perforatum*)	Co-administration contraindicated due to potential loss of virologic response and possible resistance.	
HMG-CoA reductase inhibitors	↑ lovastatin ↑ simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with ritonavir dosed as an antiretroviral medicine or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicines with ritonavir is contraindicated.	
	↑ atorvastatin ↑ rosuvastatin ↑ fluvastatin ↑ pravastatin	Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this	

		interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral medicine, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and Fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.	
Hormonal contraceptive	↓ ethinyl oestradiol	Due to reductions in ethinyl estradiol concentrations, barrier or other non-hormonal methods of contraception should be considered with concomitant ritonavir use when dosed as an antiretroviral medicines or as a pharmacokinetic enhancer. Ritonavir is likely to change the uterine bleeding profile and reduce the effectiveness of estradiol-containing contraceptives.	
Immunosuppressants	↑ ciclosporin ↑ tacrolimus ↑ everolimus	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral medicine inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of ciclosporin, tacrolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.	
Long-acting beta-	↑ salmeterol	Ritonavir inhibits CYP3A4 and as a	

adrenoceptor agonist		result a pronounced increase in the plasma concentrations of salmeterol is expected. Therefore, concomitant use is not recommended.	
Lipid-modifying medicines	↑ lomitapide	CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Due to CYP3A inhibition by ritonavir, concentrations of lomitapide are expected to increase. Concomitant use of NIRMACOM with lomitapide is contraindicated (see PI for lomitapide)	
Analgesics	↑ fentanyl	Ritonavir dosed as a pharmacokinetic enhancer inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with ritonavir.	
	↓ methadone	Increased methadone dose may be necessary when co-administered with ritonavir dosed as a pharmacokinetic enhancer due to induction of glucuronidation. Dose adjustment should be considered based on the patient's clinical response to methadone therapy.	
	↓morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as a pharmacokinetic enhancer.	

	↓pethidine	The use of pethidine and ritonavir is contraindicated due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects.
	↑piroxicam, ↑propoxyphene	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene may result in serious respiratory depression or haematologic abnormalities (see section 4.3).
Endothelin Receptor Antagonists	↑ riociguat	Serum concentrations may be increased due to CYP3A and P-gp inhibition by ritonavir. The co-administration of riociguat with NIRMACOM is not recommended (refer to riociguat PI).
	↑bosentan	Co-administration of bosentan and ritonavir may increase steady-state bosentan Cmax and AUC.
Erectile dysfunction medicines (PDE5 inhibitors)	↑ avanafil	Concomitant use of avanafil with NIRMACOM is contraindicated (see section 4.3).
	↑ sildenafil	Concomitant use of sildenafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral medicine or as a pharmacokinetic enhancer should be with caution and in no instance should sildenafil doses exceed 25 mg in 48 hours.

		Concomitant use of sildenafil with NIRMACOM is contraindicated in pulmonary arterial hypertension patients (see section 4.3).	
	↑ tadalafil	The concomitant use of tadalafil for the treatment of erectile dysfunction with ritonavir dosed as an antiretroviral medicines or as a pharmacokinetic enhancer should be with caution at reduced doses of no more than 10 mg tadalafil every 72 hours with increased monitoring for adverse reactions.	
	↑ vardenafil	Concomitant use of vardenafil with NIRMACOM is contraindicated (see section 4.3).	
Sedative/hypnotics	↑ zolpidem	Zolpidem and ritonavir may be co-administered with careful monitoring for excessive sedative effects.	
	↑clonazepam, ↑diazepam, ↑estazolam, ↑flurazepam	Ritonavir co-administration is likely to result in increased plasma concentrations of clonazepam, diazepam, estazolam and flurazepam and is therefore contraindicated.	
	↑ midazolam	Midazolam is extensively metabolised by CYP3A4. Co-administration with NIRMACOM 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, NIRMACOM should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of NIRMACOM and parenteral midazolam.	
	↑triazolam	Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore contraindicated.	
	↑alprazolam	Alprazolam metabolism is inhibited following the introduction of ritonavir. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral medicine or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.	
	↑buspirone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral medicine inhibits CYP3A and as a result is expected to increase the plasma concentrations of buspirone. Careful monitoring of therapeutic and adverse effects is recommended when buspirone concomitantly administered with ritonavir.	

Smoke cessation	↓bupropion	Bupropion is primarily metabolised by CYP2B6. Concurrent administration of bupropion with repeated doses of ritonavir is expected to decrease bupropion levels. These effects are thought to represent induction of bupropion metabolism. However, because ritonavir has also been shown to inhibit 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 reductions in bupropion concentrations may have onset several days after initiation of ritonavir co-administration.
Thyroid hormone replacement therapy	levothyroxine	Post-marketing cases have been reported indicating a potential interaction between ritonavir containing medicines and levothyroxine. Thyroid-stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending ritonavir treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

NIRMACOM is not recommended in women of childbearing potential not using effective contraceptive. Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping NIRMACOM (see section 4.5).

Pregnancy

There are no data from the use of nirmatrelvir/ritonavir as contained in NIRMACOM in pregnant women. Therefore, NIRMACOM is not recommended during pregnancy.

Breastfeeding

There are no data on the use of nirmatrelvir/ritonavir as contained in NIRMACOM in breastfeeding women. It is unknown whether nirmatrelvir is excreted in human or animal milk, and the effects of it on the breastfed infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the medicine on milk production. A risk to the infant cannot be excluded. Breastfeeding should be discontinued during treatment with NIRMACOM and for 7 days after the last dose of NIRMACOM.

Fertility

There are no available human data to on the effect of nirmatrelvir and ritonavir as contained in NIRMACOM on fertility.

4.7 Effects on ability to drive and use machines

No clinical studies have been evaluated on the effects of NIRMACOM on ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions were dysgeusia, diarrhoea, and vomiting.

b. Tabulated list of adverse reactions

System organ class	Frequency	Adverse event
Nervous system disorders	Frequent	Dysgeusia
Gastrointestinal disorder	Frequent	Diarrhoea, vomiting

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit / risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/publications/Index/8 or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9 Overdose

There is no specific antidote for overdose with **NIRMACOM**. Treatment of overdose with **NIRMACOM** should be symptomatic and supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals

ATC code: not yet assigned.

Mechanism of action

Nirmatrelvir

Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease, including the SARS-CoV-2 3CL protease. Inhibition of 3CL protease renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir was shown to be a potent inhibitor of SARS-CoV-2 3CL protease (Ki=0,00311 µM or IC50=0,0192 µM) in a biochemical enzymatic assay.

Ritonavir

Ritonavir is an HIV-1 protease inhibitor but is not active against SARS-CoV-2 3CL protease. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.

Antiviral resistance

No information on antiviral resistance is currently available to nirmatrelvir with SARS-CoV-2. Studies to evaluate selection of resistance to nirmatrelvir with SARS-CoV-2 in cell culture and clinical studies have not been completed. Only in vitro resistance selection study with murine hepatitis virus (MHV)-Mpro is available. It showed a 4,4- to 5-fold decrease in nirmatrelvir susceptibility against mutant viruses with 5 mutations (Pro55Leu, Ser144Ala, Thr129Met, Thr50Lys, Pro15Ala) in the MHV Mpro following 10 passages in cell culture. The relevance for this to SARS-CoV-2 is not known. Because nirmatrelvir is co-administered with low dose ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.

Pharmacodynamic effects

Cardiac electrophysiology

No clinically relevant effect of nirmatrelvir on QTcF interval was observed in studies. The model predicted upper

bound of 90 % confidence interval (CI) for baseline and ritonavir adjusted QTcF estimate was 1,96 ms at approximately 4-fold higher concentration than the mean steady-state peak concentration after a therapeutic dose of nirmatrelvir/ritonavir 300 mg/100 mg.

5.2 Pharmacokinetic properties

Ritonavir is administered with nirmatrelvir as a pharmacokinetic enhancer resulting in higher systemic concentrations and longer half-life of nirmatrelvir, thereby supporting a twice daily administration regimen.

Absorption

Nirmatrelvir and Ritonavir

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean nirmatrelvir (CV %) Cmax and area under the plasma concentration-time curve from 0 to infinity (AUCinf) at steady-state was 2,21 µg/mL (33) and 23,01 µg*hr/mL (23), respectively. The median (range) time to Cmax (Tmax) was 3,00 hrs. The arithmetic mean (+SD) terminal elimination half-life was 6,1 (1,8) hours.

Following oral administration of nirmatrelvir/ritonavir 300 mg/100 mg after a single dose, the geometric mean ritonavir (CV %) Cmax and AUCinf was 0,36 µg/mL and 3,60 µg*hr/mL, respectively. The median (range) time to Cmax (Tmax) was 3,98 hrs (1,48 – 4,20). The arithmetic mean (+SD) terminal elimination half-life was 6,1 (2.2) hours.

Dosing with a high fat meal modestly increased the exposure of nirmatrelvir (approximately 15 % increase in mean Cmax and 1,6 % increase in mean AUClast) relative to fasting conditions following administration of a suspension formulation of nirmatrelvir co-administered with ritonavir tablets.

Distribution

Nirmatrelvir and Ritonavir

The protein binding of nirmatrelvir in human plasma is approximately 69%. The protein binding of ritonavir in human plasma is approximately 98-99%.

Biotransformation

Nirmatrelvir

Studies suggest that nirmatrelvir is primarily metabolised by CYP3A4. Nirmatrelvir may be an inducer or substrate of other CYP enzymes. Administration of nirmatrelvir with ritonavir inhibits the metabolism of nirmatrelvir. In plasma, nirmatrelvir was observed to be unchanged. Minor oxidative metabolites were observed in the faeces and urine.

Ritonavir

Studies utilising 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. Low doses of ritonavir have shown profound effects on the pharmacokinetics of other protease inhibitors (and other medicines metabolised by CYP3A4) and other protease inhibitors may influence the pharmacokinetics of ritonavir. Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6. Ritonavir also has a high affinity for P-glycoprotein (P-gp) and may inhibit this transporter. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicines metabolised by these pathways and may result in decreased systemic exposure to such medicines, which could decrease or shorten their therapeutic effect.

Elimination

Nirmatrelvir

The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion. Approximately 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and faeces, respectively.

Ritonavir

Studies with radiolabelled ritonavir demonstrated that the elimination of ritonavir was primarily via the hepatobiliary system. Approximately 86% of radiolabel was recovered from stool, part of which is expected to be unabsorbed

ritonavir.

Special populations

Patients with renal impairment

Compared to healthy controls with no renal impairment, the Cmax and AUC of nirmatrelvir in patients with mild renal impairment was 30 % and 24 % higher, in patients with moderate renal impairment was 38 % and 87 % higher, and in patients with severe renal impairment was 48 % and 204 % higher, respectively.

Patients with hepatic impairment

Compared to healthy controls with no hepatic impairment, the PK of nirmatrelvir in individuals with moderate hepatic impairment was not significantly different.

Interaction studies conducted with nirmatrelvir/ritonavir

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 medicines 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. The effects of co-administration of nirmatrelvir/ritonavir with itraconazole (CYP3A inhibitor) is expected to increase the plasma concentrations of itraconazole, and carbamazepine (CYP3A inducer) may lead to a decrease in exposure of nirmatrelvir and ritonavir and potential loss of virologic response.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nirmatrelvir

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Colloidal silicon dioxide

Sodium stearyl fumarate

Film-coating

Opadry Yellow

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol (E1521)

Iron oxide yellow (E172)

Ritonavir

Copovidone

Colloidal silicon dioxide

Sorbitan monolaurate

Dibasic calcium phosphate

Sodium stearyl fumarate

Film coating

Opadry white

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol (E1521)

Talc (E553b)

Hydroxypropyl cellulose (E463)

Polysorbate 80 (E433)

Colloidal anhydrous silica (E551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store at or below 30 ^{o}C in well closed, light resistance containers.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

10 tablets packed in OPA/PVC aluminium foil blister. And 6 blisters packed in a carton.

6.6 Special precautions for disposal

No special requirements.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

58/20.2.8/0091

9 DATE OF FIRST AUTHORISATION

24 October 2023

10 DATE OF REVISION OF THE TEXT