CYP3A4 Inhibitor/Inducer Drug-drug Interactions - All Kinase Inhibitors[1,2]

Kinase Inhibitor	CYP3A4 Inhibitor Drug(s)	CYP3A4 Inducer Drug(s)	Recommendations on how DDIs can be managed
Afatinib	-	Rifampicin	Reduce afatinib dose to 10 mg/day if co-administration with ketoconazole is not tolerated; or administer ketoconazole using staggered dosing, preferably 6 or 12 hours apart from afatinib For patients requiring chronic therapy with a rifampicin, increase the afitinib daily dose by 10 mg as tolerated
Axitinib	Ketoconazole	Rifampicin	If use of strong CYP3A4/5 inhibitors is unavoidable, reduce the dose of axitinib by approximately half, as tolerated If use of strong CYP3A4/5 inducers is unavoidable, a gradual dose increase of axitinib is recommended, with patients carefully monitored for toxicity
Bosutinib	Ketoconazole	Rifampicin	Consider interruption or dose reduction of bosutinib if co-administration with a potent CYP3A inhibitor is necessary Avoid concomitant use of bosutinib with potent CYP3A inducers; increasing the dose of bosutinib is unlikely to sufficiently compensate for the loss of exposure
Cabozantinib	Ketoconazole	Rifampicin	Avoid co-administration of cabozantinib with CYP3A4 inhibitors/inducers
Ceritinib	Antivirals (e.g. ritonavir), macrolide antibiotics (e.g. telithromycin), antifungals (e.g. ketoconazole) and nefazodone	Rifampicin Carbamaze-pine Phenytoin Rifampicin St John's Wort	Avoid concurrent use of strong CYP3A4 inhibitors. If unavoidable, reduce the dose by approximately one third (rounded to the nearest 150 mg dosage strength) After discontinuation of a strong CYP3A4 inhibitor resume the dose that was taken prior to initiating the strong CYP3A4 inhibitor Avoid concurrent use of strong CYP3A inducers
Crizotinib	Ketoconazole	Rifampicin	Extreme caution should be taken if co-administration with a CYP3A4 inhibitor is unavoidable, the crizotinib dose should be lowered, and toxicity must be monitored If co-administration with a CYP3A4 inducer is unavoidable increase crizotinib dose gradually and monitor toxicity to obtain optimum effectiveness
Dabrafenib	Ketoconazole	-	If co-adminstration of dabrafenib with strong inhibitors/inducers of CYP3A4 is unavoidable, monitor patients closely for adverse reactions (with strong inhibitors) or loss of efficacy (with strong inducers)

DDI, drug-drug interaction

References

1. Food and Drug Administration. 2015. http://www.fda.gov/
2. European Medicines Agency. 2015. http://www.ema.europa.eu/ema/

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Kinase Inhibitor	CYP3A4 Inhibitor Drug(s)	CYP3A4 Inducer Drug(s)	Recommendations on how DDIs can be managed
Dasatinib	-	Rifampicin	If co-administration is unavoidable, monitor patients closely for toxicity and consider reducing dasatinib dose (from 100 to 20 mg/day, or from 140 to 40 mg/day) with potent CYP3A4 inhibitors, or increasing dasatinib dose with CYP3A4 inducers
Erlotinib	Ketoconazole	Rifampicin	Reduce erlotinib dose by 50-mg decrements if severe reactions occur with concomitant use of strong CYP3A4 inhibitors If co-administration with CYP3A4 inducers is unavoidable increase the erlotinib dose by 50-mg increments at 2-week intervals to a maximum of 450 mg
Gefitinib	Itraconazole	Rifampicin	Closely monitor patients for adverse reactions if gefitinib is co-administered with a CYP3A4 inhibitor
Ibrutinib	Ketoconazole	Rifampicin	Ibrutinib dose should be reduced to 140 mg once daily or withheld for up to 7 days when used concomitantly with strong CYP3A4 inhibitors If a strong CYP3A4 inducer must be used, patients must be monitored closely for lack of efficacy
Idelalisib	Ketoconazole	Rifampicin Phenytoin St. John's Wort Carbamazepine	Avoid coadministration with strong CYP3A4 inducers If patients are taking strong CYP3A inhibitors monitor for signs of toxicity Please see the idelasib summary of product characteristics and presecribing information for an extensive of products that are CYP3A4 substrates
Imatinib	Ketoconazole	Rifampicin	Consider decreasing the dose of imatinib to 300 mg/24 hours if co-administering with strong CYP3A4 inhibitors If co-administration of imatinib and a strong CYP3A4 inducer is needed, the imatinib dose should be increased to 600−700 mg/24 hours
Lapatinib	Ketoconazole	Carbamazepine	If co-administration of a strong CYP3A4 inhibitor is unavoidable, lapatinib dose should be reduced to 500 mg/day If co-administration of a strong CYP3A4 inducer is unavoidable, the dose of lapatinib should be titrated gradually from 1250 mg/day up to 4500 mg/day (HER2-positive metastatic breast cancer indication) or from 1500 mg/day up to 5500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability
Lenvatinib	Ketoconazole	Rifamipicin	No dose adjustment needed with coadministered with CYP3A4 inhibitors and inducers

DDI, drug-drug interaction

References

1. Food and Drug Administration. 2015. http://www.fda.gov/
2. European Medicines Agency. 2015. http://www.ema.europa.eu/ema/

CYP3A4 Inhibitor/Inducer Drug-drug Interactions - All Kinase Inhibitors[1,2]

Kinase Inhibitor	CYP3A4 Inhibitor Drug(s)	CYP3A4 Inducer Drug(s)	Recommendations on how DDIs can be managed
Nilotinib	Ketoconazole	Rifampicin	If administration of a strong CYP3A4 inhibitor is required, it is recommended that nilotinib therapy be interrupted if possible, otherwise close monitoring for prolongation of the QT interval is indicated In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected
Nintedanib	Ketoconazole	Rifampicin	In case of concomitant use of CYP3A4 inhibitors, patients should be closely monitored for tolerability, and adverse reactions managed with interruption, dose reduction (to 100 mg twice daily), or discontinuation of nintedanib Avoid co-administration of nintedanib with CYP3A4 inducers
Pazopanib	Ketoconazole	-	If co-administration of strong CYP3A4 inhibitors is warranted, reduce the dose of pazopanib to 400 mg In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected
Ponatinib	Ketoconazole	Rifampicin	If co-administration with a strong CYP3A4 inhibitor is warranted, reduce the starting dose of ponatinib to 30 mg once daily In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be selected
Regorafenib	-	-	If co-administration with a strong CYP3A4 inhibitor cannot be avoided, monitor regorafenib toxicity; dose adjustments are highly recommended If co-administration with a strong CYP3A4 inducers cannot be avoided, increase the regorafenib dose gradually and monitor toxicity
Ruxolitinib	Ketoconazole	Rifampicin	If co-administration with a strong CYP3A4 inhibitor cannot be avoided, ruxolitinib dose should be reduced by approximately 50%, with twice-daily administration; ruxolitinib interruption or discontinuation should also be considered If co-administration with a strong CYP3A4 inducer cannot be avoided, ruxolitinib dose should be titrated (increase by a maximum of 5 mg twice daily) based on safety and efficacy
Sorafenib	-	Rifampicin	Consider increasing the dose of sorafenib to 1,000 mg/24 hours if co-administering with rifampicin

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References

1. Food and Drug Administration. 2015. http://www.fda.gov/
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Kinase Inhibitor	CYP3A4 Inhibitor Drug(s)	CYP3A4 Inducer Drug(s)	Recommendations on how DDIs can be managed
Sunitinib	-	-	If co-administration with a strong CYP3A4 inhibitor cannot be avoided, consider reducing the sunitinib dose to a minimum of 37.5 mg daily for GIST and mRCC or 25 mg daily for pNET, based on careful monitoring of tolerability If co-administration with a CYP3A4 inducer is necessary, consider increasing the sunitinib dose in 12.5-mg increments (up to 87.5 mg/day for GIST and mRCC, or 62.5 mg/day for pNET), based on careful monitoring of tolerability
Trametinib	-	-	Trametinib is not a substrate of CYP enzymes or of P-gp. Trametinib is deacetylated via hydrolytic enzymes which are not generally associated with drug interaction risk
Vandetanib		Rifampicin	Vandetanib can be co-administered with CYP3A4 inhibitors if administered with caution Co-administration of vandetanib with potent CYP3A4 inducers is not recommended
Vemurafenib	-	-	Caution should be taken when coadministering vemurafenib with CYP3A4 inhibitors/inducers as there are currently no data on this DDI

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References

1. Food and Drug Administration. 2015. http://www.fda.gov/
2. European Medicines Agency. 2015. http://www.ema.europa.eu/ema/