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19th January 2022

Re: Nirmatrelvir/ritonavir (Paxlovid©) use in pregnancy

Dear Sir/Madam,

An assessment of the risks and benefits of treating pregnant women with COVID-19 are set out in the UKTIS monograph, *'Medications used to treat coronavirus (COVID-19) in pregnancy'* (available from www.medicinesinpregnancy.org/bumps/monographs/MEDICATIONS-USED-TO-TREAT-COVID-19-IN-PREGNANCY/).

Nirmatrelvir/ritonavir (Paxlovid©) is licensed for the treatment of COVID-19 in adults who do not require supplemental oxygen, but who are at increased risk of developing severe illness.[1] Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease which prevents viral replication.[1] Ritonavir is included in the formulation as a pharmacokinetic enhancer, to inhibit CYP3A mediated metabolism of nirmatrelvir, and does not possess pharmacodynamic activity against SARS-CoV-2 3CL protease.[1] Preclinical animal reproductive toxicity studies have not identified adverse effects on fetal morphology or embryo-fetal viability in rat or rabbit models with doses of nirmatrelvir up to 12 times the human dose (equivalence based on predicted AUC concentrations).The offspring of pregnant rabbits administered 24 times the equivalent human dose, lower fetal body weights were observed but evidence of maternal toxicity was described (impact on weight gain/food consumption).[1] There is a large amount of published evidence relating to the safety of ritonavir in human pregnancy, collected from antiretroviral and HIV/AIDS pregnancy registries. Overall, these data do not provide compelling evidence that ritonavir use in the first trimester is associated with an increased risk of malformation above the expected background rate of 2-3%.[2] There is also no evidence that liponavir/ritonavir combination therapy in pregnancy had any detectable impact on postnatal development.[3] Data investigating other adverse pregnancy outcomes following ritonavir exposure in pregnancy (such as miscarriage, preterm delivery, fetal growth impairment or stillbirth risks) are lacking. Due to a lack of human pregnancy safety data, the manufacturer of Paxlovid© does not recommend use in pregnancy. However, the benefits of use could outweigh the risks in some circumstances (see conclusion below). As CYP3A4 metabolic activity and glomerular filtration increase during pregnancy, it is unclear whether pregnancy may impact the pharmacokinetics of Paxlovid©. Further research into the efficacy of this medication in pregnancy is required.

CONCLUSION: Despite the lack of human pregnancy safety data for Paxlovid©, there may be specific circumstances where the benefits of use during pregnancy could outweigh the risks. Such circumstances may include the use in women at high risk of developing severe disease (due to non-vaccination status or clinical vulnerabilities), or in women experiencing severe symptoms of COVID-19 where other more established treatments have failed. UKTIS supports the inclusion of pregnant women in clinical trials of Paxlovid©. However, the efficacy of these treatments may not have been proven in all such clinical scenarios. Where COVID-19 antivirals are being considered for use during pregnancy, the risks and benefits should be discussed on an individual patient basis, and a system for collecting maternal and fetal outcome should be established.

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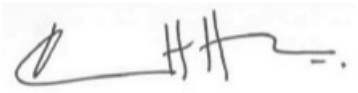
Kind regards,



Dr Kenneth K. Hodson
Head of the UK Teratology Information Service

References

1. Pfizer Limited. Paxlovid 150 mg/100 mg film-coated tablets (last updated 14 January 2022). Available from: www.medicines.org.uk/emc/product/13145
2. TERIS Teratogen Information System. Ritonavir. Available (with subscription) from www.micromedexsolutions.com
3. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR III: The PHACS SMARTT Study: assessment of the safety of in utero exposure to antiretroviral drugs. Front Immunol 7:199, 2016. PMID: 27242802