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Elinzanetant in breast cancer care: potential drug–drug interaction profile with targeted systemic therapies

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INTRODUCTION

- Elinzanetant is a hormone-free dual neurokinin (NK)-1 and NK3 receptor antagonist indicated for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with menopause, and in the EU also for VMS induced by endocrine therapy (ET).[1,2]
- OASIS-4 established elinzanetant as a first-in-class therapy for the management of VMS in women receiving ET for hormone receptor-positive breast cancer or its prevention.[3]
- While elinzanetant has been evaluated in combination with aromatase inhibitors or tamoxifen with or without GnRH analogues, there are no clinical studies of targeted breast cancer (BC) therapies (which were excluded from the OASIS-4 trial).[1-4] Defining elinzanetant's drug-drug interaction (DDI) profile with targeted BC therapies using existing DDI data is thus essential for treating physicians.

METHODS

- We searched the European Medicines Agency (EMA) website and Certara Drug Interaction Database for published DDI profiles of currently approved targeted BC therapies, and compared these with elinzanetant's DDI potential, assessed through in vitro cytochrome P450 (CYP) enzyme/transporter assays, human liver microsome and hepatocyte turnover studies, and validated in clinical DDI trials and a mass balance study.[5,6] Thresholds (weak, moderate, strong interactions) were based on guidelines for sensitive substrates of drug-metabolising enzymes or transporters.[7]

RESULTS

- Elinzanetant, a sensitive substrate and weak inhibitor of CYP isoform 3A4 (CYP3A4)[2] showed low DDI potential with 12/16 (75.0%) targeted BC therapies, needing no dose adjustment based on available data (**Tables 1, 2**).

Table 1. Potential CYP3A4-mediated drug-drug interactions with elinzanetant and targeted breast cancer therapies.

Comedication class	Comedication name	Clinically relevant DDI potential (elinzanetant as weak CYP3A4 inhibitor)	Clinically relevant DDI potential (elinzanetant as CYP3A4 substrate)	Elinzanetant dose recommendation
CDK4/6	Palbociclib[9]	↔	↔	✅
	Abemaciclib[10]	↔	↔	✅
	Ribociclib[8]	↔	↑↑/↑↑↑ (Dose-dependent CYP3A4 inhibition)	↘ Reduce (400 mg)/⛔ Avoid (600 mg)
PI3K/mTOR	Everolimus[11]	↑ (<2x increase in everolimus exposure)	↔	✅
	Alpelisib[12]	↔ (Metabolised by hydrolysis)	⚠️ Possible (Time-dependent CYP3A4 inhibitor; unknown relevance)	⚠️
	Inavolisib[13]	↔ (Metabolised by non-CYP enzymes and P-gp)	⚠️ Possible (In vitro inducer / inhibitor of CYP3A4; unknown relevance)	⚠️
AKT	Capivasertib*[14]	↔ (Not a highly sensitive CYP3A4 substrate)	↑ (Weak CYP3A4 inhibitor)	✅
PARP	Olaparib[15]	↔	↑ (Weak CYP3A4 inhibitor)	✅
	Talazoparib[16]	↔ (Minimal hepatic metabolism)	↔	✅
	Niraparib[17]	↔	↔	✅
SERD	Fulvestrant[18]	↔ (Not metabolized by CYP3A4)	↔	✅
	Elacestrant[19]	↔	↔	✅
	Imlunestrant[20]	↔ (Metabolised by sulfation, CYP3A4, UGTs)	↔	✅
TK inhibitor**	Tucatinib[21]	↔ (Metabolised primarily by CYP2C8)	↑↑↑ (Tucatinib 300 mg BD is a strong inhibitor of CYP3A4, causing a ~5.7x increase in the AUC of midazolam)	⛔ Avoid
	Neratinib[22]	↔ (Metabolised by CYP3A and FMO)	↔	✅
Chemotherapy	Capecitabine[23]	↔	↔	✅

*Capivasertib is classed as an AKT that targets the PI3K/AKT/mTOR pathway. **Tucatinib is a TKI that targets HER2 receptors; neratinib is a TKI that targets HER1, HER2, and HER4 receptors. ↔ No clinically relevant DDI; ↑ / ↑↑ / ↑↑↑ Mild / Moderate / High DDI potential; ⚠️ Caution: potential DDI; ↘ Reduce dose; ⛔ Avoid coadministration. AKT, protein kinase B (also known as AKT); AUC, area under the curve; BD, twice daily; CDK4/6, cyclin-dependent kinase 4 and 6; CYP, cytochrome P450 isoform; FMO, flavin-containing monooxygenase; HER1/2, Human Epidermal Growth Factor Receptor 1/2; PARP, poly(ADP-ribose) polymerase; P-gp, P-glycoprotein; PI3K/mTOR, phosphoinositide 3-kinase/mechanistic target of rapamycin; SERD, selective estrogen receptor degrader; TK, tyrosine kinase; UGT, UDP-glucuronosyltransferases.

- Comedication with ribociclib, a moderate (400 mg) or strong (600 mg) CYP3A4 inhibitor, requires elinzanetant dose reduction (400 mg) or avoidance (600 mg).[8]
- Comedication with alpelisib[12] and inavolisib,[13] which show CYP3A4 inhibition based on *in vitro* data, calls for caution and possible elinzanetant dose reduction until clinical DDI data are available.
- Coadministration of elinzanetant with tucatinib,[21] a strong CYP3A4 inhibitor, should be avoided.

Table 2. Elinzanetant and breast cancer comedications at a glance.

Comedication class: agent	Medications that may affect elinzanetant (CYP3A4 substrate)	Medications that elinzanetant (weak CYP3A4 inhibitor) may affect
CDK4/6 inhibitor: palbociclib, abemaciclib **PI3K/mTOR inhibitor:** everolimus **AKT inhibitor:** capivasertib **PARP inhibitor:** talazoparib, niraparib, olaparib **SERD:** fulvestrant, imlunestrant, elacestrant **TK inhibitor:** neratinib **Chemotherapy:** capecitabine	↔ No effect of comedication on elinzanetant – no dose adjustment needed ✅	✅ No effect of elinzanetant on comedication
CDK4/6 inhibitor: ribociclib	*400 mg dose (moderate inhibitor): **consider reduced dose** to 60 mg elinzanetant once daily ↘	
	*600 mg dose (strong inhibitor): **avoid use** ⛔	
PI3K/mTOR inhibitor: alpelisib, inavolisib	Use **with caution** ⚠️	
TK inhibitor: tucatinib	**Avoid use** ⛔	

↔ No clinically relevant DDI; ⚠️ Caution: potential DDI; ↘ Reduce dose; ⛔ Avoid coadministration. AKT, protein kinase B (also known as AKT); CDK4/6, cyclin-dependent kinase 4 and 6; PARP, poly(ADP-ribose) polymerase; PI3K/mTOR, phosphoinositide 3-kinase / mechanistic target of rapamycin; SERD, selective estrogen receptor degrader; TK, tyrosine kinase.

KEY TAKEAWAYS

- The recommended daily dose of elinzanetant is 120 mg (two 60 mg capsules) at bedtime.
- Elinzanetant, a weak inhibitor and sensitive substrate of CYP3A4, exhibited low DDI potential with 75% of examined targeted oral BC therapies, which required no dose adjustment.
- Use with caution with CYP3A4 inhibitors alpelisib and inavolisib based on *in vitro* data.
- When used with moderate CYP3A4 inhibitors, e.g. ribociclib 400 mg, reduce the dose to 60 mg.
- Avoid concomitant use with strong CYP3A4 inhibitors e.g. ribociclib 600 mg and tucatinib.

CONCLUSIONS

Elinzanetant has no clinically meaningful predicted DDI impact on the exposure of all targeted BC therapies; however, potential DDI effects on elinzanetant may occur with moderate or strong CYP3A4 inhibitors, including with ribociclib, alpelisib, inavolisib, and tucatinib, necessitating elinzanetant dose adjustment or avoiding coadministration.

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DISCLOSURES

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