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Ribociclib Drug-Drug Interaction and Concomitant Medication Management in Early and Advanced Breast Cancer Patients

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KEY FINDINGS & CONCLUSIONS

- No clinically relevant DDI with RIB is anticipated for commonly used statins except simvastatin, lovastatin, and atorvastatin, which are substantially metabolized by CYP3A4 and should be used with caution
- No PK DDI with RIB is anticipated for commonly used antidepressants/anxiolytics and antipsychotics except alprazolam, cariprazine, diazepam, quetiapine, and sertraline, which are substantially metabolized by CYP3A4; caution should be exercised (avoid or use with caution) for some antipsychotics and antidepressants/anxiolytics depending on their potential to prolong the QT interval
- DDIs with RIB are not expected for short-term use of corticosteroids that are administered nonsystemically; systemic corticosteroids that are CYP3A4 inducers and/or substrates such as dexamethasone should be used only for a short duration at the lowest dose possible and monitored for their adverse effects when coadministered with RIB

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INTRODUCTION

- Ribociclib (RIB) is approved for the treatment of patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC) or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant and more recently for the adjuvant treatment of patients with HR+/HER2− stage II and III early breast cancer (EBC) at a high risk of recurrence, with a starting dose of 600 mg in ABC and 400 mg in EBC
- The drug-drug interaction (DDI) profile of RIB has been previously characterized[1,2]
- RIB is a strong to moderate cytochrome P450 (CYP) 3A4 inhibitor at 600 and 400 mg, respectively, and thus caution is recommended for concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index
- RIB is also a CYP3A4 substrate, so concomitant use with strong CYP3A4 inhibitors or inducers should be avoided
- RIB causes concentration-dependent increases in the Fridericia method-corrected QT interval, and concomitant use of drugs known to prolong the QT interval or cause torsades de pointes (TdP) should be avoided

METHODS

- The impact of DDIs between RIB and potential comedications such as statins, antidepressants/anxiolytics and antipsychotics, and corticosteroids was assessed (**Table 1**)
- For statins and antidepressants/anxiolytics and antipsychotics, qualitative DDI assessment was conducted based on data in the US Food and Drug Administration (FDA) prescribing information for respective drugs, the Certara Drug Interaction Database, and cardiac safety data at www.crediblemeds.org
- For corticosteroids, a physiologically based pharmacokinetic (PBPK) simulation was performed to assess the DDI between RIB and dexamethasone, and the DDI between RIB and inhaled budesonide was assessed based on the data in the US FDA prescribing information and the Certara Drug Interaction Database
  - PBPK simulation for RIB and dexamethasone was conducted using Simcyp PBPK Simulator version 20 (Certara) with the following trial design: 10 trials × 10 patients; healthy volunteer population; 50% female; age range, 20-50 years; and once-daily treatment for 14 days with both drugs

Table 1. Comedications Assessed

Statins	Antidepressants/ anxiolytics	Antipsychotics	Steroids/ anti-inflammatory drugs
• Atorvastatin (Lipitor) • Simvastatin (Zocor) • Rosuvastatin (Crestor) • Fluvastatin (Lescol) • Pravastatin (Pravachol) • Lovastatin (Mevacor) • Pitavastatin (Livalo)	• Fluoxetine (Prozac) • Sertraline (Zoloft) • Citalopram (Celexa) • Escitalopram (Lexapro) • Venlafaxine (Effexor) • Bupropion (Wellbutrin) • Duloxetine (Cymbalta) • Alprazolam (Xanax) • Lorazepam (Ativan) • Trazodone (Desyrel) • Diazepam (Valium) • Mirtazapine (Remeron)	• Aripiprazole (Abilify) • Quetiapine (Seroquel) • Olanzapine (Zyprexa) • Cariprazine (Vraylar)	• Inhaled budesonide (Pulmicort Respules) • Dexamethasone (Decadron)

RESULTS

Statins

- No general class-wide DDI risk for statins has been observed with RIB (**Table 2**)
- Effect of RIB on statin PK
  - The effect of RIB on rosuvastatin, pravastatin, pitavastatin, and fluvastatin is considered minor with no clinical relevance since these statins are not sensitive CYP3A4 substrates
  - Only the statins that are substantially metabolized by CYP3A4, such as simvastatin, lovastatin, and atorvastatin, may have increased exposure upon comedication with RIB 400 or 600 mg
- Effect of statins on RIB PK
  - Commonly used statins are not strong CYP3A4 inhibitors or inducers, and thus they are not expected to have a clinically relevant effect on RIB exposure

Table 2. Disposition Pathways of Statins and DDI Assessment With RIB

Statins	Route of elimination[a]	Transporters[a]	Metabolic enzymes[a]	PK DDI of statins[b]	Estimated RIB impact on statin PK[c]	Estimated statin impact on RIB PK[c]	Recommendation (rationale)
Atorvastatin (Lipitor)	Metabolism	OATP1B/BCRP/ P-gp/OATP2B1/ NTCP/MRP2	CYP3A4/UGT	Caution when combining with CYP3A inhibitors, eg, itraconazole or clarithromycin	Exposure may increase <2-fold, as predicted by PBPK	No impact	**Use with caution** (RIB may increase statin exposure)
Fluvastatin (Lescol)	Metabolism	OATP1B/BCRP	CYP2C9	No expected interactions with CYP3A4 inhibitors	No impact	No impact	**No clinically relevant DDI expected**
Lovastatin (Mevacor)	Metabolism	OATP1B1	CYP3A4 (CYP2C8/ UGTs)	Strong CYP3A4 inhibitors are contraindicated	Exposure may increase >2-fold, as predicted by PBPK	No impact	**Use with caution** (RIB may increase statin exposure)
Pitavastatin (Livalo)	Metabolism/ biliary	OATP1B1/ OATP1B3 (OATP2B1/NTCP)	CYP2C9/ UGT (CYP2C8)	No expected interactions with CYP3A4 inhibitors	No impact	No impact	**No clinically relevant DDI expected**
Pravastatin (Pravachol)	Biliary/renal	OATP1B/OAT3/ MRP2/OATP2B1/ BCRP/BSEP	UGT	No significant interaction observed with strong CYP3A4 inhibitors, eg, itraconazole or diltiazem	No impact	No impact	**No clinically relevant DDI expected**
Rosuvastatin (Crestor)	Biliary/renal	OATP1B/BCRP/ OATP2B1/ OAT3/NTCP/ OATP1A2/ MRP3/MRP4	CYP2C9/ CYP2C19/ UGT	Not a CYP3A4 substrate, no clinical interactions with CYP inhibitors	No impact	No impact	**No clinically relevant DDI expected**
Simvastatin (Zocor)	Metabolism	OATP1B/P-gp/ BCRP	CYP3A4/UGT	Potent CYP3A4 inhibitors are contraindicated	Exposure may increase >2-fold, as predicted by PBPK	No impact	**Use with caution** (RIB may increase statin exposure)

DDI, drug-drug interaction; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetics; RIB, ribociclib. [a] Based on Kunze et al. 2025 and Kikuchi et al. 2023.[3,4] [b] Based on US FDA prescribing information. [c] Based on semi-quantitative data.

Antidepressants/Anxiolytics and Antipsychotics

- The impact of PK DDIs between RIB and antidepressants/anxiolytics and antipsychotics was also assessed
  - Effect of RIB on antidepressant/anxiolytic and antipsychotic PK (**Tables 3 and 4**)
    - No PK DDI is expected for commonly used antidepressants/anxiolytics and antipsychotics, such as aripiprazole, citalopram, escitalopram, duloxetine, fluoxetine, lorazepam, mirtazapine, olanzapine, trazodone, and venlafaxine, when coadministered with RIB 400 or 600 mg
    - Alprazolam, cariprazine, diazepam, quetiapine, and sertraline are CYP3A4 substrates, and their exposure may increase when coadministered with RIB 400 or 600 mg
  - Effect of antidepressants/anxiolytics and antipsychotics on RIB PK
    - Commonly used antidepressants/anxiolytics and antipsychotics are not strong CYP3A4 inhibitors or inducers, and thus they are not expected to have a clinically relevant effect on RIB exposure
- Antidepressants/anxiolytics and antipsychotics with TdP risk
  - Coadministration of RIB with antidepressants/anxiolytics and antipsychotics with a known or conditional TdP risk and a potential exposure increase induced by RIB should be avoided
  - Coadministration of RIB with antidepressants/anxiolytics and antipsychotics with a conditional or possible TdP risk should be used with caution

Table 3. Disposition Pathways of Antidepressants/Anxiolytics and DDI Assessment With RIB

Antidepressants /anxiolytics	Metabolic enzymes	PK DDI of antidepressants/anxiolytics[a]	Estimated RIB impact on antidepressant/ anxiolytic PK[b]	Estimated antidepressant/ anxiolytic impact on RIB PK[b]	TdP risk of antidepressants /anxiolytics[c]	Recommendation (rationale)
Alprazolam (Xanax)	CYP3A4	Alprazolam is contraindicated with ketoconazole and itraconazole, potent CYP3A inhibitors that increase the plasma alprazolam concentration 3.98- and 2.70-fold	Exposure may increase with RIB 400 or 600 mg	No impact	No risk listed	**Use with caution** (Potential increase in alprazolam exposure)
Bupropion (Wellbutrin)	CYP2B6/ CYP3A4	Minor involvement of CYP3A4 in metabolism	No impact	No impact	No risk listed	**No clinically relevant DDI expected**
Citalopram (Celexa)	CYP3A4/ CYP2C19	Racemic citalopram 40 mg and ketoconazole 200 mg did not significantly affect citalopram PK	No impact	No impact	Known TdP risk	**Avoid use** (Known TdP risk with citalopram)
Diazepam (Valium)	CYP2C19/ CYP3A4	Fluvoxamine (strong CYP2C19 inhibitor) increased diazepam AUC 2.8-fold; grapefruit juice (intestinal CYP3A4 inhibitor) changed diazepam AUC 3.24-fold	Exposure may increase with RIB 400 or 600 mg	No impact	No risk listed	**Use with caution** (RIB may increase diazepam exposure)
Duloxetine (Cymbalta)	CYP1A2/ CYP2D6	Not a CYP3A4 substrate	No impact	No impact	No risk listed	**No clinically relevant DDI expected**
Escitalopram (Lexapro)	CYP3A4/ CYP2C19	Racemic citalopram 40 mg and ketoconazole 200 mg did not significantly affect citalopram PK	No impact	No impact	Known TdP risk	**Avoid use** (Known TdP risk with escitalopram)
Fluoxetine (Prozac)	CYP2D6/ CYP2C19	Not a CYP3A4 substrate	No impact	No impact	Conditional TdP risk	**Use with caution** (Conditional TdP risk with fluoxetine)
Lorazepam (Ativan)	UGT2B15	Not a CYP3A4 substrate	No impact	No impact	No risk listed	**No clinically relevant DDI expected**
Mirtazapine (Remeron)	CYP3A4 (CYP2D6/ CYP1A2)	The potent CYP3A4 inhibitor ketoconazole increased the AUC of a 30-mg mirtazapine dose by ≈50%	No impact	No impact	Possible TdP risk	**Use with caution** (Possible TdP risk with mirtazapine)
Sertraline (Zoloft)	CYP3A4/ CYP2C19	Grapefruit juice (250 mL TID for 6 days), an intestinal inhibitor of CYP3A4, increased sertraline AUC by 100%	Exposure may increase with RIB 400 or 600 mg	No impact	Conditional TdP risk	**Avoid use** (Conditional TdP risk, and RIB may increase sertraline exposure)
Trazodone (Desyrel)	CYP3A4	Concomitant trazodone and a strong CYP3A4 inhibitor (ritonavir) increased trazodone exposure over trazodone alone by 2.37-fold	No clinically relevant impact	No impact	Conditional TdP risk	**Use with caution** (Conditional TdP risk with trazodone)
Venlafaxine (Effexor)	CYP2D6	Not a CYP3A4 substrate	No impact	No impact	Possible TdP risk	**Use with caution** (Possible TdP risk with venlafaxine)

AUC, area under the curve; DDI, drug-drug interaction; PK, pharmacokinetics; RIB, ribociclib; TdP, torsades de pointes; TID, 3 times a day. [a] Based on US FDA prescribing information and the Certara Drug Interaction Database. [b] Based on semi-quantitative data. [c] Based on www.crediblemeds.org.

Table 4. Disposition Pathways of Antipsychotics and DDI Assessment With RIB

Antipsychotics	Metabolic enzymes	PK DDI of antipsychotics[a]	Estimated RIB impact on antipsychotic PK[b]	Estimated antipsychotic impact on RIB PK[b]	Antipsychotic TdP risk[c]	Recommendation (rationale)
Aripiprazole (Abilify)	CYP3A4/ CYP2D6	Concomitant strong CYP3A4 or CYP2D6 inhibitor use increased aripiprazole AUC by 64%	No clinically relevant impact	No impact	Possible TdP risk	**Use with caution** (Possible TdP risk with aripiprazole)
Cariprazine (Vraylar)	CYP3A4 (CYP2D6)	Concomitant cariprazine use with ketoconazole increased cariprazine exposure by 3.88-fold	Exposure may increase with RIB 400 or 600 mg	No impact	No risk listed	**Use with caution** (RIB may increase cariprazine exposure)
Olanzapine (Zyprexa)	CYP1A2/ CYP2D6/ UGTs	Not a CYP3A4 substrate	No impact	No impact	Conditional TdP risk	**Use with caution** (Conditional TdP risk with olanzapine)
Quetiapine (Seroquel)	CYP3A4	Ketoconazole increased quetiapine AUC by 6.2-fold; quetiapine dose should be reduced 6-fold when coadministered with strong CYP3A4 inhibitors	Exposure may increase with RIB 400 or 600 mg	No impact	Conditional TdP risk	**Avoid use** (Conditional TdP risk, and RIB may increase quetiapine exposure)

AUC, area under the curve; DDI, drug-drug interaction; PK, pharmacokinetics; RIB, ribociclib; TdP, torsades de pointes. [a] Based on US FDA prescribing information and the Certara Drug Interaction Database. [b] Based on semi-quantitative data. [c] Based on www.crediblemeds.org.

Corticosteroids

- DDIs with RIB are not expected for short-term use of corticosteroids that are administered nonsystemically (eg, topical, inhaled, ocular drop, or local injection)
- Systemically administered corticosteroids that induce CYP3A4 activity, such as dexamethasone, may reduce RIB exposure if they are used chronically (**Table 5**)
  - The extent of the decrease in RIB exposure depends on the dexamethasone dose, and doses of ≤5 mg are not estimated to have a clinically relevant DDI
  - Dexamethasone is a CYP3A4 substrate, and its exposure may be increased (<2-fold) when coadministered with RIB 400 or 600 mg
- Budesonide is a sensitive CYP3A4 substrate, so caution is recommended for long-term use of inhaled budesonide (Pulmicort Respules) with RIB 600 mg since budesonide exposure may increase
  - Use of inhaled budesonide with RIB 400 mg is not expected to have a major DDI

Table 5. PBPK Model–Predicted DDIs Between RIB and Dexamethasone

Object drug (substrate)[a]	Precipitant drug[a]	Object drug geometric mean $C_{max,ss}$ ratio (with/without precipitant drug)	Object drug geometric mean $AUC_{0\text{-}24h,ss}$ ratio (with/without precipitant drug)
RIB 400 mg	DEX 5 mg	0.84	0.74
RIB 400 mg	DEX 10 mg	0.78	0.65
RIB 400 mg	DEX 20 mg	0.71	0.56
RIB 600 mg	DEX 5 mg	0.85	0.76
RIB 600 mg	DEX 10 mg	0.79	0.67
RIB 600 mg	DEX 20 mg	0.72	0.58
DEX 5 mg	RIB 400 mg	1.42	2.10
DEX 10 mg	RIB 400 mg	1.38	1.96
DEX 20 mg	RIB 400 mg	1.34	1.84
DEX 5 mg	RIB 600 mg	1.58	2.63
DEX 10 mg	RIB 600 mg	1.53	2.45
DEX 20 mg	RIB 600 mg	1.49	2.29

$AUC_{0\text{-}24h,ss}$, area under the curve from 0 to 24 h at steady state; $C_{max,ss}$, maximum concentration at steady state; DDI, drug-drug interaction; DEX, dexamethasone; PBPK, physiologically based pharmacokinetics; RIB, ribociclib. Data based on PBPK simulation. [a] The object drug is the drug whose PK is affected or altered by another drug (precipitant drug); the precipitant drug affects or alters the PK of another drug (the object drug).

References

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Disclosures

YJ, FH, LS, JPZ, and **HS** report employment with and stock ownership in Novartis.