

Drug Administration and Grapefruit

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Date of Revision: September 2019

The following is an overview of drug administration and grapefruit consumption. This information is not intended to present a comprehensive review; the reader is therefore encouraged to seek additional and confirmatory information.

Table 1 outlines the known and predicted effects of grapefruit consumption on the pharmacokinetics and pharmacodynamics of drugs, as well as management options. The information is based on product monographs in CPS and the references listed at the conclusion of this document. If a drug is not listed in the table, there may be no information or inconclusive information about the interaction. The recommendations in the table are not absolute; interpretation of the information requires clinical judgment and evaluation of the interaction. Where possible, the table provides potential alternative drugs that are known or predicted not to interact. These are intended as a guide only as appropriateness of the potential alternative drugs listed is dependent on the condition being treated and individual patient factors.

Grapefruit acts as an irreversible inhibitor of the drug metabolizing enzyme CYP3A4, mainly in the small intestine and to a much lesser extent in the liver, to increase the systemic concentration of drugs. The active constituents in grapefruit are furanocoumarins. Furanocoumarins are not found in sweet orange juice and therefore no interaction occurs; however, they are present in bitter (Seville) orange, lime and pomelo, which also cause the effect. A single quantity of 200 mL of grapefruit juice can cause a significant pharmacokinetic interaction. Repeated consumption of a normal amount of grapefruit during the day can enhance the magnitude of the interaction. Since there is prolonged inhibitory effect on intestinal CYP3A4-mediated drug metabolism, separating administration of drug from ingestion of grapefruit, even by many hours, will not prevent an interaction. Moreover, the magnitude of the interaction is markedly variable among individuals and cannot be predicted prior to exposure. Although most studies have used grapefruit juice prepared from frozen concentrate, all forms of grapefruit (fresh juice and whole fruit) have the potential to inactivate intestinal CYP3A4 activity.^{[1][2][3][4][5][6][7]}

Grapefruit-affected medications meet 3 essential criteria: 1) oral route of administration (little or no effect observed with parenterally administered drugs) 2) very low (<10%) to intermediate (30%–70%) intrinsic oral bioavailability and 3) extensive metabolism by CYP3A4.

The clinical significance of any particular grapefruit-drug interaction is mainly dependent on the seriousness of the dose-related drug toxicity and the extent of increase in the systemic drug concentration. Medications with serious toxicities (e.g., torsades de pointes, complete heart block, rhabdomyolysis, nephrotoxicity, myelotoxicity and respiratory depression) as well as medications used to treat serious conditions where the interaction might result in clinically significant loss of efficacy are indicated in **underlined bold** type in Table 1. Medications with lower inherent oral bioavailability have the possibility for greater increase in systemic drug concentration. Drugs with very low inherent bioavailability can have a pharmacokinetic interaction with grapefruit that is analogous to consuming several times the dose ingested without grapefruit. In most cases, the mean increase in oral bioavailability is indicated in the table as modest (<50% increase), moderate (50%–100% increase) or marked (>100% increase).

Patients over 45 years of age are the prime purchasers of grapefruit and are commonly prescribed interacting drugs. Thus, they are a population with substantial exposure to the combination. Additionally, individuals over 70 years of age are particularly vulnerable, as they may have a pronounced pharmacokinetic interaction as well as decreased capacity to compensate for excessive systemic drug concentrations. Empirically avoid grapefruit and other interacting citrus fruits in older individuals if they are taking a medication with potentially serious toxicity and low inherent bioavailability (possibility of a marked increase in systemic drug concentration) until the combination is proven safe. Employ an alternative medication known not to interact with grapefruit whenever possible.

Published case reports of grapefruit-associated drug overdose/toxicity generally occurred in patients on a stabilized drug regimen who added grapefruit to their diet on a regular basis. These adverse events happened after concomitant drug and grapefruit ingestion for several days and were associated with usual or high amounts of grapefruit consumption.

A flow diagram that provides a comprehensive and systematic approach for predicting clinical relevance of grapefruit-drug interactions and recommendations for management is available.^[8]

Cautionary statements regarding consumption of other fruits or foods with grapefruit-affected drugs are included in the table where appropriate, based on pharmacokinetic interactions documented in controlled clinical studies. These include Seville orange,^{[9][10]} lime^[11] and pomelo.^[12] Pomegranate, coffee, cranberry, lemon, star fruit, grape and other fruits are not included. Although pomegranate juice and coffee substantially inhibited in vitro CYP3A4 activity, both showed no effect in clinical drug interaction studies.^{[13][14][15][16]} Cranberry juice demonstrated no or very modest clinical interaction.^{[17][18][19]} Lemon juice is also without a clinical effect.^[20] Star fruit, grape and a range of other fruits currently appear to have been identified based only on in vitro or in vivo animal data.

Grapefruit, orange and/or apple juices can also act by a different mechanism to have the opposite effect, i.e., decreased absorption of some drugs. Flavonoid-mediated inhibition of the intestinal drug uptake transporter organic anion transporting polypeptide 1A2 (OATP1A2) appears to be involved. This interaction has the potential to occur in patients who take their medication with a fruit juice but may be avoided with an interval of 4 hours between consumption of juice and administration of drug.^{[21][22][23][24][25]} Research shows that grapefruit may also inhibit the intestinal uptake transporter OATP2B1.^[26] Further studies are needed to establish significance of these interactions. The mean decrease in oral bioavailability is indicated in Table 1 as modest (20%–30% decrease), moderate (>30%–50% decrease) and marked (>50% decrease).

Table 1: Drug Administration and Grapefruit

Drug ^[a]	Grapefruit Effect	Management
abemaciclib	<ul style="list-style-type: none"> Manufacturer states that grapefruit, grapefruit juice and products containing grapefruit extract should be avoided.^[27] Abemaciclib is primarily eliminated by CYP3A4 metabolism and has a mean absolute oral bioavailability of 45%.^[27] Co-administration of a CYP3A inhibitor (clarithromycin) resulted in a 3.4-fold increase in the plasma exposure of abemaciclib.^[27] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for venous thromboembolism, neutropenia, hepatotoxicity, diarrhea.
aliskiren	<ul style="list-style-type: none"> Study in healthy subjects; markedly reduced aliskiren C_{max} and AUC likely due to decreased systemic bioavailability via OATP2B1 and/or OATP1A2 inhibition.^{[28][29]} Study in healthy subjects; orange juice and apple juice markedly reduced C_{max} and AUC likely due to decreased systemic bioavailability via OATP2B1 inhibition.^[29] 	<ul style="list-style-type: none"> Avoid consumption of grapefruit, orange or apple juice while taking aliskiren. Administer aliskiren with a glass of water on an empty stomach. If grapefruit, orange or apple juice consumed during drug therapy, clinical monitoring required, especially for lack of efficacy.
amiodarone	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased amiodarone AUC and C_{max}.^[30] Case report of prolonged QT_c interval with associated torsades de pointes following consumption of amiodarone with large amounts of grapefruit juice.^[31] Manufacturer states that grapefruit juice should not be taken during treatment with oral amiodarone.^[32] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for bradycardia, prolonged QT_c interval, torsades de pointes, elevation of liver enzymes. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—sotalol.
apixaban	<ul style="list-style-type: none"> Predicted to increase systemic apixaban concentration moderately.^[6] Manufacturer states that substances moderately inhibiting the apixaban elimination pathways, CYP3A4 and/or Pgp are expected to increase apixaban concentration.^[33] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for symptoms of bleeding, e.g., hematoma, hemorrhage. Potential alternative drugs (depending on indication, patient factors): known not to interact—warfarin; predicted not to interact—dabigatran, edoxaban.
aprepitant	<ul style="list-style-type: none"> Predicted to increase systemic aprepitant concentration moderately.^[6] Manufacturer states that concomitant administration of a CYP3A4 inhibitor should be approached with caution.^[34] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for drowsiness, headache.
atazanavir	<ul style="list-style-type: none"> Manufacturer states that combination with drugs that inhibit CYP3A4 may increase plasma atazanavir concentration.^[35] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction.

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
		<ul style="list-style-type: none"> If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for jaundice and cardiac conduction abnormalities including PR prolongation and AV block, as well as QT_c prolongation and torsades de pointes.
atenolol	<ul style="list-style-type: none"> Study in healthy subjects; orange juice moderately reduced atenolol AUC and C_{max} likely due to decreased systemic bioavailability via OATP1A2 inhibition.^[36] Interaction with grapefruit inferred from studies with orange juice. 	<ul style="list-style-type: none"> Avoid consumption of grapefruit or orange juice within 4 h of intake of atenolol. If grapefruit consumed during drug therapy, clinical monitoring required, especially for lack of efficacy. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—metoprolol.
atorvastatin	<ul style="list-style-type: none"> Studies in healthy subjects; markedly increased atorvastatin AUC and C_{max}.^{[37][38][39]} Case reports of rhabdomyolysis with consumption of normal amounts of grapefruit.^{[40][41]} Manufacturer states that consumption of excessive grapefruit juice with atorvastatin is not recommended.^[42] Atorvastatin is likely less affected than lovastatin and simvastatin. Administration of the moderate CYP3A4 inhibitors clarithromycin or erythromycin in patients taking atorvastatin, lovastatin or simvastatin has been found to be associated with higher risk of hospitalization due to rhabdomyolysis or acute kidney injury and all-cause mortality in older adults.^[43] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for myopathy, rhabdomyolysis, acute renal failure. Potential alternative drugs (depending on indication, patient factors): known not to interact—pravastatin; predicted not to interact—fluvastatin, rosuvastatin.
axitinib	<ul style="list-style-type: none"> Predicted to increase systemic axitinib concentration modestly. Manufacturer states that grapefruit, grapefruit juice and products containing grapefruit extract may increase axitinib plasma concentration and should be avoided.^[44] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for hypertension and hypertensive crisis, thrombotic events, cardiac dysfunction, gastrointestinal hemorrhage.
benzodiazepines	see diazepam, triazolam	
bilastine	<ul style="list-style-type: none"> Manufacturer indicates that concomitant grapefruit juice ingestion decreased bilastine bioavailability by approximately 30% through inhibition of OATP1A2.^[45] 	<ul style="list-style-type: none"> Avoid consumption of grapefruit or orange juice within 4 h of intake of bilastine. If grapefruit consumed during drug therapy, clinical monitoring required, especially for lack of efficacy. Potential alternative drugs (depending on indication, patient factors): known not to interact—desloratadine.^[46]
bosutinib	<ul style="list-style-type: none"> Manufacturer states that products and juices containing grapefruit or other fruits that are known to inhibit CYP3A4 should be avoided at all times.^[47] See the introductory text of this document for a discussion of other fruits/foods that may be reported to inhibit CYP3A4. 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes, gastrointestinal and hepatic toxicity, cardiac failure, fluid retention (e.g., pulmonary edema, pleural and pericardial effusion), hemorrhage.
brigatinib	<ul style="list-style-type: none"> Manufacturer states that grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided.^[48] Manufacturer states that a strong CYP3A4 inhibitor (itraconazole) increased brigatinib C_{max} by 21% and increased AUC by 101% (2-fold).^[49] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for interstitial lung disease, hypertension, bradycardia, hyperglycemia, and elevation of creatine phosphokinase, hepatic enzymes, lipase or amylase.
budesonide (oral)	<ul style="list-style-type: none"> Study in healthy subjects; markedly increased budesonide AUC and C_{max}.^[49] Manufacturer states that ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration.^[50] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for hyperglycemia, Cushingoid features.
buprenorphine (buccal)	<ul style="list-style-type: none"> Manufacturer states that grapefruit juice may lead to elevated plasma concentrations of buprenorphine, with an increase in dose-related toxicity.^[51] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolongation of QT_c interval, torsades de pointes, respiratory depression.
bupirone	<ul style="list-style-type: none"> Study in healthy subjects; markedly increased bupirone AUC and C_{max}.^[52] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for sedation, psychomotor impairment. Potential alternative drugs (depending on indication, patient factors): known not to interact—alprazolam; predicted not to interact—oxazepam, temazepam.
cabozantinib	<ul style="list-style-type: none"> Manufacturer states that foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 should not be consumed during treatment.^[53] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for thromboembolism, hypertension and hypertensive crisis, prolongation of the QT_c interval, torsades de pointes, serious GI perforations and fistulas, severe hemorrhage, hepatotoxicity.
calcium channel blockers	see diltiazem, felodipine, nifedipine, nimodipine, verapamil	
cannabis (oral)	<ul style="list-style-type: none"> Theoretically, grapefruit juice may increase serum concentrations of cannabis components, including delta⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD).^[54] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for sedation, dizziness, postural hypotension, acute psychosis, anxiety episodes, confusion, psychomotor impairment.

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
carbamazepine	<ul style="list-style-type: none"> Study in epileptic patients; modestly increased carbamazepine AUC, C_{max} and trough concentration.^[55] Manufacturer states that consumption of grapefruit juice or grapefruit can increase the effect of carbamazepine.^[56] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for drowsiness, dizziness, headache, ataxia, diplopia, nausea, vomiting. Potential alternative drugs (depending on indication, patient factors): known not to interact—phenytoin; predicted not to interact—clonazepam.
carvedilol	<ul style="list-style-type: none"> Study in healthy subjects; modestly increased carvedilol AUC.^[57] 	<ul style="list-style-type: none"> If grapefruit consumed during drug therapy, clinical monitoring required, especially for low blood pressure, bradycardia.
ciprofloxacin	<ul style="list-style-type: none"> Study in healthy subjects; orange juice modestly reduced ciprofloxacin AUC and C_{max} likely due to decreased systemic bioavailability via OATP1A2 inhibition.^[58] Interaction with grapefruit inferred from studies with orange juice. 	<ul style="list-style-type: none"> Avoid consumption of grapefruit or orange juice within 4 h of intake of ciprofloxacin. If grapefruit consumed during drug therapy, clinical monitoring required, especially for lack of efficacy.
<u>clomipramine</u>	<ul style="list-style-type: none"> Predicted to increase systemic clomipramine concentration modestly.^[59] Manufacturer states that caution is required when prescribing clomipramine to patients taking grapefruit and grapefruit juice.^[60] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolongation of QT_c interval, torsades de pointes, drowsiness, hypotension, respiratory depression, anticholinergic effects, agitation.
<u>clopidogrel</u>	<ul style="list-style-type: none"> Studies in healthy subjects; reduced antiplatelet activity and markedly decreased formation of active metabolite.^{[61][62]} 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required for lack of efficacy. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—ASA.
colchicine	<ul style="list-style-type: none"> Study in healthy subjects; negligible change in pharmacokinetic parameters of colchicine.^[63] Case report of near fatal colchicine toxicity in a child following high chronic consumption of grapefruit juice.^[64] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for vomiting, alopecia, pancytopenia.
<u>crizotinib</u>	<ul style="list-style-type: none"> Predicted to increase systemic crizotinib concentration moderately.^[6] Manufacturer states that ingestion of grapefruit while on crizotinib therapy should be avoided.^[65] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for myelosuppression, bradycardia, hepatotoxicity, prolongation of QT_c interval, torsades de pointes.
<u>cyclophosphamide</u>	<ul style="list-style-type: none"> May impair activation of cyclophosphamide to its active metabolites resulting in reduced effectiveness.^[6] Manufacturer recommends avoiding concomitant administration with grapefruit juice.^[66] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for lack of efficacy.
<u>cyclosporine</u>	<ul style="list-style-type: none"> Several studies in healthy subjects and transplant patients; moderately increased cyclosporine AUC and C_{max}.^{[67][68]} Manufacturer states that grapefruit and grapefruit juice should be avoided with oral cyclosporine.^[69] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for nephrotoxicity, hepatotoxicity, excessive immunosuppression.
darifenacin	<ul style="list-style-type: none"> Predicted to increase systemic darifenacin concentration markedly.^{[6][70]} 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, monitor for excessive antimuscarinic effects, e.g., dry mouth, constipation, acute urinary retention.
<u>dasatinib</u>	<ul style="list-style-type: none"> Predicted to increase systemic dasatinib concentration.^[6] Manufacturer states that CYP3A4 inhibitors may increase dasatinib drug levels and should be avoided.^[71] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for myelosuppression, bleeding, prolongation of QT_c interval, torsades de pointes.
<u>dextromethorphan</u>	<ul style="list-style-type: none"> Study in healthy subjects; grapefruit and Seville orange juice markedly increased dextromethorphan AUC and C_{max}.^[10] 	<ul style="list-style-type: none"> Grapefruit and Seville orange contraindicated. Lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for severe dizziness, somnolence, anxiety, hallucinations.
diazepam	<ul style="list-style-type: none"> Study in healthy subjects; markedly increased diazepam AUC and C_{max}.^[72] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for increased sedation. Potential alternative drugs (depending on indication, patient factors): known not to interact—alprazolam; predicted not to interact—lorazepam, oxazepam, temazepam.
dienogest	<ul style="list-style-type: none"> Manufacturer states that grapefruit juice may increase plasma levels of progestogens and result in undesirable effects.^[73] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for headache, breast discomfort, depressed mood, acne.
diltiazem	<ul style="list-style-type: none"> Manufacturer states that grapefruit may increase the plasma concentration of orally administered diltiazem in some patients, and that grapefruit and grapefruit juice should be avoided if an interaction is suspected.^[74] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for headache, irregular heartbeat, edema, unexplained weight gain, chest pain.
docetaxel	<ul style="list-style-type: none"> Case report of reduced elimination of intravenous docetaxel with grapefruit juice.^[75] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for myelotoxicity.

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
domperidone	<ul style="list-style-type: none"> Predicted to increase systemic domperidone concentration markedly.^[6] Manufacturer states that caution should be exercised if domperidone is used with CYP3A4 inhibitors, as they may increase plasma levels of domperidone.^[76] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—metoclopramide.
dronedarone	<ul style="list-style-type: none"> Study in healthy subjects; markedly increased dronedarone AUC and C_{max}.^[77] Manufacturer states that patients should be warned to avoid grapefruit juice beverages while taking dronedarone.^[77] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—sotalol.
elbasvir/grazoprevir combination	<ul style="list-style-type: none"> Manufacturer states that ketoconazole (a strong CYP3A4 inhibitor) increased the AUC and C_{max} of elbasvir 1.8-fold and 1.3-fold respectively and the AUC and C_{max} of grazoprevir 3-fold and 1.3-fold respectively, and that strong CYP3A inhibitors are not recommended.^[78] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for decreased hemoglobin, elevated ALT, elevated bilirubin, other signs of hepatotoxicity.
epplerenone	<ul style="list-style-type: none"> Study in healthy subjects; modestly increased epplerenone AUC and C_{max}.^[79] Manufacturer states that grapefruit juice caused approximately 25% increase in exposure and that caution should be used with mild and moderate CYP3A4 inhibitors.^[79] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for hyperkalemia, serious arrhythmias, hypotension, abnormal renal function, dizziness. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—spironolactone.
erlotinib	<ul style="list-style-type: none"> Predicted to increase systemic erlotinib concentration moderately.^{[6][80]} 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for myelosuppression, bleeding.
erythromycin	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased erythromycin C_{max} and AUC.^[81] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for gastrointestinal disturbances, prolonged QT_c interval, torsades de pointes, deafness. Potential alternative drugs (depending on indication, patient factors): known not to interact—clarithromycin.
ethinyl estradiol	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased ethinyl estradiol AUC and C_{max}.^[82] Case report of massive deep vein thrombosis following grapefruit consumption for 3 days.^[83] One epidemiological study showed correlation with increased breast cancer risk^[84] but this was not confirmed in a follow-up investigation.^[85] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for hypercoagulability.
etoposide	<ul style="list-style-type: none"> Study in cancer patients; markedly reduced etoposide AUC and C_{max} likely due to decreased systemic bioavailability via OATP1A2 inhibition.^[86] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Apple juice and orange juice may have similar effects. If grapefruit consumed during drug therapy, caution and clinical monitoring required for lack of efficacy of etoposide.
etravirine	<ul style="list-style-type: none"> Predicted to increase etravirine systemic concentration.^[6] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for skin rash.
everolimus	<ul style="list-style-type: none"> Predicted to increase everolimus systemic concentration markedly.^[6] Manufacturer advises that grapefruit and grapefruit juice should be avoided during everolimus therapy.^[87] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for renal, hematopoietic, gastrointestinal, cardiac toxicities.
felodipine	<ul style="list-style-type: none"> Studies in healthy subjects and hypertensive patients; markedly increased felodipine AUC and C_{max}.^{[88][89][90]} Manufacturer states that consumption of grapefruit juice prior to or during treatment with felodipine should be avoided.^[91] Administration of the moderate CYP3A4 inhibitors clarithromycin or erythromycin in patients taking dihydropyridine calcium channel blockers (amlodipine, felodipine, nifedipine) has been found to be associated with higher risk of hospitalization due to hypotension, shock or acute kidney injury in older adults.^{[92][93]} 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for flushing, headache, peripheral edema, hypotension.
fentanyl (sublingual)	<ul style="list-style-type: none"> Predicted to increase fentanyl systemic concentration moderately.^[6] Manufacturers warn that the oral bioavailability of swallowed fentanyl may be increased, causing dangerously high plasma drug concentration and fatal respiratory depression.^[94] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for increased sedation, respiratory depression (e.g., shallow or decreased breathing), slow heart rate, small pupils. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—hydromorphone, morphine.
fesoterodine	<ul style="list-style-type: none"> Predicted to increase systemic concentration of the active form (metabolite) of fesoterodine moderately.^[6] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for possible excessive antimuscarinic effects, e.g., dry mouth, constipation, acute urinary retention.

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
fibanserin	<ul style="list-style-type: none"> Manufacturer states that concomitant use with moderate or strong inhibitors of CYP3A4 (including grapefruit) causes a significant increase in fibanserin concentration and is contraindicated.^[95] Fibanserin is primarily eliminated by CYP3A4 metabolism and has a mean absolute oral bioavailability of 33%.^[95] Ketoconazole increased AUC and C_{max} of fibanserin 4.5-fold and 1.8-fold respectively.^[95] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for dizziness, severe hypotension, syncope, CNS depression (fatigue, somnolence, sedation).
fexofenadine	<ul style="list-style-type: none"> Studies in healthy subjects; markedly lower fexofenadine AUC and C_{max} likely due to decreased systemic bioavailability via intestinal OATP1A2 and OATP2B1 inhibition.^{[13][21][22][23][24][25]} 	<ul style="list-style-type: none"> Avoid consumption of grapefruit within 4 h of intake of fexofenadine. Apple juice and orange juice had effects similar to those of grapefruit juice.^{[25][96][97]} If grapefruit consumed during drug therapy, monitor for lack of efficacy of fexofenadine. Potential alternative drugs (depending on indication, patient factors): known not to interact—desloratadine.^[46]
fluvoxamine	<ul style="list-style-type: none"> Studies in healthy male subjects; moderately increased fluvoxamine AUC and C_{max}.^[98] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for early signs or symptoms of serotonin syndrome, e.g., tremor, agitation, mental status changes, diarrhea. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—citalopram, escitalopram, paroxetine.
HMG-CoA reductase inhibitors	see atorvastatin, lovastatin, simvastatin	
ibrutinib	<ul style="list-style-type: none"> Manufacturer states that grapefruit and Seville orange must not be consumed during treatment.^[99] Manufacturer also reports that ketoconazole (a strong CYP3A4 inhibitor) increased C_{max} and AUC of ibrutinib 29-fold and 24-fold respectively.^[99] Manufacturer states that simulations with moderate CYP3A inhibitors (diltiazem, erythromycin) resulted in a 6-fold to 9-fold increase in the AUC of ibrutinib.^[99] One study found absolute oral bioavailability of ibrutinib to be 3.9% in a fasting state, 8.4% after a standard breakfast and 15.9% after 240 mL grapefruit juice on the previous evening and 30 min before dosing.^[100] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for atrial fibrillation, infection, fever, major hemorrhagic events, cytopenias, diarrhea.
imatinib	<ul style="list-style-type: none"> Predicted to increase imatinib systemic concentration modestly.^[6] Manufacturer recommends caution when administering with grapefruit juice because of concern for increased systemic imatinib concentration.^[101] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for heart failure, hemorrhage, fluid retention.
itraconazole	<ul style="list-style-type: none"> Studies in healthy subjects; variable effects including moderately decreased, unchanged and moderately increased itraconazole AUC and C_{max}.^{[102][103][104][105]} 	<ul style="list-style-type: none"> If grapefruit consumed during drug therapy, monitor patient for efficacy of itraconazole.
ivabradine	<ul style="list-style-type: none"> Manufacturer indicates that grapefruit increased ivabradine exposure >2-fold and should be avoided during treatment.^[106] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for bradycardia (including severe, with dizziness, fatigue, hypotension), prolonged QT_c interval, arrhythmias (including atrial fibrillation, ventricular fibrillation, torsades de pointes).
ivacaftor	<ul style="list-style-type: none"> Manufacturer indicates that grapefruit may increase plasma concentration of ivacaftor and that grapefruit and Seville orange should be avoided during treatment.^[107] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for headache, dizziness, upper respiratory tract infection, hepatic abnormalities, hypoglycemia.
ketamine (oral)	<ul style="list-style-type: none"> Study in healthy subjects; markedly increased ketamine AUC and C_{max}.^[108] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for hallucinations and loss of coordination, motor skills. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—hydromorphone, morphine.
lapatinib	<ul style="list-style-type: none"> Predicted to increase systemic lapatinib concentration.^[6] Manufacturer states that concomitant treatment with inhibitors of CYP3A4, including grapefruit juice, should be avoided.^[109] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for hepatotoxicity, decreased left ventricular ejection fraction, QT_c interval prolongation, torsades de pointes, diarrhea.
loperamide	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased AUC and C_{max} of loperamide. However, administration of usual dose (16 mg/day) did not produce miosis (indicator of opioid CNS effect) with or without grapefruit juice.^[110] Loperamide at a high dose (70–100 mg/day) has been used to alleviate opioid withdrawal symptoms.^[111] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, monitor for opioid CNS effects, e.g., drowsiness, respiratory depression, small pupils.
lorlatinib	<ul style="list-style-type: none"> Manufacturer states that taking lorlatinib with foods that are strong CYP3A inhibitors (e.g., grapefruit products) may increase lorlatinib plasma concentrations and should be avoided.^[112] Lorlatinib is eliminated primarily by CYP3A4 and UGT1A4 metabolism and has a mean absolute oral bioavailability of 81%.^[112] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, monitor for PR interval prolongation and AV block, increased serum cholesterol and triglycerides, CNS effects (cognitive, mood, speech), hallucinations.

(cont'd)

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
losartan	<ul style="list-style-type: none"> Study in healthy subjects; moderately decreased AUC and C_{max} of major active metabolite of losartan.^[113] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, monitor for decreased efficacy, e.g., increased blood pressure.
<u>lovastatin</u>	<ul style="list-style-type: none"> Studies in healthy subjects; markedly increased AUC and C_{max} of major active metabolite of lovastatin.^[114] Manufacturer states that grapefruit juice should be avoided during lovastatin therapy.^[115] Lovastatin and simvastatin are likely more affected than atorvastatin. Administration of the moderate CYP3A4 inhibitors clarithromycin or erythromycin in patients taking atorvastatin, lovastatin or simvastatin has been found to be associated with higher risk of hospitalization due to rhabdomyolysis or acute kidney injury and all-cause mortality in older adults.^[43] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for myopathy, rhabdomyolysis, acute renal failure. Potential alternative drugs (depending on indication, patient factors): known not to interact—pravastatin; predicted not to interact—fluvastatin, rosuvastatin.
<u>lurasidone</u>	<ul style="list-style-type: none"> Predicted to increase lurasidone systemic concentration markedly.^[6] Manufacturer states that grapefruit, grapefruit juice and products containing grapefruit extract should be avoided during treatment with lurasidone.^[116] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for orthostatic hypotension, syncope, prolongation of QT_c interval, torsades de pointes. Potential alternative drugs (depending on indication, patient factors): known not to interact—haloperidol; predicted not to interact—olanzapine, risperidone.
<u>maraviroc</u>	<ul style="list-style-type: none"> Predicted to increase systemic maraviroc concentration markedly.^[6] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for postural hypotension, syncope. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—enfuvirtide.
methadone	<ul style="list-style-type: none"> Study in patients undergoing methadone maintenance treatment; modestly increased AUC for methadone.^[117] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for sedation, respiratory depression (e.g., shallow or decreased breathing), slow heart rate, small pupils.
methylprednisolone (oral)	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased methylprednisolone AUC and C_{max}.^[118] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for hyperglycemia, Cushingoid features. Potential alternative drugs (depending on indication, patient factors): known not to interact—prednisone.
<u>midostaurin</u>	<ul style="list-style-type: none"> Manufacturer states that grapefruit, grapefruit juice and products containing grapefruit extract may increase midostaurin plasma concentration and should be avoided.^[119] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes, cardiac failure, febrile neutropenia, symptoms of interstitial lung disease and pneumonitis.
mifepristone	<ul style="list-style-type: none"> Manufacturer states that grapefruit juice may inhibit mifepristone's metabolism, increasing its serum levels.^[120] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for prolonged or heavy vaginal bleeding.
<u>mirabegron</u>	<ul style="list-style-type: none"> Predicted to increase systemic mirabegron concentration moderately.^[121] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, (especially in females) for prolonged QT_c interval, torsades de pointes, hypertension, elevated heart rate.
<u>naloxegol</u>	<ul style="list-style-type: none"> Manufacturer states that consumption of grapefruit or grapefruit juice while taking naloxegol should be avoided. Manufacturer also states that ketoconazole (a strong CYP3A4 inhibitor) is contraindicated in patients taking naloxegol as it increased naloxegol AUC and C_{max} 12.9-fold and 9.6-fold respectively.^[122] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for opioid withdrawal syndrome.
<u>netupitant</u>	<ul style="list-style-type: none"> Manufacturer states that consumption of grapefruit or grapefruit juice should be avoided during treatment with netupitant.^[123] Manufacturer states that ketoconazole and erythromycin (CYP3A4 inhibitors) caused a 1.8-fold and 1.3-fold increase respectively in netupitant AUC.^[123] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes, psychomotor impairment, serotonin syndrome or neuroleptic malignant syndrome-like events.
nifedipine	<ul style="list-style-type: none"> Studies in healthy subjects; moderately increased AUC and C_{max}.^{[88][124]} Case reports of peripheral edema and hypotension.^{[125][126][127]} Manufacturer states that the administration of nifedipine with grapefruit juice should be avoided.^[128] Administration of the moderate CYP3A4 inhibitors clarithromycin or erythromycin in patients taking dihydropyridine calcium channel blockers (amlodipine, felodipine, nifedipine) has been found to be associated with higher risk of hospitalization due to hypotension, shock or acute kidney injury in older adults.^{[92][93]} 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for flushing, headache, peripheral edema, hypotension.
<u>nilotinib</u>	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased nilotinib AUC and C_{max}.^[129] Manufacturer states that products containing grapefruit and similar fruits that are known to inhibit CYP3A4 should be avoided.^[130] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction.

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
		<ul style="list-style-type: none"> If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes, neutropenia, thrombocytopenia.
nimodipine	<ul style="list-style-type: none"> Study in healthy subjects and hypertensive patients; moderately increased AUC and C_{max}.^[131] Manufacturer states that consumption of grapefruit juice prior to or during treatment with nimodipine should be avoided.^[132] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for flushing, headache, peripheral edema, hypotension.
nintedanib	<ul style="list-style-type: none"> Manufacturer indicates that grapefruit may increase plasma concentration of nintedanib and that this fruit should be avoided during treatment. Manufacturer also states that ketoconazole (a strong CYP3A4 inhibitor) increased nintedanib C_{max} by 1.8-fold and AUC by 1.6-fold.^[133] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for more frequent adverse events (diarrhea, nausea, vomiting, abdominal pain, elevations in liver enzymes and bilirubin) as well as arterial thromboembolic events (myocardial infarction), gastrointestinal perforation and hemorrhage.
olaparib	<ul style="list-style-type: none"> Manufacturer states that patients should avoid grapefruit and other fruits that are known to inhibit CYP3A4, as these may increase olaparib plasma concentration.^[134] See the introductory text of this document for a discussion of other fruits/foods that may be reported to inhibit CYP3A4. 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for anemia, neutropenia, thrombocytopenia and lymphopenia.
osimertinib	<ul style="list-style-type: none"> Manufacturer states that a strong CYP3A4 inhibitor (itraconazole) decreased osimertinib C_{max} by approximately 20% and increased AUC by approximately 24%. Because of the seriousness of the overdose toxicity and potential for high interindividual variability in the extent of the pharmacokinetic changes, the interaction with grapefruit may be clinically relevant in certain patients.^[135] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for prolonged QT_c interval and torsades de pointes.
oxycodone	<ul style="list-style-type: none"> Study of healthy subjects; moderately increased oxycodone AUC and C_{max} and modestly impaired mental function.^[136] Manufacturer states that grapefruit juice may lead to an increase in oxycodone plasma concentration, which would result in enhanced or prolonged opioid effects.^[137] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for sedation, respiratory depression (e.g., shallow or decreased breathing), slow heart rate, small pupils. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—hydromorphone, morphine.
palbociclib	<ul style="list-style-type: none"> Manufacturer states that grapefruit, grapefruit juice and products containing grapefruit extract may increase palbociclib plasma concentration and should be avoided.^[138] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for QT_c interval prolongation, torsades de pointes, myelosuppression, infection, pulmonary embolism.
pazopanib	<ul style="list-style-type: none"> Manufacturer advises avoidance of grapefruit and other foods known to affect CYP3A4 and Pgp activity during therapy because of concern for increased systemic pazopanib concentration.^[139] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for hepatotoxicity, hypertension, QT_c interval prolongation, torsades de pointes, arterial thrombotic events, hemorrhage, gastrointestinal perforation, fistula. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—sorafenib.
phosphodiesterase inhibitors	see sildenafil, tadalafil, vardenafil	
pimozide	<ul style="list-style-type: none"> Predicted to increase systemic pimozide concentration moderately.^{[6][140]} 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for torsades de pointes, extrapyramidal symptoms, hypotension. Potential alternative drugs (depending on indication, patient factors): known not to interact—haloperidol; predicted not to interact—olanzapine, risperidone.
pirfenidone	<ul style="list-style-type: none"> Study in healthy subjects; moderately decreased pirfenidone C_{max} possibly due to decreased systemic bioavailability via OATP1A2 inhibition.^[141] 	<ul style="list-style-type: none"> Avoid grapefruit or orange within 4 h of intake of pirfenidone. If grapefruit consumed during drug therapy, clinical monitoring required especially for lack of efficacy.
ponatinib	<ul style="list-style-type: none"> Manufacturer states that products containing grapefruit and other similar fruits that are known to inhibit CYP3A4 should be avoided at all times.^[142] See the introductory text of this document for a discussion of other fruits/foods that may be reported to inhibit CYP3A4. Coadministration with ketoconazole (a strong CYP3A4 inhibitor) resulted in ponatinib AUC and C_{max} values that were 78% and 47% higher respectively than those for ponatinib alone.^[143] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for serious adverse events (some fatal) including vascular occlusion (arterial and venous thrombosis), heart failure, hemorrhagic events, hepatotoxicity, myelosuppression.
prasugrel	<ul style="list-style-type: none"> May impair activation of prasugrel to its active metabolite, resulting in reduced effectiveness. One study in healthy subjects showed grapefruit juice modestly reduced AUC and moderately reduced C_{max} of the active metabolite; however, antiplatelet efficacy was reduced only slightly.^[144] 	<ul style="list-style-type: none"> If grapefruit consumed during drug therapy, clinical monitoring required, especially for lack of efficacy.
praziquantel	<ul style="list-style-type: none"> Study in healthy subjects; markedly increased praziquantel AUC and C_{max}.^[145] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for dizziness, headache, somnolence.

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
<u>primaquine</u>	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased primaquine AUC and C_{max}.^[146] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for myelotoxicity, e.g., agranulocytosis, leukopenia, leukocytosis. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—doxycycline.
propafenone	<ul style="list-style-type: none"> Predicted to increase systemic propafenone concentration markedly in 5–7% of population who are poor CYP2D6 metabolizers.^[6] Manufacturer states that patients should be closely monitored and the dose adjusted accordingly when propafenone is administered with grapefruit.^[147] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for bradycardia, conduction disorders (e.g., sinoatrial, atrioventricular or intraventricular block), proarrhythmic effects (e.g., tachycardia, ventricular fibrillation).
protease inhibitors	see saquinavir mesylate	
<u>quetiapine</u>	<ul style="list-style-type: none"> Predicted to increase systemic quetiapine concentration markedly.^{[6][148]} Manufacturer states that quetiapine exposure is increased with CYP3A4 inhibitors.^[149] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for dizziness, somnolence, hypotension, cerebrovascular events, tardive dyskinesia, suicidal thoughts or behaviours. Potential alternative drugs (depending on indication, patient factors): known not to interact—haloperidol; predicted not to interact—olanzapine, risperidone.
<u>quinidine</u>	<ul style="list-style-type: none"> Studies in healthy subjects; moderately increased quinidine AUC and C_{max}.^{[150][151]} 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes.
repaglinide	<ul style="list-style-type: none"> Study in healthy subjects; modestly increased repaglinide AUC and C_{max} but no major change in blood glucose.^[152] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, monitor for hypoglycemia. Potential alternative drugs (depending on indication, patient factors): known not to interact—glyburide; predicted not to interact—metformin, sitagliptin.
<u>ribociclib</u>	<ul style="list-style-type: none"> Manufacturer states that ribociclib should not be administered with grapefruit, grapefruit juice or grapefruit-containing products.^[153] Manufacturer states that ritonavir (a strong CYP3A4 inhibitor) increased ribociclib exposure in healthy adults by 3.21-fold.^[153] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes, thromboembolic events, hepatotoxicity, neutropenia.
<u>rilpivirine</u>	<ul style="list-style-type: none"> Manufacturer states that grapefruit and grapefruit juice should be avoided with rilpivirine.^[154] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—nevirapine.
rivaroxaban	<ul style="list-style-type: none"> Predicted to increase rivaroxaban systemic concentration modestly.^[6] Manufacturer states that inhibitors of CYP3A4 may result in changes in rivaroxaban exposure.^[155] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for bleeding. Potential alternative drugs (depending on indication, patient factors): known not to interact—warfarin; predicted not to interact—dabigatran, edoxaban.
<u>rupatadine</u>	<ul style="list-style-type: none"> Manufacturer states that grapefruit juice increased the systemic exposure to rupatadine by 3.5 times, that rupatadine has been associated with QT_c interval prolongation, that 1 event of torsades de pointes has been reported during postmarket use and that concomitant use of rupatadine is contraindicated in patients taking CYP3A4 inhibitors.^[156] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolonged QT_c interval, torsades de pointes, signs and symptoms of rhabdomyolysis (increased serum creatine kinase, myalgias, muscular weakness), tachycardia, atrial fibrillation, syncope. Potential alternative drugs (depending on indication, patient factors): known not to interact—desloratadine.^[146]
<u>ruxolitinib</u>	<ul style="list-style-type: none"> Manufacturer states that ketoconazole (a strong CYP3A4 inhibitor) increased the AUC of ruxolitinib by 91% and that the dose of ruxolitinib should be reduced to approximately 50% if used in combination with a strong CYP3A4 inhibitor. Manufacturer also states that erythromycin (a moderate CYP3A4 inhibitor) increased the AUC of ruxolitinib by 27% and that no dosage adjustment of ruxolitinib is recommended with a mild or moderate CYP3A4 inhibitor.^[157] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for hematological adverse reactions, including thrombocytopenia, anemia and neutropenia, decreased heart rate and prolongation of the PR interval. Bleeding (in some cases fatal) and serious infections (in some cases fatal) have been reported.
saquinavir mesylate	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased saquinavir AUC and C_{max}.^[158] 	<ul style="list-style-type: none"> Since saquinavir is generally well tolerated, clinical significance of interaction is unknown. Potential alternative drugs (depending on indication, patient factors): known not to interact—fosamprenavir, indinavir.
saxagliptin	<ul style="list-style-type: none"> Predicted to increase systemic saxagliptin concentration modestly.^[6] Manufacturer states that grapefruit may give rise to a modest increase in saxagliptin concentration.^[159] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, monitor for hypoglycemia. Potential alternative drugs (depending on indication, patient factors): known not to interact—glyburide; predicted not to interact—metformin, sitagliptin.
sertraline	<ul style="list-style-type: none"> Study in patients being treated for depression; modestly increased sertraline trough concentration.^[160] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction.

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
		<ul style="list-style-type: none"> If grapefruit consumed during drug therapy, clinical monitoring required, especially for early signs or symptoms of serotonin syndrome, e.g., tremor, agitation, mental status changes, diarrhea. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—citalopram, escitalopram, paroxetine.
sildenafil	<ul style="list-style-type: none"> Study in healthy men; moderately increased AUC and C_{max}.^[161] Manufacturer states that grapefruit juice may give rise to modest increases in plasma levels of sildenafil.^[162] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for hypotension.
silodosin	<ul style="list-style-type: none"> Predicted to increase silodosin systemic concentration moderately. Manufacturer states that silodosin should not be coadministered with potent inhibitors of CYP3A4.^[163] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for dizziness, weakness, syncope.
simvastatin	<ul style="list-style-type: none"> Studies in healthy subjects; markedly increased AUC and C_{max} of major active metabolite of simvastatin.^{[164][165][166]} Case report of rhabdomyolysis with consumption of normal amount of grapefruit.^[167] Manufacturer states that grapefruit juice should be avoided during simvastatin therapy.^[168] Simvastatin and lovastatin are more affected than atorvastatin. Administration of the moderate CYP3A4 inhibitors clarithromycin or erythromycin in patients taking atorvastatin, lovastatin or simvastatin has been found to be associated with higher risk of hospitalization due to rhabdomyolysis or acute kidney injury and all-cause mortality in older adults.^[43] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for myopathy, rhabdomyolysis, acute renal failure. Potential alternative drugs (depending on indication, patient factors): known not to interact—pravastatin; predicted not to interact—fluvastatin, rosuvastatin.
sirolimus	<ul style="list-style-type: none"> Predicted to increase systemic sirolimus concentration markedly.^[6] Manufacturer of Rapamune specifically recommends taking with either water or orange juice.^[169] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for thrombocytopenia, hyperlipidemia.
solifenacin	<ul style="list-style-type: none"> Predicted to increase solifenacin AUC and C_{max} modestly.^[6] Manufacturer recommends not exceeding a 5 mg daily dose of solifenacin when administered with potent CYP3A4 inhibitors.^[170] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolongation of QT_c interval, dry mouth, constipation.
stiripentol	<ul style="list-style-type: none"> Manufacturer states that stiripentol degrades rapidly in an acidic environment and should not be taken with fruit juices. Manufacturer states that the impact of CYP3A4 inhibitors on the metabolism of stiripentol is not known.^[171] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Other acidic fruit juices should be avoided. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for lack of efficacy of stiripentol due to degradation of the drug in an acidic environment.
sunitinib	<ul style="list-style-type: none"> Study in healthy subjects; modestly increased AUC and C_{max}.^[172] Manufacturer states that concomitant administration of sunitinib with grapefruit juice should be avoided.^[174] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolongation of QT_c interval, torsades de pointes. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—sorafenib.
suvorexant	<ul style="list-style-type: none"> Manufacturer states that grapefruit juice is an inhibitor of CYP3A, which may result in increased plasma concentrations of suvorexant.^[173] Suvorexant is primarily eliminated by CYP3A4 metabolism and has a mean absolute oral bioavailability of 82%.^[173] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, the manufacturer has recommended a dose of 5 mg. This dose may be increased if tolerated; it should not exceed the usual starting dose of 10 mg. Clinical monitoring is required, especially for daytime CNS depressant effects (e.g., somnolence, impaired psychomotor performance), particularly for risk of falling asleep while driving and other activities requiring complete mental alertness. Also, monitor for worsening of depression, suicidal thoughts and actions.
tacrolimus	<ul style="list-style-type: none"> Predicted to increase systemic tacrolimus concentration markedly.^{[6][175]} Case reports of profoundly increased tacrolimus blood concentration and nephrotoxicity.^{[177][178]} Manufacturer states that grapefruit juice should be avoided.^[179] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for QT_c interval prolongation, torsades de pointes, GI perforation, new-onset diabetes mellitus, nephrotoxicity, immunosuppression-related infections, neurotoxicities.
tacrolimus, prolonged-release	<ul style="list-style-type: none"> Manufacturer states that grapefruit and grapefruit juice inhibit CYP3A enzymes, resulting in increased tacrolimus whole blood trough concentrations, increasing the risk of serious adverse reactions. Patients should avoid eating grapefruit or drinking grapefruit juice in combination with tacrolimus.^[176] The oral bioavailability of tacrolimus PA was approximately 50% higher as compared with both tacrolimus immediate and other extended-release formulations at steady state.^[176] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for QT_c interval prolongation, torsades de pointes, GI perforation, new-onset diabetes mellitus, nephrotoxicity, immunosuppression-related infections, neurotoxicities.
tadalafil	<ul style="list-style-type: none"> Predicted to increase systemic tadalafil concentration moderately.^[6] Manufacturer states that grapefruit juice may give rise to modest increases in plasma tadalafil levels.^[180] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for hypotension.
tamsulosin	<ul style="list-style-type: none"> Predicted to increase systemic tamsulosin concentration moderately.^[6] Manufacturer states that tamsulosin should be used with caution in combination with moderate inhibitors of CYP3A4.^[181] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction.

(cont'd)

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Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^[a]	Grapefruit Effect	Management
		<ul style="list-style-type: none"> If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for symptoms of orthostatic hypotension, e.g., dizziness, weakness, syncope.
<u>ticagrelor</u>	<ul style="list-style-type: none"> Study in healthy subjects; markedly increased ticagrelor AUC and C_{max} with enhanced antiplatelet effect.^[182] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for bleeding. Potential alternative drugs (depending on indication, patient factors): predicted not to interact—ASA.
<u>tofacitinib</u>	<ul style="list-style-type: none"> Manufacturer states that consuming grapefruit juice should be avoided.^[183] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for serious infection (possibly leading to hospitalization or death), lymphoma and other malignancies.
tolvaptan	<ul style="list-style-type: none"> Study in healthy subjects; moderately increased tolvaptan AUC and C_{max} with enhanced drug effect.^[184] Manufacturer states that coadministration of grapefruit juice results in a 1.8-fold increase in exposure to tolvaptan and that concomitant use should be avoided.^[185] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for urinary frequency, thirst, dry mouth.
triazolam	<ul style="list-style-type: none"> Studies in healthy subjects; moderately increased triazolam AUC and C_{max} and enhanced psychomotor impairment.^{[186][187][188]} 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for increased drowsiness, sedation. Potential alternative drugs (depending on indication, patient factors): known not to interact—alprazolam; predicted not to interact—lorazepam, oxazepam, temazepam.
ulipristal	<ul style="list-style-type: none"> Manufacturer states that coadministration of moderate or potent CYP3A4 inhibitors is not recommended.^[189] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for headache, hot flashes.
<u>vandetanib</u>	<ul style="list-style-type: none"> Manufacturer states that products and juices containing grapefruit, Seville oranges or fruits known to inhibit CYP3A4 should be avoided at all times.^[190] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If these fruits are consumed during drug therapy, caution and clinical monitoring required, especially for prolongation of QT_c interval, torsades de pointes, heart failure, hypertensive crisis.
varidenafil	<ul style="list-style-type: none"> Predicted to increase systemic vardenafil concentration moderately.^[6] Manufacturer states that grapefruit juice gives rise to modest increases in plasma levels of vardenafil.^[191] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for hypotension.
<u>vemurafenib</u>	<ul style="list-style-type: none"> Manufacturer states that grapefruit, grapefruit juice and other foods that are known to affect CYP3A4 should be avoided during treatment with vemurafenib.^[192] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for myelosuppression, prolongation of QT_c interval, torsades de pointes.
<u>venetoclax</u>	<ul style="list-style-type: none"> Manufacturer states that consumption of grapefruit and other fruits that may inhibit CYP3A4 is contraindicated during treatment as they can increase serum levels of venetoclax.^[193] See the introductory text of this document for a discussion of other fruits/foods that may be reported to inhibit CYP3A4. Manufacturer also states that ketoconazole (a strong CYP3A4 inhibitor) increased venetoclax C_{max} 2.3-fold and AUC 6-fold.^{[193][194]} 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for tumor lysis syndrome, neutropenia, anemia, thrombocytopenia, infection (particularly pneumonia, upper respiratory tract infection).
<u>verapamil</u>	<ul style="list-style-type: none"> Studies in healthy subjects; 2 of 3 studies showed moderately increased verapamil AUC and C_{max}.^{[195][196][197]} Case report of toxic serum levels of verapamil/norverapamil with complete heart block, marked bradycardia and hypotension.^[198] Manufacturer states that grapefruit juice increased the AUC for R-verapamil and S-verapamil by up to 49% and 37% respectively. The increase in C_{max} for R-verapamil and S-verapamil were up to 75% and 51% respectively.^[199] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for arrhythmias (e.g., heart block, bradycardia), hypotension.
vilazodone	<ul style="list-style-type: none"> Manufacturer states that vilazodone dose should not exceed 20 mg daily if co-administered with a strong inhibitor of CYP3A4.^[200] 	<ul style="list-style-type: none"> Avoid grapefruit. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, clinical monitoring required, especially for serotonin syndrome, lethargy, restlessness, hallucinations, disorientation.

(cont'd)

Table 1: Drug Administration and Grapefruit (cont'd)

Drug ^a	Grapefruit Effect	Management
vortioxetine	<ul style="list-style-type: none"> Manufacturer indicates that vortioxetine is extensively metabolized by several CYPs (CYP2D6 primarily) but also CYP3A4.^[201] Plasma vortioxetine levels were about 2-fold higher in CYP2D6 poor metabolizers.^[201] Manufacturer states that strong CYP3A4 inhibitors may cause clinically relevant increases in drug exposure in CYP2D6 poor metabolizers.^[201] 	<ul style="list-style-type: none"> Avoid grapefruit unless patient is known to be a CYP2D6 extensive metabolizer. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for nausea, dizziness, diarrhea, fatigue, sedation, sexual dysfunction.
ziprasidone	<ul style="list-style-type: none"> Predicted to increase systemic ziprasidone concentration moderately.^[6] Manufacturer states that coadministration with potent CYP3A4 inhibitors has the potential to increase ziprasidone serum concentration.^[202] 	<ul style="list-style-type: none"> Grapefruit contraindicated. Seville orange, lime and pomelo may also cause the interaction. If grapefruit consumed during drug therapy, caution and clinical monitoring required, especially for prolongation of QTc interval, torsades de pointes, orthostatic hypotension. Potential alternative drugs (depending on indication, patient factors): known not to interact—haloperidol; predicted not to interact—olanzapine, risperidone.

^a Bolded, underlined text is used to highlight medications with serious toxicities or cases where the interaction may be of important clinical significance.

Abbreviations: AUC = area under the concentration curve; C_{max} = maximum concentration; OATP1A2 = organic anion transporting polypeptide 1A2; OATP2B1 = organic anion transporting polypeptide 2B1; Pgp = P-glycoprotein.

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