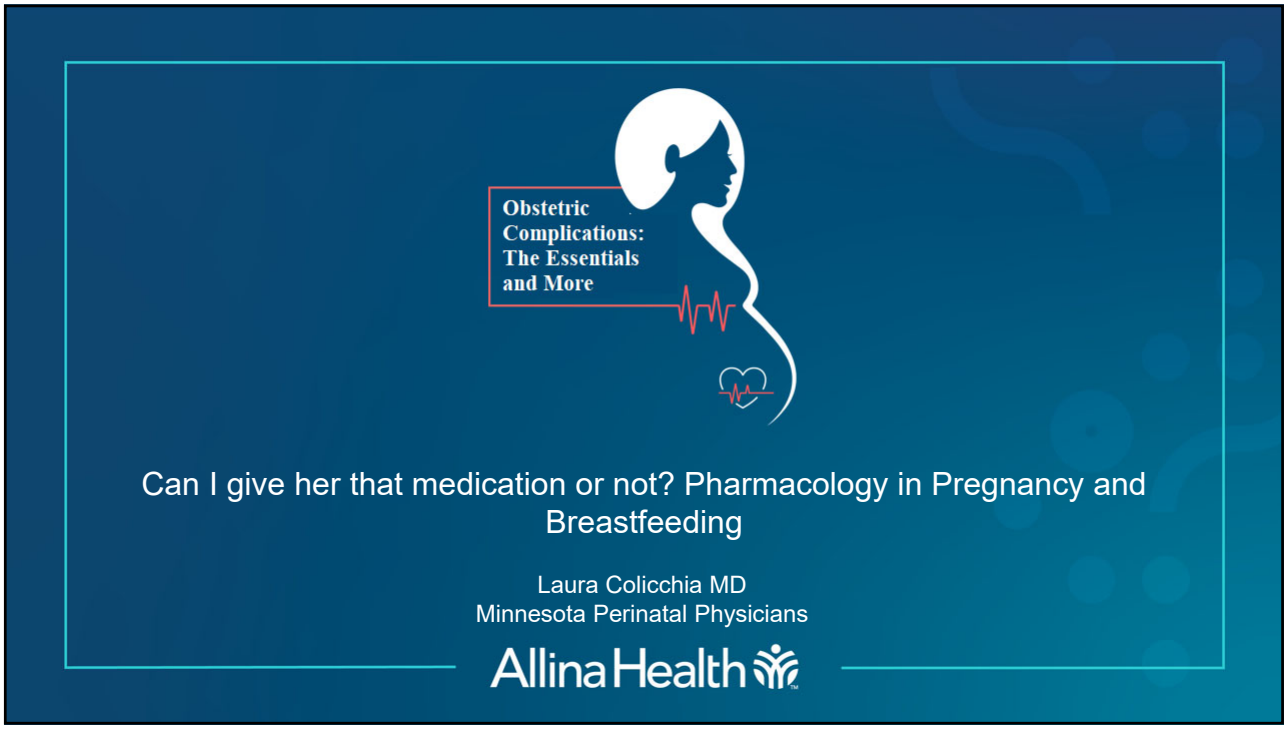

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CASE PRESENTATION #1

18yo G1P0 @ 16w0d presents to the ED after a witnessed seizure at home

-- history of known seizure disorder

-- continued lamotrigine at her pre-pregnancy dose during the pregnancy

2

CASE PRESENTATION #2

October 2021

30yo G2P1001 @ 28 weeks gestation admitted for respiratory distress

-- COVID test positive

-- Started on O2 via high flow nasal cannula with rapidly increasing O2 requirement

-- transferred to ICU for further care

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CASE PRESENTATION #3

40yo G4P2022 on postpartum day #1 s/p SVD with shortness of breath and severe hypertension

-- pregnancy c/b chronic HTN, on lisinopril pre-preg and no antihypertensives during pregnancy

-- CXR shows pulmonary edema

-- BPs 180s-200s/100s-110s

-- transferred to the ICU

-- she is breastfeeding and strongly desires to continue nursing x 1 year

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CASE PRESENTATION #4

21yo G2P1011 4 weeks postpartum presents to the ED with suicidal ideation

-- History of major depressive disorder, discontinued fluoxetine when she found out she was pregnant

-- Breastfeeding baby without issue

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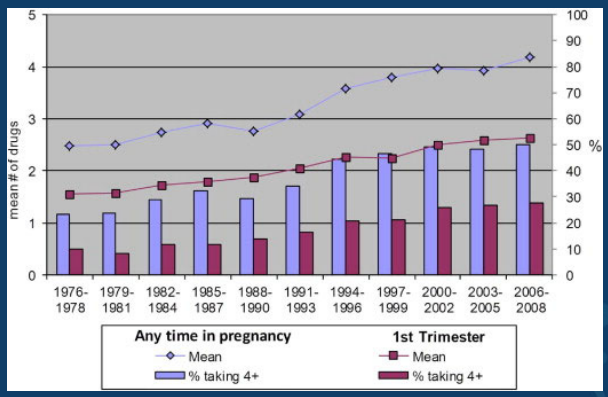
USE OF PRESCRIPTION AND OTC MEDICATION IS WIDESPREAD DURING PREGNANCY …

-- 84.5% of women report any medication use during pregnancy

-- Number of medications used continues to increase – average of 4.2 medications per pregnancy



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Sitka C, "Drugs in Pregnancy: Optimizing Care of our Pregnant Patients" Obstet and Gynecol Clinics of N America 2023 50(1): xix-xx.
Mitchell et al "Medication Use During Pregnancy, with Particular Focus on Prescription Drugs 1976-2008" Am J Obstet Gynecol 2011 205(1):5.1e1-8

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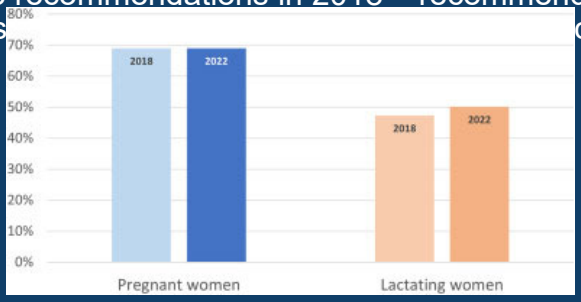
… BUT MEDICATION SAFETY DATA IS LIMITED AND CONFLICTING

2018: 68% of NIH-funded phase 3 and phase 4 clinical trials excluded pregnant women, 47% excluded breastfeeding women

PRGLAC committee recommendations in 2018 – recommend many changes to research regulations ctating women



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Thiele L, Spong C, "Inclusion of Pregnant and Lactating People in Clinical Research: Lessons Learned and Opportunities" *Obstet and Gynecol Clinics of N America* 2023 50(1): 17-25.

7

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… BUT MEDICATION SAFETY DATA IS LIMITED AND CONFLICTING

The US Food and Drug Administration (FDA) has recognized the harm of excluding pregnant patients from research, acknowledging that "the frequent lack of information based on clinical data often leaves the healthcare provider and patient reluctant to treat the underlying condition, which in some cases may result in more harm to the woman and the fetus than if she had been treated."

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Research Committee, SMFM "Society for Maternal Fetal Medicine Special Statement: COVID-19 Research in Pregnancy: Progress and Potential" Am J Obstet Gynecol 2021 225(6); B19-31.

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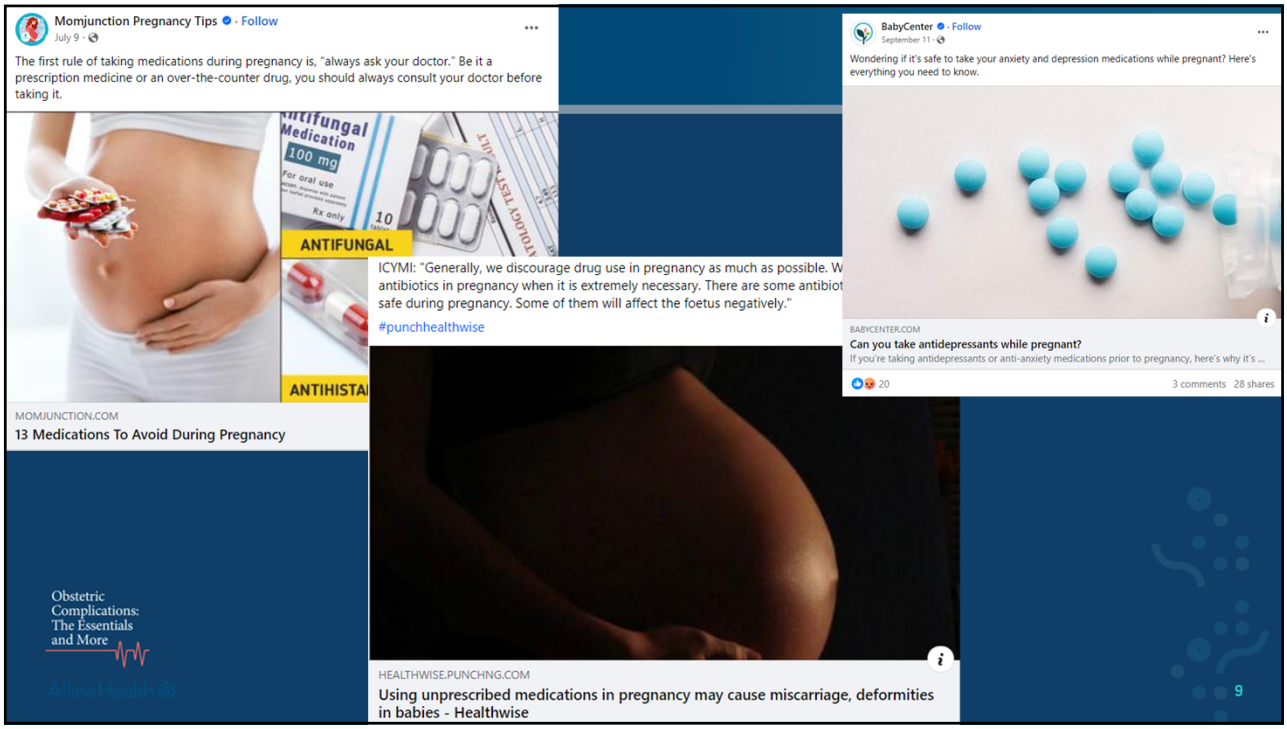

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FDA PREGNANCY AND LACTATION LABELING RULE

2015 – FDA removes the former A,B,C,D,X category scheme in favor of the Pregnancy and Lactation Labeling Rule

-- information includes risk summaries and available human and animal data for use in pregnant, breastfeeding and females and males of reproductive potential

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Thiele L, Spong C, "Inclusion of Pregnant and Lactating People in Clinical Research: Lessons Learned and Opportunities" *Obstet and Gynecol Clinics of N America* 2023 50(1): 17-25.

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FDA PREGNANCY AND LACTATION LABELING RULE

Rule in Phase-Out	New PLLR
Pregnancy risk letter categories (A, B, C, D, X) assigned.	Pregnancy risk letter categories eliminated.
Section 8.1 Pregnancy Section 8.2 Labor and Delivery	Combined to form one section: 8.1 Pregnancy • Pregnancy Exposure Registry • Risk Summary • Clinical Considerations • Data
Section 8.3 Nursing Mothers	Becomes Section 8.2 Lactation • Risk Summary • Clinical Considerations • Data
Requirement to update the label as information becomes outdated	Requirement to update the label as information becomes outdated
–	New section added: 8.3 Females and Males of Reproductive Potential* • Pregnancy Testing • Contraception • Infertility

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Pernia S and DeMaagd G, "The New Pregnancy and Lactation Labeling Rule" *Pharmacy and Therapeutics* 2016 41(11): 713-5.

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data on the use of nirmatrelvir during pregnancy are insufficient 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 *(see Data)*. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

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 11 times higher than clinical exposure at the approved human dose of PAXLOVID. 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 approved human dose of PAXLOVID *(see Data)*.

In embryo-fetal developmental studies with ritonavir, no evidence of adverse developmental outcomes was observed following oral administration of ritonavir to pregnant rats and rabbits at systemic exposures (AUC) 5 (rat) or 8 (rabbits) times higher than clinical exposure at the approved human dose of PAXLOVID *(see Data)*.

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, preterm 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 3,500 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 2.4% [95% confidence interval (CI): 1.9%, 2.9%] following first-trimester exposure to ritonavir-containing regimens and 2.9% (95% CI: 2.4%, 3.5%) 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 GD 7 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 (AUC_{24}) in rats was approximately 9 times higher than clinical exposures at the approved human dose of PAXLOVID. 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 (AUC_{24}) in rabbits was approximately 11 times higher than clinical exposures at the approved human dose of PAXLOVID. No other significant developmental toxicities (malformations and embryo-fetal lethality) were observed 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 (AUC_{24}) approximately 3 times higher than clinical exposures at the approved human dose of PAXLOVID. 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 showed no adverse findings. Although no difference in body weight was noted at birth when comparing offspring born to nirmatrelvir-treated versus control animals, a decrease in the body weight of offspring was observed on Postnatal Day (PND) 17 (8% decrease) and PND 21 (up to 7% decrease) in the absence of maternal toxicity. No significant differences in offspring body weight were observed from PND 28 to PND 56. The maternal systemic exposure (AUC_{24}) at 1,000 mg/kg/day was approximately 9 times higher than clinical exposures at the approved human dose of PAXLOVID. No body weight changes in the offspring were noted at 300 mg/kg/day, where maternal systemic exposure (AUC_{24}) was approximately 6 times higher than clinical exposures at the approved human dose of PAXLOVID.

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 in rats and GD 6 through 19 in rabbits). No evidence of teratogenicity due to ritonavir was observed in rats and rabbits at systemic exposures (AUC) 5 (rats) or 8 (rabbits) times higher than exposure at the approved human dose of PAXLOVID. 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 (AUC) approximately 10 times higher than exposure at the approved human dose of PAXLOVID. In rabbits, resorptions, decreased litter size, and decreased fetal weights were observed at maternally toxic doses, at systemic exposures greater than 8 times higher than exposure at the approved human dose of PAXLOVID. In a PPND study in rats, administration of 0, 15, 35, and 60 mg/kg/day ritonavir from GD 6 through PND 20 resulted in no developmental toxicity, at ritonavir systemic exposures greater than 10 times the exposure at the approved human dose of PAXLOVID.

8.2 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

PAXLOVID- nirmatrelvir and ritonavir Pfizer Laboratories Div Pfizer Inc Highlights of Prescribing Information https://labeling.pfizer.com/ShowLabeling.aspx?id=19599#section-8 Accessed 10/13/23

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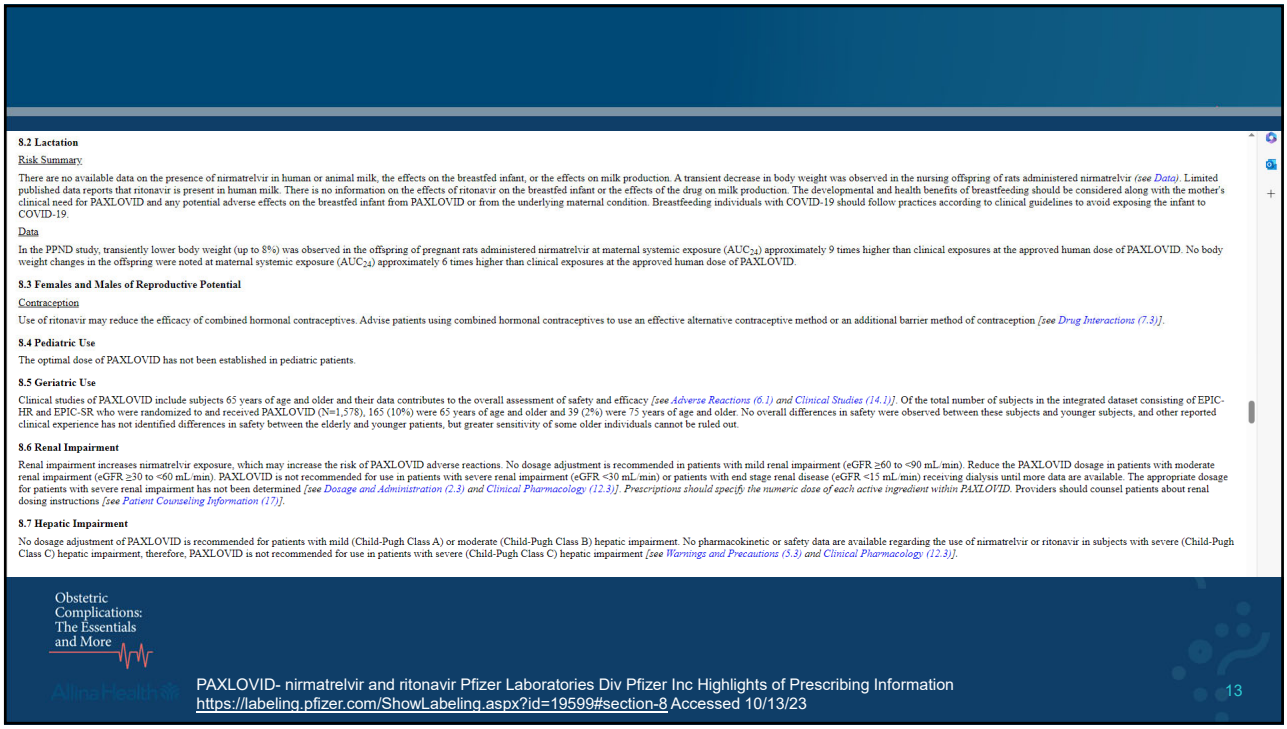

8.2 Lactation

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 PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID 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 PPND study, transiently lower body weight (up to 8%) was observed in the offspring of pregnant rats administered nirmatrelvir at maternal systemic exposure (AUC_{24}) approximately 9 times higher than clinical exposures at the approved human dose of PAXLOVID. No body weight changes in the offspring were noted at maternal systemic exposure (AUC_{24}) approximately 6 times higher than clinical exposures at the approved human dose of PAXLOVID.

8.3 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 *[see Drug Interactions (7.3)]*.

8.4 Pediatric Use

The optimal dose of PAXLOVID has not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of PAXLOVID include subjects 65 years of age and older and their data contributes to the overall assessment of safety and efficacy *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Of the total number of subjects in the integrated dataset consisting of EPIC-HR and EPIC-SR who were randomized to and received PAXLOVID (N=1,578), 165 (10%) were 65 years of age and older and 39 (2%) were 75 years of age and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in safety between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Renal impairment increases nirmatrelvir exposure, which may increase the risk of PAXLOVID adverse reactions. No dosage adjustment is recommended in patients with mild renal impairment (eGFR ≥60 to <90 mL/min). Reduce the PAXLOVID dosage in patients with moderate renal impairment (eGFR ≥30 to <60 mL/min). PAXLOVID is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min) or patients with end stage renal disease (eGFR <15 mL/min) receiving dialysis until more data are available. The appropriate dosage for patients with severe renal impairment has not been determined *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. Prescriptions should specify the numeric dose of each active ingredient within PAXLOVID.* Providers should counsel patients about renal dosing instructions *[see Patient Counseling Information (17)]*.

8.7 Hepatic Impairment

No dosage adjustment of PAXLOVID is recommended for 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 (Child-Pugh Class C) hepatic impairment, therefore, PAXLOVID is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

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PAXLOVID- nirmatrelvir and ritonavir Pfizer Laboratories Div Pfizer Inc Highlights of Prescribing Information https://labeling.pfizer.com/ShowLabeling.aspx?id=19599#section-8 Accessed 10/13/23

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