

Cobicistat (Tybost, COBI)

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Animal Studies

Carcinogenicity

No increases in tumor incidence were seen in male and female mice at cobicistat (COBI) exposures that were 7 and 16 times the exposure observed in humans who received the recommended dose. In rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses up to twice the typical human exposure. The follicular cell findings are considered rat-specific and not relevant to humans.¹

Reproduction/Fertility

COBI did not affect fertility in male or female rats.¹

Teratogenicity/Adverse Pregnancy Outcomes

Studies in pregnant rats and rabbits have shown no evidence of teratogenicity, even with rat COBI exposures that were 1.4 times higher than the recommended human exposure and rabbit COBI exposures that were 3.3 times higher than the recommended human exposure.¹

Placental and Breast Milk Passage

No information is available on placental passage of COBI. Studies in rats have shown that COBI is secreted in breast milk.²

Human Studies in Pregnancy

Pharmacokinetics

COBI pharmacokinetics (PKs) have been described in pregnant and postpartum women who were taking concomitant elvitegravir (EVG), atazanavir (ATV), and darunavir (DRV). In a study of 30 pregnant women who were receiving elvitegravir/cobicistat (EVG/c), the area under the curve (AUC) for COBI was 44% lower in the second trimester and 59% lower in the third trimester than during the postpartum period. Trough COBI concentrations (24 hours post-dose) were 60% lower in the second trimester and 76% lower in the third trimester than during the postpartum period. Trough COBI concentrations were below the assay quantitation limit (<10 ng/mL) in 65% of women during the second trimester, 73% of women during the third trimester, and 24% of postpartum women.³ Two other studies have described decreases of similar magnitudes in COBI exposures when COBI is coadministered with DRV in pregnant women.^{4,5} In one of these abstracts, COBI AUC was decreased by 63% in the second trimester and 49% in the third trimester compared to the AUC postpartum. Trough COBI concentrations decreased by 83% in both the second and third trimesters.

The pharmacoenhancing effect of COBI on EVG was impacted during pregnancy; EVG AUC was reduced by 44% and trough concentrations were reduced by 89% in the third trimester when compared to postpartum AUC and trough concentrations. EVG apparent oral clearance during pregnancy and postpartum was negatively associated with COBI AUC.³

The pharmacoenhancing effect of COBI on ATV and DRV was also impacted during pregnancy. For DRV, AUC based on total DRV concentrations was 56% (in the second trimester) and 50% (in the third trimester) lower than the AUC postpartum, and AUC based on unbound concentrations was 45% and 40% lower, respectively. The effect on DRV trough concentrations was more pronounced, with both total and unbound concentrations showing essentially identical decreases of 92% (in the second trimester) and 88% to 89% (in the third trimester) when compared to postpartum trough concentrations. One of six women in this study experienced virologic failure during the third trimester, and virologic failure continued through the postpartum period.⁵ For ATV, trough ATV concentrations were 80% and 85% lower in the second and third trimesters compared to historical

ATV trough concentrations in nonpregnant adults with HIV.⁶ Because of these substantial reductions in drug exposures during pregnancy, use of COBI-boosted EVG, ATV, or DRV **is not recommended** for patients starting or changing regimens during pregnancy.⁷⁻⁹

A study reported in a conference abstract evaluated tenofovir alafenamide (TAF) exposure in pregnant women when TAF was administered as a daily 10-mg dose with COBI 150 mg. There were no differences between TAF exposure during pregnancy and TAF exposure postpartum in the same women. The authors concluded that no dose adjustment is needed during pregnancy for TAF when it is coadministered with COBI.¹⁰ However, TAF 10 mg with COBI is only available in fixed-dose combination products that also include either DRV or EVG, which are not recommended for use during pregnancy. Another study described TAF exposure in pregnant women when administered as a 25-mg dose with a pharmacoenhancer (either RTV 100 mg or COBI 150 mg). TAF exposures during pregnancy and postpartum did not differ.¹¹

Placental and Breast Milk Passage

A study in 10 pregnant women who received EVG/c found a median ratio of cord blood to maternal plasma COBI concentrations of 0.09. This study also found measurable concentrations of COBI in placental tissue and cord blood peripheral blood mononuclear cells (PBMC), with a cord-blood-to-maternal-PBMC ratio of 0.49.¹² In another study, 7 of 15 pregnant women who received EVG/c had quantifiable plasma COBI concentrations at delivery. The median cord blood-to-maternal-plasma ratio for COBI concentration was 0.09. In 27 neonates born to mothers who were receiving EVG/c, COBI was below the assay quantitation limit of 10 ng/mL in all washout PK samples taken between 2 hours and 9 days postdelivery.³ No data are available on breast milk passage of COBI in humans.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to COBI to detect at least a twofold increase in the risk of overall birth defects in the general population. However, no such increase in the risk of birth defects has been observed with COBI. Among cases of first-trimester exposure to COBI that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.9% (16 of 410 live births; 95% confidence interval, 2.3% to 6.3%) compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.²

Excerpt from Table 10

Note: When using FDC tablets, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) <i>Trade Name</i>	Formulation	Dosing Recommendations ^a	Use in Pregnancy
<p>Cobicistat (COBI) <i>Tybost</i></p> <p>(ATV/c) <i>Evotaz</i></p> <p>(EVG/c/FTC/TAF) <i>Genvoya</i></p> <p>(DRV/c) <i>Prezcobix</i></p> <p>(EVG/c/FTC/TDF) <i>Stribild</i></p> <p>(DRV/c/FTC/TAF) <i>Symtuza</i></p>	<p>COBI (Tybost) <i>Tablet:</i></p> <ul style="list-style-type: none"> • COBI 150 mg <p>ATV/c (Evotaz):</p> <ul style="list-style-type: none"> • ATV 300 mg/ COBI 50 mg tablet <p>EVG/c/FTC/TAF (Genvoya):</p> <ul style="list-style-type: none"> • EVG 150 mg/ COBI 150 mg FTC 200 mg/ TAF 10 mg tablet <p>DRV/c (Prezcobix):</p> <ul style="list-style-type: none"> • DRV 800 mg/ COBI 150 mg tablet <p>EVG/c/FTC/TDF (Stribild):</p> <ul style="list-style-type: none"> • EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg tablet <p>DRV/c/FTC/TAF (Symtuza):</p> <ul style="list-style-type: none"> • DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg tablet 	<p>Standard Adult Doses <i>COBI (Tybost):</i></p> <ul style="list-style-type: none"> • When used as an alternative PK booster with ATV or DRV, the dose is one tablet once daily with food <p><i>ATV/c (Evotaz):</i></p> <ul style="list-style-type: none"> • One tablet once daily with food <p><i>EVG/c/FTC/TAF (Genvoya):</i></p> <ul style="list-style-type: none"> • One tablet once daily with food <p><i>DRV/c (Prezcobix):</i></p> <ul style="list-style-type: none"> • One tablet once daily with food <p><i>EVG/c/FTC/TDF (Stribild):</i></p> <ul style="list-style-type: none"> • One tablet once daily with food <p><i>DRV/c/FTC/TAF (Symtuza):</i></p> <ul style="list-style-type: none"> • One tablet once daily with food <p>Pregnancy <i>PKs in Pregnancy:</i></p> <ul style="list-style-type: none"> • Based on limited data, COBI exposure and its pharmacoenhancing effect on ATV, DRV, and EVG are markedly reduced in pregnancy. • When coadministered with COBI, TAF 	<p>Low placental transfer to fetus.^b</p> <p>No evidence of human teratogenicity (can rule out twofold increase in overall birth defects).</p> <p>Use of COBI-boosted ATV, DRV, or EVG is not recommended in pregnancy.</p>

Generic Name (Abbreviation) <i>Trade Name</i>	Formulation	Dosing Recommendations ^a	Use in Pregnancy
		<p>exposure is not significantly different between pregnancy and the postpartum period.</p> <p><i>Dosing in Pregnancy:</i></p> <ul style="list-style-type: none"> Although COBI exposure is markedly reduced during pregnancy, higher-than-standard doses have not been studied. The Panel recommends RTV as the preferred pharmacoenhancer for PIs and INSTIs during pregnancy until more data are available on COBI activity during pregnancy. <p>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF, TDF, ATV, DRV, EVG).</p>	

^a Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10](#)).

^b Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6

Moderate: 0.3–0.6

Low: <0.3

Key: ARV = antiretroviral; ATV/c = atazanavir/cobicistat; COBI = cobicistat; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; INSTIs = integrase strand transfer inhibitors; PIs = protease inhibitors; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

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