SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of the medicinal product

Nirmatrelvir Tablets 150 mg; Ritonavir Tablets USP 100 mg Co-Pack

2. Qualitative and quantitative composition

Each film coated Tablet contains 150 mg of Nirmatrelvir

Each film coated Tablet contains 100 mg of Ritonavir USP

3 . Pharmaceutical form

Film Coated Tablets

4. Clinical particulars

4.1 Therapeutic indications

Nirmatrelvir and Ritonavir is used for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

4.2 Posology and method of administration

Dosage for Emergency Use of Nirmatrelvir and Ritonavir
Nirmatrelvir and Ritonavir is Combi pack of Nirmatrelvir and Ritonavir tablets.
Nirmatrelvir must be co-administered with Ritonavir. Failure to correctly co-administer Nirmatrelvir lRitonavir may result in plasma levels of Nirmatrelvir that are insufficient to achieve the desired therapeutic effect.
The dosage for Nirmatrelvir and Ritonavir is 300 mg Nirmatrelvir (two 150 mg tablets) with 100 mg Ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within Nirmatrelvir and Ritonavir. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2.

The 5-day treatment course of Nirmatrelvir and Ritonavir should be initiated as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. Should a patient

require hospitalization due to severe or critical COVID-19 after starting treatment with Nirmatrelvir and Ritonavir, the patient should complete the full 5-day treatment course per the healthcare provider's discretion.

If the patient misses a dose of Nirmatrelvir and Ritonavir within 8 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

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

Important Dosing Information in Patients with Renal Impairment

No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dosage of Nirmatrelvir and Ritonavir is 150 mg Nirmatrelvir and 100 mg Ritonavir twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within Nirmatrelvir and Ritonavir. Providers should counsel patients about renal dosing instructions.

Nirmatrelvir and Ritonavir is not recommended in patients with severe renal impairment (eGFR <30 mL/min) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined.

Use in Patients with Hepatic Impairment

No dosage adjustment 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 subjects with severe hepatic impairment (Child-Pugh Class C); therefore, Nirmatrelvir and Ritonavir is not recommended for use in patients with severe hepatic impairment.

Important Drug Interactions with Nirmatrelvir and Ritonavir

No dosage adjustments is required when co-administered with other products containing Ritonavir or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.

Consider the potential for drug interactions prior to and during therapy and review concomitant medications during Nirmatrelvir and Ritonavir therapy.

4.3 Contraindications

Nirmatrelvir and Ritonavir is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (Nirmatrelvir or Ritonavir) or any other components of the product.

Nirmatrelvir and Ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:

- Alpha -adrenoreceptor antagonist: alfuzosin 1
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

Nirmatrelvir and Ritonavir is contraindicated with drugs that are potent CYP3A inducers where significantly reduced Nirmatrelvir or Ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. Nirmatrelvir and Ritonavir cannot be started
immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (hypericum perforatum)

4.4 Special warnings and precautions for use

There are limited clinical data available for Nirmatrelvir and Ritonavir. Serious and unexpected adverse events may occur that have not been previously reported with Nirmatrelvir and Ritonavir use.

Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of Nirmatrelvir and Ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving Nirmatrelvir and Ritonavir, may increase plasma concentrations of medications metabolized by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of Nirmatrelvir and Ritonavir, respectively.

These interactions may lead to:

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

See Table 1 for clinically significant drug interactions, including contraindicated drugs. Consider the potential for drug interactions prior to and during Nirmatrelvir and Ritonavir therapy; review concomitant medications during Nirmatrelvir and Ritonavir therapy and monitor for the adverse reactions associated with the concomitant medications.

Allergic Reactions/Hypersensitivity

Hypersensitivity reactions have been reported with Nirmatrelvir + Ritonavir including urticaria, angioedema, dyspnea, mild skin eruptions, and pruritus. Cases of anaphylaxis, TEN, and Stevens-Johnson syndrome have also been reported with ritonavir, a component of Nirmatrelvir + Ritonavir. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Nirmatrelvir + Ritonavir and initiate appropriate medications and/or supportive care.

Hepatotoxicity

Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving Ritonavir. Therefore, caution should be exercised when administering Nirmatrelvir and Ritonavir 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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for Nirmatrelvir and Ritonavir to Affect Other Drugs

Combipack of Nirmatrelvir tablets and Ritonavir tablets is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of Nirmatrelvir and Ritonavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 1.

Potential for Other Drugs to Affect Nirmatrelvir and Ritonavir

Nirmatrelvir and Ritonavir are CYP3A substrates; therefore, drugs that induce CYP3A may decrease Nirmatrelvir and Ritonavir plasma concentrations and reduce Nirmatrelvir and Ritonavir therapeutic effect.

Established and Other Potentially Significant Drug Interactions

Table 1 provides listing of clinically significant drug interactions, including contraindicated drugs. Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with Nirmatrelvir and Ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

Although lamivudine is a substrate of BCRP and P-gp *in vitro*, given its high absolute bioavailability, (see section 5.2), inhibitors of these efflux transporters are unlikely to result in a clinically relevant impact on lamivudine concentrations.

Table 1: Established and Other Potentially Significant Drug Interactions

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor	alfuzosin	↑ alfuzosin	Co-administration contraindicated due

antagonist			to potential hypotension
Analgesics	pethidine, piroxicam, propoxyphene	↑ pethidine ↑ piroxicam ↑ propoxyphene	Co-administration contraindicated due to potential for serious respiratory depression or hematologic abnormalities
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening
Antiarrhythmics	amiodarone, dronedarone, flecainide, propafenone, quinidine	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias
Antiarrhythmics	bepridil, lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics if available.
Anticancer drugs	abemaciclib, ceritinib,	↑ anticancer drug	Avoid co-administration of

	dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine		encorafenib or ivosidenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant hematologic or gastrointestinal side effects. For further information, refer to individual product label for anticancer drug.
Anticoagulants	warfarin rivaroxaban	↑↓ warfarin ↑ rivaroxaban	Closely monitor INR if co-administration with warfarin is necessary. Increased bleeding risk with rivaroxaban. Avoid concomitant use.
Anticonvulsants	carbamazepinea phenobarbital,	↓nirmatrelvir/ritonavir	Co-administration contraindicated due

	phenytoin	↑ carbamazepine ↓ phenobarbital ↓ phenytoin	to potential loss of virologic response and possible resistance
Antidepressants	bupropion trazodone	↓ bupropion and active metabolite hydroxybupropion ↑ trazodone	Monitor for an adequate clinical response to bupropion. Adverse reactions of nausea, dizziness, hypotension, and syncope have been observed following co-administration of trazodone and ritonavir. A lower dose of trazodone should be considered.
Antifungals	voriconazole, ketoconazole, isavuconazonium sulfate itraconazolea	↓ voriconazole ↑ ketoconazole ↑isavuconazonium sulfate ↑ itraconazole ↑nirmatrelvir/ ritonavir	Avoid concomitant use of voriconazole.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment

Anti-HIV protease inhibitors	amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir	↑ protease Inhibitor	Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased Nirmatrelvir + Ritonavir or protease inhibitor adverse events with concomitant use of these protease inhibitors
Anti-HIV	didanosine, delavirdine, efavirenz maraviroc, nevirapine, raltegravir, zidovudine bictegravir/ emtricitabine/ tenofovir	↑ didanosine ↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	
Anti-infective	clarithromycin, erythromycin	clarithromycin ↑ erythromycin	
Antimycobacterial	rifampin	↓nirmatrelvir/ ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as

			rifabutin should be considered
Antimycobacterial	bedaquiline rifabutin	↑ bedaquiline ↑ rifabutin	Refer to the bedaquiline product label for further information.
Antipsychotics	lurasidone, pimozide, clozapine	↑ lurasidone ↑ pimozide ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias
Antipsychotics	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nicardipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with Nirmatrelvir + Ritonavir.
Cardiac glycosides.	digoxin	↑ digoxin	Caution should be exercised when co-administering Nirmatrelvir +

			Ritonavir with digoxin, with appropriate monitoring of serum digoxin levels
Endothelin receptor Antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of Nirmatrelvir + Ritonavir.
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑dihydroergotamine ↑ ergotamine ↑methylergonovine	Co-administration contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system
Hepatitis C direct acting antivirals	elbasvir/ grazoprevir, glecaprevir/ pibrentasvir ombitasvir/ paritaprevir / ritonavir and dasabuvir sofosbuvir/ velpatasvir/ voxilaprevir	↑ antiviral	Increased grazoprevir concentrations can result in ALT elevations. It is not recommended to co-administer ritonavir with glecaprevir/ pibrentasvir. Patients on ritonavir-containing HCV regimens

			should continue their treatment as indicated. Monitor for increased Nirmatrelvir + Ritonavir or HCV drug adverse events with concomitant use
Herbal products	St. John's Wort (hypericum perforatum)	↓ nirmatrelvir/ ritonavir	Co-administration contraindicated due to potential loss of virologic response and possible resistance
HMG-CoA reductase inhibitors	lovastatin, simvastatin	↑ lovastatin ↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis. Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of Nirmatrelvir + Ritonavir.
HMG-CoA reductase inhibitors.	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with Nirmatrelvir + Ritonavir

Hormonal contraceptive	ethinyl estradiol	↓ ethinyl estradiol	An additional, non-hormonal method of contraception should be considered.
Immunosuppressants	cyclosporine, tacrolimus, sirolimus	↑ cyclosporine ↑ tacrolimus ↑ sirolimus	Therapeutic concentration monitoring is recommended for immunosuppressants. Avoid use of Nirmatrelvir + Ritonavir when close monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and Nirmatrelvir + Ritonavir. If co-administered, refer to individual product label for immunosuppressant for further information.
Long-acting beta-adrenoceptor agonist.	salmeterol	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular

			adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia
Narcotic analgesics	fentanyl methadone	↑ fentanyl ↓ methadone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when fentanyl is concomitantly administered with Nirmatrelvir + Ritonavir. Monitor methadone-maintained patients closely for evidence of withdrawal effects and adjust the methadone dose accordingly
PDE5 inhibitor	sildenafil (Revatio®) when used for pulmonary arterial hypertension	↑ sildenafil	Co-administration contraindicated due to the potential for sildenafil associated adverse events, including visual abnormalities

			hypotension, prolonged erection, and syncope
Sedative/hypnotics	triazolam, oral midazolam	↑ triazolam ↑ midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression
Sedative/hypnotics	Midazolam (administered parenterally	↑ midazolam	Co-administration of midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.
Systemic corticosteroids	betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone,	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative

	methylprednisolone, mometasone, prednisone, triamcinolone		corticosteroids including beclomethasone and prednisolone should be considered.

4.6 Pregnancy and lactation

Pregnancy

Risk Summary

There are no available human data on the use of Nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Published observational studies on Ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with Ritonavir are insufficient to identify a drug-associated risk of miscarriage. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy.

In an embryo-fetal development study with Nirmatrelvir, reduced fetal body weights following oral administration of Nirmatrelvir to pregnant rabbits were observed at systemic exposures (AUC) approximately 10 times higher than clinical exposure at the authorized human dose of Nirmatrelvir and Ritonavir. No other adverse developmental outcomes were observed in animal reproduction studies with Nirmatrelvir at systemic exposures (AUC) greater than or equal to 3 times higher than clinical exposure at the authorized human dose of Nirmatrelvir and Ritonavir.

In animal reproduction studies with Ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of Ritonavir to pregnant rats and rabbits at doses (based on body surface area conversions) or systemic exposures (AUC) greater than or equal to 3 times higher than clinical doses or exposure at the authorized human dose of Nirmatrelvir and Ritonavir.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo-fetal Risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, pre-term birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Human Data

Ritonavir

Based on prospective reports to the antiretroviral pregnancy registry of live births following exposure to ritonavir-containing regimens (including over 3,400 live births exposed in the first-trimester and over 3,500 live births exposed in the second and third trimesters), there was no difference in the rate of overall birth defects for ritonavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The prevalence of birth defects in live births was 2.3% (95% confidence interval [CI]: 1.9%-2.9%) following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%-3.6%) following second and third trimester exposure to ritonavir-containing regimens. While placental transfer of ritonavir and fetal ritonavir concentrations are generally low, detectable levels have been observed in cord blood samples and neonate hair.

Animal Data

Nirmatrelvir

Embryo-fetal developmental (EFD) toxicity studies were conducted in pregnant rats and rabbits administered oral nirmatrelvir doses of up to 1,000 mg/kg/day during organogenesis [on Gestation Days (GD) 6 through 17 in rats and 6 through 19 in rabbits]. No biologically significant developmental effects were observed in the rat EFD study. At the highest dose of 1,000 mg/kg/day, the systemic nirmatrelvir exposure (AUC24) in rats was approximately 8 times higher than clinical exposures at the authorized human dose of Nirmatrelvir + Ritonavir. In the rabbit EFD study, lower fetal body weights (9%

decrease) were observed at 1,000 mg/kg/day in the absence of significant maternal toxicity findings.

At 1,000 mg/kg/day, the systemic exposure (AUC24) in rabbits was approximately 10 times higher than clinical exposures at the authorized human dose Nirmatrelvir + Ritonavir. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed at up to the highest dose tested, 1,000 mg/kg/day. No developmental effects were observed in rabbits at 300 mg/kg/day resulting in systemic exposure (AUC24) approximately 3 times higher than clinical exposures at the authorized human dose of Nirmatrelvir + Ritonavir. A pre- and postnatal developmental (PPND) study in pregnant rats administered oral nirmatrelvir doses of up to 1,000 mg/kg/day from GD 6 through Lactation Day (LD) 20 is ongoing and only interim data through postnatal day (PND) 56 are currently available.

Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir treated versus control animals, a decrease (8% in males and females) in the body weight of offspring was observed at PND 17. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC24) at 1,000 mg/kg/day was approximately 8 times higher than clinical exposures at the authorized human dose of Nirmatrelvir + Ritonavir. No body weight changes in the offspring were noted at 300 mg/kg/day, resulting in systemic exposure (AUC24) approximately 5 times higher than clinical exposures at the authorized human dose of Nirmatrelvir + Ritonavir.

Ritonavir

Ritonavir was administered orally to pregnant rats (at 0, 15, 35, and 75 mg/kg/day) and rabbits (at 0, 25, 50, and 110 mg/kg/day) during organogenesis (on GD 6 through 17 and 6 through 19, respectively). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) approximately 4 times higher than exposure at the authorized human dose of Nirmatrelvir + Ritonavir. Increased incidences of early resorptions, ossification delays, and developmental variations, as well as decreased fetal body weights were observed in rats in the presence of maternal toxicity, at systemic exposures approximately 4 times higher than exposure at the authorized human dose of Nirmatrelvir + Ritonavir. A slight increase in the incidence of cryptorchidism was also noted in rats (at a maternally toxic dose) at an exposure approximately 5 times the exposure at the authorized human dose of Nirmatrelvir + Ritonavir. In rabbits, resorptions, decreased litter size, and decreased fetal weights were

observed at maternally toxic doses approximately 11 times higher than the authorized human dose of Nirmatrelvir + Ritonavir, based on a body surface area conversion factor. In a pre- and postnatal development study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through postnatal day 20 resulted in no developmental toxicity, at ritonavir doses 3 times higher than the authorized human dose of Nirmatrelvir + Ritonavir, based on a body surface area conversion factor.

Lactation

Risk Summary

There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir (see Data). 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 drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nirmatrelvir + Ritonavir and any potential adverse effects on the breastfed infant from Nirmatrelvir + Ritonavir or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data

In the pre- and postnatal developmental study, body weight decreases (up to 8%) were observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC24) approximately 8 times higher than clinical exposures at the authorized human dose of Nirmatrelvir + Ritonavir. No body weight changes in the offspring were noted at maternal systemic exposure (AUC24) approximately 5 times higher than clinical exposures at the authorized human dose of Nirmatrelvir + Ritonavir.

Females and Males of Reproductive Potential

Contraception

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception.

Pediatric Use

Nirmatrelvir + Ritonavir is not authorized for use in pediatric patients younger than 12 years of age or weighing less than 40 kg. The safety and effectiveness of Nirmatrelvir + Ritonavir have not been established in pediatric patients. The authorized adult dosing regimen is expected to result in comparable serum exposures of nirmatrelvir and ritonavir in patients 12 years of age and older and weighing at least 40 kg as observed in adults, and adults with similar body weight were included in the trial EPIC-HR.

Geriatric Use

Clinical studies of Nirmatrelvir + Ritonavir include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy. Of the total number of subjects in EPIC-HR randomized to receive Nirmatrelvir + Ritonavir (N=1,120), 13% were 65 years of age and older and 3% were 75 years of age and older.

Renal Impairment

Systemic exposure of nirmatrelvir increases in renally impaired patients with increase in the severity of renal impairment.

No dosage adjustment is needed in patients with mild renal impairment. In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), reduce the dose of Nirmatrelvir + Ritonavir to 150 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Prescriptions should specify the numeric dose of each active ingredient within Nirmatrelvir + Ritonavir. Providers should counsel patients about renal dosing instructions.

Nirmatrelvir + Ritonavir is not recommended in patients with severe renal impairment (eGFR <30 mL/min based on CKD-EPI formula) until more data are available; the appropriate dosage for patients with severe renal impairment has not been determined.

Hepatic Impairment

No dosage adjustment of Nirmatrelvir + Ritonavir is needed for patients with either 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 subjects with severe hepatic impairment

(Child-Pugh Class C), therefore, Nirmatrelvir + Ritonavir is not recommended for use in patients with severe hepatic impairment

4.7 Effects on ability to drive and use machines

The influence of Nirmatrelvir + Ritonavir on the ability to drive or use machine is unknown.

4.8 Undesirable Effects

Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of Nirmatrelvir + Ritonavir that supported the EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. Additional adverse events associated with Nirmatrelvir + Ritonavir may become apparent with more widespread use.

The safety of Nirmatrelvir + Ritonavir is based on data from Study C4671005 (EPIC-HR), a Phase 2/3 randomized, placebo-controlled trial in non-hospitalized adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection. A total of 2,224 symptomatic adult subjects 18 years of age and older who are at high risk of developing severe COVID-19 illness received at least one dose of either Nirmatrelvir + Ritonavir (n=1,109) or placebo (n=1,115). Adverse events were those reported while subjects were on study medication and through Day 34 after initiating study treatment. Nirmatrelvir 300 mg (two 150 mg tablets) with 100 mg ritonavir] or matching placebo were to be taken twice daily for 5 days.

Adverse events (all grades regardless of causality) in the Nirmatrelvir + Ritonavir group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%).

The proportions of subjects who discontinued treatment due to an adverse event were 2% in the Nirmatrelvir + Ritonavir group and 4% in the placebo group.

Required Reporting for Serious Adverse Events and Medication Errors

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above

ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form (https://www.heteroworld.com) or by Hetero Helpline No.1800-120-8689 and for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.com.

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race).
- A statement "Nirmatrelvir + Ritonavir use for COVID-19 under Emergency Use Authorization (EUA)" under the "Describe Event, Problem, or Product Use/Medication Error" heading.
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/ disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's pre-existing medical conditions and use of concomitant products.
- Information about the product (e.g., dosage, route of administration).

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from CDSCO for information about adverse events and medication errors associated with Nirmatrelvir + Ritonavir.

*Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

4.9 Overdose

Treatment of overdose with Nirmatrelvir + Ritonavir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Nirmatrelvir + Ritonavir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals

ATC code: Not yet assigned.

Mechanism of action

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir inhibited the activity of recombinant SARS-CoV-2 Mpro in a biochemical assay with a Ki value of 3.1 nM and an IC50 value of 19.2 nM. Nirmatrelvir was found to bind directly to the SARS-CoV-2 Mpro active site by X-ray crystallography.

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

Microbiology

Antiviral Activity

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 (USA-WA1/2020 isolate) infection of differentiated normal human bronchial epithelial (dNHBE) cells with EC50 and EC90 values of 62 nM and 181 nM, respectively, after 3 days of drug exposure.

Nirmatrelvir had similar cell culture antiviral activity (EC50 values ≤3-fold relative to USA-WA1/2020) against SARS-CoV-2 isolates belonging to the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Lambda (C.37) variants. The Beta (B.1.351) variant was the least susceptible tested

variant with approximately 3-fold reduced susceptibility relative to the USA-WA1/2020 isolate.

No data are available regarding the activity of nirmatrelvir against the SARS-CoV-2 Omicron (B.1.1.529) variant in cell culture. However, in a biochemical assay, the Mpro P132H substitution found in the Omicron variant did not reduce nirmatrelvir activity (Ki fold change <1) compared to the USA-WA1/2020 enzyme.

Antiviral Activity Against SARS-CoV-2 in Animal Models

Nirmatrelvir showed antiviral activity in BALB/c and 129 mice infected with mouse-adapted SARS-CoV-2. Oral administration of nirmatrelvir at 300 mg/kg or 1,000 mg/kg twice daily initiated 4 hours post-inoculation or 1,000 mg/kg twice daily initiated 12 hours post-inoculation resulted in reduction of lung viral titers and ameliorated indicators of disease (weight loss and lung pathology) compared to placebo-treated animals.

Antiviral Resistance

Phenotypic assessments were conducted to characterize the impact of naturally occurring SARS-CoV-2 Mpro polymorphisms on the activity of nirmatrelvir in a biochemical assay using recombinant Mpro enzyme. The clinical significance of these polymorphisms is unknown, and it is also unknown if results from the biochemical assay are predictive of antiviral activity in cell culture. The following Mpro amino acid substitutions were associated with reduced nirmatrelvir activity (≥3-fold higher Ki values): G15S (4.4-fold), T135I (3.5-fold), S144A (91.9-fold), H164N (6.4-fold), H172Y (233-fold), Q189K (65.4-fold), and D248E (3.7-fold). G15S is present in the Lambda variant, which did not have reduced susceptibility to nirmatrelvir (relative to USA-WA1/2020d) in cell culture.

In addition, three SARS-CoV-2 Mpro amino acid positions where polymorphisms have not been naturally observed were evaluated by substituting alanine at these positions and assessing their impact on activity in biochemical assays. These Mpro amino acid substitutions were associated with reduced nirmatrelvir activity (i.e., higher Ki values): Y54A (23.6-fold), F140A (39.0-fold), and E166A (33.4-fold). The clinical significance of substitutions at these Mpro positions is unknown.

Cell culture resistance selection studies with nirmatrelvir using mouse hepatitis virus (MHV, a betacoronavirus used as a surrogate) resulted in the emergence of Mpro amino acid substitutions P15A, T50K, P55L, T129M, and/or S144A. The clinical relevance of these changes is not known. The

presence of the substitutions P55L and S144A was associated with reduced nirmatrelvir susceptibility (~4- to 5-foldthose whose anti-hepatitis B therapy was withdrawn (see section 4.4).

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Immune response syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Paediatric population

There are no clinical study data on the effects of Dolutegravir and Lamivudine in the paediatric population. Individual components have been investigated in adolescents (12 to 17 years).

Based on limited available data with the dolutegravir single entity or lamivudine single entity used in combination with other antiretroviral agents to treat adolescents (12 to 17 years), there were no additional types of adverse reactions beyond those observed in the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No specific symptoms or signs have been identified following acute overdose with dolutegravir or lamivudine, apart from those listed as adverse reactions.

There is no specific treatment for an overdose of Dolutegravir and Lamivudine. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR25.

Mechanism of action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Lamivudine, via its active metabolite 5'-triphosphates (TP) (an analogue for cytidine), inhibits reverse transcriptase of HIV-1 and HIV-2 through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine triphosphate shows significantly less affinity for host cell DNA polymerases.

Pharmacodynamic effects

Antiviral activity in cell culture

Dolutegravir and lamivudine have been shown to inhibit replication of lab-strains and clinical isolates of HIV in a number of cell types, including transformed T cell lines, monocyte/macrophage derived lines and primary cultures of activated peripheral blood mononuclear cells (PMBCs) and monocyte/macrophages. The concentration of active substance necessary to effect viral replication by 50% (IC_{50} - half maximal inhibitory concentration) varied according to virus and host cell type.

The IC_{50} for dolutegravir in various lab-strains using PBMC was 0.5 nM, and when using MT-4 cells it ranged from 0.7-2 nM. Similar IC_{50}s were seen for clinical isolates without any major difference between subtypes; in a panel of 24 HIV-1 isolates of clades A, B, C, D, E, F and G and group O the mean IC_{50} value was 0.2 nM (range 0.02-2.14). The mean IC_{50} for 3 HIV-2 isolates was 0.18 nM (range 0.09-0.61).

The median or mean IC_{50} values for lamivudine against lab-strains of HIV-1 ranged from 0.007 to 2.3 μM. The mean IC_{50} against lab-strains of HIV-2 (LAV2 and EHO) ranged from 0.16 to 0.51 μM for lamivudine. The IC_{50} values of lamivudine against HIV-1 subtypes (A-G) ranged from 0.001 to 0.170 μM, against Group O from 0.030 to 0.160 μM and against HIV-2 isolates from 0.002 to 0.120 μM in peripheral blood mononuclear cells.

HIV-1 isolates (CRF01_AE, n=12; CRF02_AG, n=12; and Subtype C or CRF_AC, n=13) from 37 untreated patients in Africa and Asia were susceptible to lamivudine (IC_{50} fold changes < 3.0). Group O isolates from antiviral naïve patients tested for lamivudine activity were highly sensitive.

Effect of human serum

In 100% human serum, the mean fold shift for dolutegravir activity was 75 fold, resulting in protein adjusted IC_{90} of 0.064 μg/mL. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36%).

Resistance

Dolutegravir and Lamivudine is indicated in the absence of documented or suspected resistance to the integrase inhibitor class and to lamivudine (see section 4.1). For information around in vitro resistance, and cross resistance to other agents of the integrase- and NRTI class, please refer to the SmPCs of dolutegravir and lamivudine.

None of the twelve subjects in the dolutegravir plus lamivudine group or the nine subjects in the dolutegravir plus tenofovir disoproxil/emtricitabine FDC group that met virological withdrawal criteria through Week 144 across the GEMINI-1 (204861) and GEMINI-2 (205543) studies had treatment emergent integrase inhibitor or NRTI class resistance.

In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase inhibitor class, or to the NRTI class was seen (n=1118

follow-up of 48-96 weeks).

Effects on electrocardiogram

No relevant effects were seen with dolutegravir on the QTc interval, with doses exceeding the clinical dose by approximately three fold. A similar study was not conducted with lamivudine.

Clinical efficacy and safety

Antiretroviral naïve subjects

The efficacy of Dolutegravir and Lamivudine is supported by data from 2 identical 148-week, Phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority controlled trials GEMINI-1 (204861) and GEMINI-2 (205543). A total of 1433 HIV-1 infected antiretroviral treatment-naïve adult subjects received treatment in the trials. Subjects were enrolled with a screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL. Subjects were randomised to a two-drug regimen of dolutegravir 50 mg plus lamivudine 300 mg once daily or dolutegravir 50 mg plus tenofovir disoproxil/emtricitabine 245/200 mg once daily. The primary efficacy endpoint for each GEMINI trial was the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 (Snapshot algorithm for the ITT-E population). Double blind therapy will continue up to week 96, followed by open label therapy up to week 148.

At baseline, in the pooled analysis, the median age of subjects was 33 years, 15% were female, 69% were white, 9% were CDC Stage 3 (AIDS), 20% had HIV-1 RNA >100,000 copies/mL, and 8% had CD4+ cell count less than 200 cells per mm^3; these characteristics were similar between studies and treatment arms.

In the primary week 48 analysis, dolutegravir plus lamivudine was non-inferior to dolutegravir plus tenofovir disoproxil/emtricitabine FDC in GEMINI-1 and GEMINI-2 studies. This was supported by the pooled analysis, see Table 3.

Table 3 Virologic Outcomes of Randomised Treatment of GEMINI at Week 48 (Snapshot algorithm)

GEMINI-1 and GEMINI-2 Pooled Data*	
DTG + 3TC	**DTG + TDF/FTC**

N=716	N=717	
HIV-1 RNA <50 copies/mL	91%	93%
Treatment Difference † (95% confidence intervals)	-1.7 (-4.4, 1.1)	
Virologic non response	3%	2%
Reasons		
Data in window and ≥50 copies/mL	1%	<1%
Discontinued for lack of efficacy	<1%	<1%
Discontinued for other reasons and ≥50 copies/mL	<1%	<1%
Change in ART	<1%	<1%
No virologic data at Week 48 window	6%	5%
Reasons		
Discontinued study due to adverse event or death	1%	2%
Discontinued study for other reasons	4%	3%
Missing data during window but on study	<1%	0%
HIV-1 RNA <50 copies/mL by baseline covariates		
	n/N (%)	n/N (%)
Baseline Plasma Viral Load (copies/mL)		
≤100,000	526 / 576 (91%)	531 / 564 (94%)
>100,000	129 / 140 (92%)	138 / 153 (90%)
Baseline CD4+ (cells/ mm^3)		
≤200	50 / 63 (79%)	51 / 55 (93%)
>200	605 / 653 (93%)	618 / 662 (93%)
HIV-1 subtype		
B	424 / 467 (91%)	452 / 488 (93%)
A	84 / 86 (98%)	74 / 78 (95%)
Other	147 / 163 (90%)	143 / 151 (95%)
Gender		
Male	555 / 603 (92%)	580 / 619 (94%)
Female	100 / 113 (88%)	89 / 98 (91%)
Race		
White	451 / 484 (93%)	473 / 499 (95%)
African-American/African Heritage/Other	204 / 232 (88%)	196 / 218 (90%)

* The results of the pooled analysis are in line with those of the individual studies, for which the primary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil /emtricitabine FDC) was met. The adjusted difference was -2.6 (95% CI: -6.7; 1.5) for GEMINI-1 and -0.7 (95% CI: -4.3; 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%.

† Based on CMH-stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm^3 vs. >200 cells/mm^3). Pooled analysis also stratified by study. Assessed using a non-inferiority margin of 10%.

N = Number of subjects in each treatment group

At 96 weeks in the TANGO study, the proportion of subjects with HIV-1 RNA ≥50 c/mL (Snapshot) was 0.3% and 1.1% in the dolutegravir/lamivudine and TBR groups, respectively. Based on a non-inferiority margin of 4%, dolutegravir/lamivudine remained non-inferior to TBR, as the upper bound of the 95% CI for the adjusted treatment difference (-2.0%; 0.4%) was less than 4% for the ITT E Population.

The median change from baseline in CD4+ T-cell counts at week 96 was 61 cells/mm^3 in the dolutegravir/lamivudine arm and 45 cells/mm^3 in the TBR arm.

Paediatric population

The efficacy of Dolutegravir and Lamivudine, or the dual combination of dolutegravir plus lamivudine (as single entities) has not been studied in children or adolescents.

The European Medicines Agency has deferred the obligation to submit the results of studies with Dolutegravir and Lamivudine in one or more subsets of the paediatric population in the treatment of HIV infection.

5.2 Pharmacokinetic properties

When administered in fasted state, bioequivalence regarding C_{max} was achieved for dolutegravir, when comparing Dolutegravir and Lamivudine to dolutegravir 50 mg co-administered with lamivudine 300 mg. Dolutegravir AUC_{0-t} was 16% higher for Dolutegravir and Lamivudine than for dolutegravir 50 mg co-administered with lamivudine 300 mg. This increase is not considered clinically relevant.

When administered in fasted state, bioequivalence was achieved for lamivudine AUC, when comparing Dolutegravir and Lamivudine to lamivudine 300 mg co-administered with dolutegravir 50 mg. Lamivudine C_{max} for Dolutegravir and Lamivudine was 32% higher than lamivudine 300 mg co-

administered with dolutegravir 50 mg. The higher lamivudine C_{max}, is not considered clinically relevant.

Absorption

Dolutegravir and lamivudine are rapidly absorbed following oral administration. The absolute bioavailability of dolutegravir has not been established. The absolute bioavailability of oral lamivudine in adults is approximately 80-85%. For Dolutegravir and Lamivudine, the median time to maximal plasma concentration (t_{max}) is 2.5 hours for dolutegravir and 1.0 hour for lamivudine, when dosed under fasted conditions.

Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects. In HIV-1–infected adult subjects following dolutegravir 50 mg once daily, the steady-state pharmacokinetic parameters (geometric mean [%CV]) based on population pharmacokinetic analyses were $AUC_{(0-24)}$ = 53.6 (27) µg.h/mL, C_{max} = 3.67 (20) µg/mL, and C_{min} = 1.11 (46) µg/mL. Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days, the mean (CV) steady-state C_{max} is 2.04 µg/mL (26%) and the mean (CV) $AUC_{(0-24)}$ is 8.87 µg.h/mL (21%).

Administration of a single Dolutegravir and Lamivudine tablet with a high fat meal increased dolutegravir $AUC_{(0-\infty)}$ and C_{max} by 33% and 21%, respectively, and decreased the lamivudine C_{max} by 30% compared to fasted conditions. The lamivudine $AUC_{(0-\infty)}$ was not affected by a high fat meal. These changes are not clinically significant. Dolutegravir and Lamivudine may be administered with or without food.

Distribution

The apparent volume of distribution of dolutegravir (Vd/F) is 17-20 L. Intravenous studies with lamivudine showed that the mean apparent volume of distribution is 1.3 L/kg.

Dolutegravir is highly bound (> 99%) to human plasma proteins based on *in vitro* data. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. Total blood and plasma drug-related radioactivity concentration ratios averaged between 0.441 to 0.535, indicating minimal association of radioactivity with blood cellular components. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin (<35 g/L) as seen in subjects with moderate hepatic impairment. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays

limited plasma protein binding *in vitro* (< 16%- 36% to serum albumin).

Dolutegravir and lamivudine are present in cerebrospinal fluid (CSF). In 13 treatment-naïve subjects on stable dolutegravir plus abacavir/lamivudine regimen, dolutegravir concentration in CSF averaged 18 ng/mL (comparable to unbound plasma concentration, and above the IC_{50}). The mean ratio of CSF/serum lamivudine concentrations 2-4 hours after oral administration was approximately 12%. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Dolutegravir is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue and vaginal tissue were 6-10% of those in corresponding plasma at steady state. AUC in semen was 7% and 17% in rectal tissue of those in corresponding plasma at steady state.

Biotransformation

Dolutegravir is primarily metabolized via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in plasma; renal elimination of unchanged active substance is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces. It is unknown if all or part of this is due to unabsorbed active substance or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Thirty-two percent of the total oral dose is excreted in the urine, represented by ether glucuronide of dolutegravir (18.9% of total dose), N-dealkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose).

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of unchanged lamivudine. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5-10%).

Drug interactions

In vitro, dolutegravir demonstrated no direct, or weak inhibition (IC_{50}>50 μM) of the enzymes cytochrome P_{450} (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 CYP3A, UGT1A1 or UGT2B7, or the transporters Pgp, BCRP, BSEP, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OCT1, MATE2-K, multidrug resistance-associated protein (MRP) 2 or

MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Based on this data, dolutegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of major enzymes or transporters (see section 4.5).

In vitro, dolutegravir was not a substrate of human OATP 1B1, OATP 1B3 or OCT 1.

In vitro, lamivudine did not inhibit or induce CYP enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and demonstrated no or weak inhibition of OATP1B1, OAT1B3, OCT3, BCRP, P-gp, MATE1 or MATE2-K. Lamivudine is therefore not expected to affect the plasma concentrations of medicinal products that are substrates of these enzymes or transporters.

Lamivudine was not significantly metabolised by CYP enzymes.

Elimination

Dolutegravir has a terminal half-life of ~14 hours. The apparent oral clearance (CL/F) is approximately 1 L/hr in HIV-infected patients based on a population pharmacokinetic analysis.

The observed lamivudine half-life of elimination is 18 to 19 hours. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was 16 to 19 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/h/kg, predominantly by renal clearance (> 70%) via the organic cationic transport system. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance < 50 mL/min (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship(s)

In a randomized, dose-ranging trial, HIV-1–infected subjects treated with dolutegravir monotherapy (ING111521) demonstrated rapid and dose-dependent antiviral activity, with mean decline in HIV-1 RNA of 2.5 $\log_{10}$ at day 11 for 50 mg dose. This antiviral response was maintained for 3 to 4 days after the last dose in the 50 mg group.

Special patient populations

Children

The pharmacokinetics of dolutegravir in 10 antiretroviral treatment-experienced HIV-1 infected adolescents (12 to 17 years) showed that dolutegravir 50 mg once daily dosage resulted in dolutegravir

exposure comparable to that observed in adults who received dolutegravir 50 mg once daily.

Limited data are available in adolescents receiving a daily dose of 300 mg of lamivudine. Pharmacokinetic parameters are comparable to those reported in adults.

Elderly

Population pharmacokinetic analysis of dolutegravir using data in HIV-1 infected adults showed that there was no clinically relevant effect of age on dolutegravir exposure.

Pharmacokinetic data for dolutegravir and lamivudine in subjects >65 years of age are limited.

Renal impairment

Pharmacokinetic data have been obtained for dolutegravir and lamivudine separately.

Renal clearance of unchanged active substance is a minor pathway of elimination for dolutegravir. A study of the pharmacokinetics of dolutegravir was performed in subjects with severe renal impairment (CLcr <30 mL/min). No clinically important pharmacokinetic differences between subjects with severe renal impairment (CLcr <30 mL/min) and matching healthy subjects were observed. Dolutegravir has not been studied in patients on dialysis, though differences in exposure are not expected.

Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance.

Based on the lamivudine data, Dolutegravir and Lamivudine is not recommended for patients with creatinine clearance of < 50 mL/min.

Hepatic impairment

Pharmacokinetic data has been obtained for dolutegravir and lamivudine separately.

Dolutegravir is primarily metabolized and eliminated by the liver. A single dose of 50 mg of dolutegravir was administered to 8 subjects with moderate hepatic impairment (Child-Pugh class B) and to 8 matched healthy adult controls. While the total dolutegravir concentration in plasma was similar, a 1.5 to 2 fold increase in unbound exposure to dolutegravir was observed in subjects with moderate hepatic impairment compared to healthy controls. No dosage adjustment is considered necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic

impairment on the pharmacokinetics of dolutegravir has not been studied.

Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

Polymorphisms in drug metabolising enzymes

There is no evidence that common polymorphisms in drug metabolising enzymes alter dolutegravir pharmacokinetics to a clinically meaningful extent. In a meta-analysis using pharmacogenomics samples collected in clinical studies in healthy subjects, subjects with UGT1A1 (n=7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n=41).

Gender

Population PK analyses using pooled pharmacokinetic data from clinical studies where dolutegravir or lamivudine was administered to adults in combination with other ARVs revealed no clinically relevant effect of gender on the exposure of dolutegravir or lamivudine. There is no evidence that a dose adjustment of dolutegravir or lamivudine would be required based on the effects of gender on PK parameters.

Race

Population PK analyses using pooled pharmacokinetic data from clinical studies where dolutegravir was administered to adults in combination with other ARVs revealed no clinically relevant effect of race on the exposure of dolutegravir. The pharmacokinetics of dolutegravir following single dose oral administration to Japanese subjects appear similar to observed parameters in Western (US) subjects. There is no evidence that a dose adjustment of dolutegravir or lamivudine would be required based on the effects of race on PK parameters.

Co-infection with Hepatitis B or C

Population pharmacokinetic analysis indicated that hepatitis C virus co-infection had no clinically relevant effect on the exposure to dolutegravir. There are limited pharmacokinetic data on subjects with hepatitis B co-infection (see section 4.4).

5.3 Preclinical safety data

There are no data available on the effects of the combination of dolutegravir and lamivudine in animals.

Carcinogenesis and mutagenesis

Dolutegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in viv*o rodent micronucleus assay. Lamivudine was not mutagenic in bacterial tests, but consistent with other nucleoside analogues, inhibits cellular DNA replication in *in vitro* mammalian tests such as the mouse lymphoma assay. The results from two in vivo rat micronucleus tests with lamivudine were negative. Lamivudine has not shown any genotoxic activity in the *in vivo* studies.

The carcinogenic potential of a combination of dolutegravir and lamivudine has not been tested. Dolutegravir was not carcinogenic in long term studies in the mouse and rat. In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential.

Reproductive toxicology studies

In reproductive toxicity studies in animals, dolutegravir and lamivudine were shown to cross the placenta.

Oral administration of dolutegravir to pregnant rats at doses up to 1000 mg/kg daily from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity (37.2 times the 50 mg human clinical exposure, based on AUC following single dose in the fasted state). Oral administration of dolutegravir to pregnant rabbits at doses up to 1000 mg/kg daily from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity (0.55 times the 50 mg human clinical exposure, based on AUC following single dose in the fasted state). In rabbits, maternal toxicity (decreased food consumption, scant/no faeces/urine, suppressed body weight gain) was observed at 1000 mg/kg (0.55 times the 50 mg human clinical exposure, based on AUC following single dose in the fasted state).

Lamivudine was not teratogenic in animal studies but there were indications of an increase in early embryonic deaths in rabbits at relatively low systemic exposures, comparable to those achieved in

humans. A similar effect was not seen in rats even at very high systemic exposure.

Fertility studies in rats have shown that dolutegravir or lamivudine have no effect on male or female fertility.

Repeated dose toxicity

The effect of prolonged daily treatment with high doses of dolutegravir has been evaluated in repeat oral dose toxicity studies in rats (up to 26 weeks) and in monkeys (up to 38 weeks). The primary effect of dolutegravir was gastrointestinal intolerance or irritation in rats and monkeys at doses that produce systemic exposures approximately 28.5 and 1.1 times the 50 mg human clinical exposure following single dose in the fasted state based on AUC, respectively. Because gastrointestinal (GI) intolerance is considered to be due to local active substance administration, mg/kg or mg/m^2 metrics are appropriate determinates of safety cover for this toxicity. GI intolerance in monkeys occurred at 30 times the human mg/kg equivalent dose (based on 50 kg human), and 11 times the human mg/m^2 equivalent dose for a total daily clinical dose of 50 mg.

6. Pharmaceutical particulars

6.1 List of excipients

Dry mixing

Lamivudine USP

Microcrystalline cellulose USP/NF

Granulation

Purified water, IHS/USP/Ph.Eur®

Extra Purified water, IHS/USP/Ph.Eur®

Pre-Lubrication & Lubrication

Microcrystalline cellulose USP/NF

Sodium starch Glycolate Type-A USP/NF

Magnesium stearate USP/NF

Dry mixing

Dolutegravir sodium, IH**

Microcrystalline cellulose USP/NF

Mannitol, USP

Sodium starch Glycolate, Type-A USP

Povidone, USP

Granulation

Purified water, IHS/USP/Ph.Eur@

Extra Purified water, IHS/USP/Ph.Eur®

Pre-Lubrication & Lubrication

Sodium starch Glycolate Type-A USP/NF

Sodium stearyl Fumarate USP/NF

Film- Coating

Opadry White 03F180011, IHS

Purified Water, IHS/USP/Ph.Eur®

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

30’s HDPE Container

High Density Polyethylene Container 60cc with 33 mm Neck

90’s HDPE Container

High Density Polyethylene Container 120cc with 38 mm Neck

180’s HDPE Container

High Density Polyethylene Container 250cc with 53 mm Neck

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorisation holder

M/s.Hetero Labs Limited,

7-2-A2, Hetero Corporate,

Industrial Estates, Sanathnagar,

Hyderabad, Zip- 500 018, Telangana State,

India.

8. Marketing authorisation number(s)
08658/10132/NMR/2022

9. Date of first authorisation/renewal of the authorisation
May 12, 2023

10. Date of revision of the text