TEXAS Health and Human Services

Medicaid Drug Use Criteria

Ivacaftor (Kalydeco®) and Combination Therapy

- Developed: October 2012
- Revised: January 2020; November 2019; December 2017; February 2016; June 2014.

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

Ivacaftor is categorized as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. Cystic fibrosis (CF) occurs as a result of CFTR genetic mutations causing mucosal obstruction of the distal lung airway and submucosal glands. Malfunction of the CFTR alters electrolyte homeostasis which changes cell potentials and can lead to organ damage in CF patients. Patient genotyping shows that approximately 4% of the 30,000 CF patients in America are believed to have a G551D-CFTR mutation. Ivacaftor targets multi-organ chloride channels at the

surface of epithelial cells to enhance the opening of the G551D-CFTR protein. Ivacaftor (Kalydeco®) was initially FDA-approved for treating CF patients age six years and older who have a G551D mutation of the CFTR gene in 2012. More recently, ivacaftor has gained FDA approval to include CF adult patients with the following CFTR gene mutations: E56K, G178R, S549R, G551D, G551S, G1244E, S1251N, G1069R, S1255P, R1070Q, R117H, S549N, G1349D, R117C, A455E, S945L, R1070W, 3272-26A→G, P67L, E193K, S977F, F1074L, 3849+10kbC→T, R74W, L206W, D579G, F1052V, D1152H, D110E, R347H, 711+3A→G, K1060T, D1270N, D110H, R352Q, E831X, A1067T, and 2789+5G→A. Ivacaftor is indicated in pediatric CF patients 6 months to 17 years of age with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H CFTR gene mutations, as well as pediatric patients 12 to 17 years of age heterozygous for the F508del mutation and a second mutation with predicted responsiveness to ivacaftor. Patients who are homozygous for the F508del mutation in the CFTR gene are unaffected by ivacaftor potentiation.

A combination product containing lumacaftor and ivacaftor (Orkambi®) was approved in July 2015 for use in patients 2 years and older who are homozygous for the F508del mutation in the CFTR gene. The F508del mutation is the most common cause of CF, with approximately half of the CF population in the U.S. being homozygous for the mutation. The combined effect of lumacaftor and ivacaftor increases the quantity (lumacaftor) and function (ivacaftor) of the F508del-CFTR ion channel, resulting in improved channel function and clinical benefit.

Tezacaftor/ivacaftor (Symdeko®) combination therapy, approved in February 2018, is FDA-approved for CF in patients six years of age and older homozygous for the F508del mutation or who have at least one mutation in the CFTR gene responsive to tezacaftor/ivacaftor, including E56K, R117C, A455E, S945L, R1070W, 3272-26A→G, P67L, E193K, F508del*, S977F, F1074L, 3849+10kbC→T, R74W, L206W, D579G, F1052V, D1152H, D110E, R347H, 711+3A→G, K1060T, D1270N, D110H, R352Q, E831X, A1067T, and 2789+5G→A. Tezacaftor increases the amount of mature CFTR at the cell surface by expediting cellular processing and trafficking of normal and select mutant forms of CFTR, while ivacaftor enhances channel-opening probability of CFTR proteins at the cell surface. Combined therapy improves CFTR function at the cell surface and increases chloride transport.

The newest ivacaftor formulation, Trikafta®, was approved in October 2019 and combines ivacaftor with elexacaftor and tezacaftor to manage CF patients 12 years of age and older who have at least one F508del mutation in the CFTR gene, which targets approximately 85% of CF patients in the United States. Both elexacaftor

and tezacaftor increase the amount of mature CFTR at the cell surface by expediting cellular processing and trafficking of normal and select mutant forms of CFTR, while ivacaftor enhances channel-opening probability of CFTR proteins at the cell surface. Combined therapy improves CFTR function at the cell surface and increases chloride transport.

1.1 Adults

Recommended adult ivacaftor doses as monotherapy and combination therapy are summarized in Tables 1 and 2. Dosage adjustments for ivacaftor monotherapy and combination therapy when administered adjunctively with cytochrome P450 3A4 inhibitors are summarized in Table 3. Dosages in patient profiles exceeding these recommendations will be reviewed.

Table 1. Maximum Recommended Adult Ivacaftor Dosages: Monotherapy

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
CF (patients with one mutation in CFTR gene responsive to ivacaftor potentiation)	ivacaftor (Kalydeco®)	150 mg oral tablets	150 mg orally every 12 hours with fat-containing food

- CF = cystic fibrosis
- CFTR = cystic fibrosis transmembrane conductance regulator

Table 2. Maximum Recommended Adult Ivacaftor Dosages: Combination Therapy

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
CF (patients homozygous for F508del mutation in the CFTR gene)	lumacaftor/ ivacaftor (Orkambi®)	100 mg/125 mg, 200 mg/125 mg oral tablets	400 mg/250 mg (2 x 200 mg lumacaftor/125 mg ivacaftor tablets) orally every 12 hours with fat-containing food

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
CF (patients homozygous for F508del mutation or have at least one mutation in the CFTR gene responsive to tezacaftor/ivacaftor)	tezacaftor/ ivacaftor (Symdeko®)	tezacaftor 50 mg/ivacaftor 75 mg; ivacaftor 75 mg oral tablets tezacaftor 100 mg/ivacaftor 150 mg; ivacaftor 150 mg oral tablets	tezacaftor 100 mg/ivacaftor 150 mg in morning and ivacaftor 150 mg in evening approximately 12 hours apart with fat-containing food
CF (patients have at least one F508del mutation in the CFTR gene)	elexacaftor/ tezacaftor/ ivacaftor (Trikafta®)	elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg oral tablet; ivacaftor 150 mg oral tablet	2 tablets (elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg) in morning and one ivacaftor 150 mg tablet in evening approximately 12 hours apart with fat-containing food

- CF = cystic fibrosis
- CFTR = cystic fibrosis transmembrane conductance regulator

Table 3. Ivacaftor Adult Dosage Adjustments with Concurrent CYP3A4 Inhibitor Therapy

Ivacaftor Drug Name	Concurrent CYP3A4 Inhibitor Therapy	Dosage Recommendations*
ivacaftor (Kalydeco®)	strong CYP3A inhibitors (e.g., ketoconazole)	ivacaftor dosages should be reduce to 150 mg twice weekly
ivacaftor (Kalydeco®)	moderate CYP3A inhibitors (e.g., erythromycin, fluconazole)	ivacaftor dosages should be reduce to 150 mg once daily
lumacaftor/ ivacaftor (Orkambi®	strong CYP3A inhibitors (e.g., ketoconazole)	lumacaftor/ivacaftor dosages shoul be reduced to 200 mg/125 mg once daily in patients receiving strong CYP3A inhibitors for the first week, followed by lumacaftor 400 mg/ivacaftor 250 mg every 12 hour thereafter; no dosage adjustments are needed if CYP3A inhibitors are initiated in patients already taking lumacaftor/ivacaftor

Ivacaftor Drug Name	Concurrent CYP3A4 Inhibitor Therapy	Dosage Recommendations*
lumacaftor/ ivacaftor (Orkambi®	moderate CYP3A inhibitors (e.g., erythromycin, fluconazole)	no dosage adjustments necessary
tezacaftor/ ivacaftor (Symdeko®	strong CYP3A inhibitors (e.g., ketoconazole)	Day 1: tezacaftor/ivacaftor 100 mg/150 once daily in morning Days 2 and 3: no dosages administered Day 4: tezacaftor/ivacaftor 100 mg/150 once daily in morning The evening ivacaftor dose should NOT be given Continue twice weekly (morning) administration schedule, with 3-4 days between dosages
tezacaftor/ ivacaftor (Symdeko®	moderate CYP3A inhibitors (e.g., erythromycin, fluconazole)	Day 1: tezacaftor/ivacaftor 100 mg/150 once daily in morning Day 2: ivacaftor 150 mg once daily in morning The evening ivacaftor dose should NOT be given Continue alternate day (morning) administration schedule
elexacaftor/ tezacaftor/ ivacaftor (Trikafta®)	strong CYP3A inhibitors (e.g., ketoconazole)	2 tablets (elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg) in morning twice weekly, with 3-4 days between dosages The evening ivacaftor dose should NOT be given
elexacaftor/ tezacaftor/ ivacaftor (Trikafta®)	moderate CYP3A inhibitors (e.g., erythromycin, fluconazole)	Day 1: 2 tablets (elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg) in morning Day 2: ivacaftor 150 mg once daily in morning The evening ivacaftor dose should NOT be given Continue alternate day (morning) administration schedule

- CYP3A/3A4 = cytochrome P450 3A/3A4
- * All dosages should be given with a fat-containing meal

1.2 Pediatrics

Tables 4 and 5 summarize ivacaftor dosing recommendations as monotherapy and combination therapy for pediatric patients. Ivacaftor safety and efficacy in children less than 6 months of age have not been established. Safety and efficacy of

lumacaftor/ivacaftor combination therapy in children less than 2 years of age have not been established. Tezacaftor/ivacaftor safety and efficacy have not been determined in children below 6 years of age, while elexacaftor/tezacaftor/ivacaftor efficacy/safety have not been established in children/adolescents younger than 12 years of age. Dosage adjustments for ivacaftor monotherapy and combination therapy when administered concomitantly with cytochrome P450 3A4 inhibitors are summarized in Table 6. Ivacaftor is not recommended for use concurrently with CYP3A strong inducers.

Table 4. Maximum Recommended Pediatric Ivacaftor Dosages: Monotherapy

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage
CF (patients homozygous for the F508del mutation in CFTR gene)	ivacaftor (Kalydeco®)	25 mg, 50 mg, 75 mg oral granules 150 mg oral tablets	children/ adolescents 6-17 years: 150 mg orally every 12 hours with fat-containing food infants/ children 6 months to 5 years (greater than 14 kg): 75 mg as oral granules every 12 hours with fat-containing food infants/ children 6 months to 5 years (7 kg to less than 14 kg) 50 mg as oral granules every 12 hours with fat-containing food infants/ children 6 months to 5 years (5 kg to less than 7 kg): 25 mg as oral granules every 12 hours with fat-containing food

- CF = cystic fibrosis
- CFTR = cystic fibrosis transmembrane conductance regulator

Table 5. Maximum Recommended Pediatric Ivacaftor Dosages: Combination Therapy

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
CF (patients homozygous for *F508del* mutation in the CFTR gene)	lumacaftor / ivacaftor (Orkambi®)	100 mg / 125 mg, 150 mg / 188 mg oral granules 100 mg / 125 mg, 200 mg / 125 mg oral tablets	*children / adolescents 12 years and older:* 400 mg / 250 mg (2 x 200 mg lumacaftor / 125 mg ivacaftor tablets) orally every 12 hours with fat-containing food *children 6-11 years:* 200 mg / 250 mg (2 x 100 mg lumacaftor / 125 mg ivacaftor tablets) orally every 12 hours with fat-containing food *children 2-5 years (greater than or equal to 14 kg):* 150 mg / 188 mg oral granules every 12 hours with fat-containing food *children 2-5 years (less than 14 kg):* 100 mg / 125 mg oral granules every 12 hours with fat-containing food

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
			children / adolescents 12-17 years: tezacaftor 100 mg / ivacaftor 150 mg in morning and ivacaftor 150 mg in evening approximately 12 hours apart with fat-containing food
CF (patients homozygous for ***F508del*** mutation or have at least one mutation in the CFTR gene responsive to tezacaftor / ivacaftor)	tezacaftor / ivacaftor (Symdeko®)	tezacaftor 50 mg / ivacaftor 75 mg oral tablet; ivacaftor 75 mg oral tablet tezacaftor 100 mg / ivacaftor 150 mg oral tablet; ivacaftor 150 mg oral tablet	***children 6-11 years (greater than or equal to 30 kg):*** tezacaftor 100 mg / ivacaftor 150 mg in morning and ivacaftor 150 mg in evening approximately 12 hours apart with fat-containing food ***children 6-11 years (less than 30 kg):*** tezacaftor 50 mg / ivacaftor 75 mg in morning and ivacaftor 75 mg in evening approximately 12 hours apart with fat-containing food

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
CF (patients have at least one *F508del* mutation in the CFTR gene)	elexacaftor / tezacaftor / ivacaftor (Trikafta®)	elexacaftor 100 mg / tezacaftor 50 mg / ivacaftor 75 mg oral tablet; ivacaftor 150 mg oral tablet	*children / adolescents 12-17 years:* 2 tablets (elexacaftor 100 mg / tezacaftor 50 mg / ivacaftor 75 mg) in morning and one ivacaftor 150 mg tablet in evening approximately 12 hours apart with fat-containing food

CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator

Table 6. Ivacaftor Pediatric Dosage Adjustments with Concurrent CYP3A4 Inhibitor Therapy

Ivacaftor Drug Name	Concurrent CYP3A4 Inhibitor Therapy	Dosage Recommendations*
ivacaftor (Kalydeco®)	strong CYP3A inhibitors (e.g., ketoconazole)	*Greater than or equal to 6 years of age:* 150 mg twice weekly *6 months to less than 6 years of age:* *Greater than or equal to 14 kg:* 75 mg granule packet twice weekly *7 to less than 14 kg:* 50 mg granule packet twice weekly *5 to less than 7 kg:* 25 mg granule packet twice weekly

Ivacaftor Drug Name	Concurrent CYP3A4 Inhibitor Therapy	Dosage Recommendations*
ivacaftor (Kalydeco®)	moderate CYP3A inhibitors (e.g., erythromycin, fluconazole)	***Greater than or equal to 6 years of age:*** 150 mg orally once daily ***6 months to less than 6 years of age:*** ***Greater than or equal to 14 kg:*** 75 mg granule packet orally once daily ***7 to less than 14 kg:*** 50 mg granule packet orally once daily ***5 to less than 7 kg:*** 25 mg granule packet orally once daily
lumacaftor/ ivacaftor (Orkambi®)	strong CYP3A inhibitors (e.g., ketoconazole)	***Greater than or equal to 12 years:*** lumacaftor/ivacaftor dosages should be reduced to 200 mg/125 mg once daily for the first week, followed by 2 tablets (lumacaftor 400 mg/ivacaftor 250 mg) every 12 hours thereafter; no dosage adjustments are needed if CYP3A inhibitors are initiated in patients already taking lumacaftor/ivacaftor ***6 to 11 years:*** lumacaftor/ivacaftor dosages should be reduced to 100 mg/125 mg once daily for the first week, followed by 2 tablets (lumacaftor 200 mg/ivacaftor 250 mg) every 12 hours thereafter; no dosage adjustments are needed if CYP3A inhibitors are initiated in patients already taking lumacaftor/ivacaftor

Ivacaftor Drug Name	Concurrent CYP3A4 Inhibitor Therapy	Dosage Recommendations*
lumacaftor/ ivacaftor (Orkambi®)	strong CYP3A inhibitors (e.g., ketoconazole)	***2 to 5 years (greater than or equal to 14 kg):*** lumacaftor/ivacaftor dosages should be reduced to 1 granule packet (150 mg/188 mg) every other day for the first week, followed by 1 granule packet (lumacaftor 150 mg/ivacaftor 188 mg) every 12 hours thereafter; no dosage adjustments are needed if CYP3A inhibitors are initiated in patients already taking lumacaftor/ivacaftor ***2 to 5 years (less than 14 kg):*** lumacaftor/ivacaftor dosages should be reduced to 1 granule packet (150 mg/125 mg) every other day for the first week, followed by 1 granule packet (lumacaftor 150 mg/ivacaftor 125 mg) every 12 hours thereafter; no dosage adjustments are needed if CYP3A inhibitors are initiated in patients already taking lumacaftor/ivacaftor
lumacaftor/ ivacaftor (Orkambi®)	moderate CYP3A inhibitors (e.g., erythromycin, fluconazole)	no dosage adjustments necessary

Ivacaftor Drug Name	Concurrent CYP3A4 Inhibitor Therapy	Dosage Recommendations*
tezacaftor/ ivacaftor (Symdeko®)	strong CYP3A inhibitors (e.g., ketoconazole)	***greater than or equal to 6 years to less than 12 years greater than or equal to 30 kg; children/ adolescents greater than or equal to 12 years:*** **Day 1: tezacaftor/ivacaftor 100 mg/150 once daily in morning** **Days 2 and 3: no dosages administered** **Day 4: tezacaftor/ivacaftor 100 mg/150 once daily in morning** **The evening ivacaftor dose should NOT be given** ***Continue twice weekly (morning) administration schedule, with 3-4 days between dosages*** ***greater than or equal to 6 years to less than 12 years less than 30 kg:*** **Day 1: tezacaftor/ivacaftor 50 mg/75 once daily in morning** **Days 2 and 3: no dosages administered** **Day 4: tezacaftor/ivacaftor 50 mg/75 once daily in morning** **The evening ivacaftor dose should NOT be given** ***Continue twice weekly (morning) administration schedule, with 3-4 days between dosages***

Ivacaftor Drug Name	Concurrent CYP3A4 Inhibitor Therapy	Dosage Recommendations*
tezacaftor/ ivacaftor (Symdeko®)	moderate CYP3A inhibitors (e.g., erythromycin, fluconazole)	*greater than or equal to 6 years to* less than *12 years greater than or equal to 30 kg; children/ adolescents greater than or equal to 12 years:* Day 1: tezacaftor/ivacaftor 100 mg/150 once daily in morning Day 2: ivacaftor 150 mg once daily in morning The evening ivacaftor dose should NOT be given *Continue alternate day (morning) administration schedule* *greater than or equal to 6 years to less than 12 years less than 30 kg:* Day 1: tezacaftor/ivacaftor 50 mg/75 once daily in morning Day 2: ivacaftor 75 mg once daily in morning The evening ivacaftor dose should NOT be given *Continue alternate day (morning) administration schedule*
elexacaftor/ tezacaftor/ ivacaftor (Trikafta®)	strong CYP3A inhibitors (e.g., ketoconazole)	*greater than or equal to* 12 years of age: 2 tablets (elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg) in morning twice weekly, with 3-4 days between dosages The evening ivacaftor dose should NOT be given

Ivacaftor Drug Name	Concurrent CYP3A4 Inhibitor Therapy	Dosage Recommendations*
elexacaftor/ tezacaftor/ ivacaftor (Trikafta®)	moderate CYP3A inhibitors (e.g., erythromycin, fluconazole)	*greater than or equal to* 12 years of age: Day 1: 2 tablets (elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg) in morning Day 2: ivacaftor 150 mg once daily in morning The evening ivacaftor dose should NOT be given *Continue alternate day (morning) administration schedule*

CYP3A = cytochrome P450 3A

1.3 Dosing in Renal Impairment

Because ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor have not been studied in patients with renal insufficiency, these medications should be used cautiously in patients with CrCl ≤ 30 mL/min.

1.4 Dosing in Hepatic Impairment

It is recommended that ALT and AST values be assessed prior to initiating ivacaftor, every 3 months during the first year, and annually thereafter. Dosing should be interrupted in patients with ALT or AST values of greater than 5 times the upper limit of normal (ULN). Following the resolution of transaminase elevations, consider the benefits and risks of resuming ivacaftor.

Tables 7 and 8 summarize ivacaftor dosing recommendations in adults and pediatric patients with hepatic impairment.

Table 7. Ivacaftor Dosing in Hepatic Impairment (Adults, Pediatric Patients greater than or equal to 6 Years)

Child-Pugh Class	Recommendation
A	No dosage adjustment
B	150 mg once daily

Child-Pugh Class	Recommendation
C	150 mg once daily or less frequently (not studied)

Table 8. Ivacaftor Dosing in Hepatic Impairment (Pediatric Patients 6 Months to less than 6 Years)

Child-Pugh Class	Recommendation
A	No dosage adjustment
B	greater than or equal to 14 kg: 75 mg granule packet once daily 7 to less than 14 kg: 50 mg granule packet once daily 5 to less than 7 kg: 25 mg granule packet once daily
C	greater than or equal to 14 kg: 75 mg granule packet once daily o frequently (not studied) 7 to less than 14 kg: 50 mg granule packet once daily or less frequ (not studied) 5 to less than 7 kg: 25 mg granule packet once daily or less frequently (not studied)

Tables 9 and 10 summarize lumacaftor/ivacaftor dosing recommendations in adult and pediatric patients with hepatic impairment.

Table 9. Lumacaftor / Ivacaftor Dosing in Hepatic Impairment (Adults, Pediatric Patients greater than or equal to 6 Years)

Child-Pugh Class	Recommendation
A	No dosage adjustment
B	Lumacaftor 400 mg/ivacaftor 250 mg in morning, and lumacaftor 2 mg/ivacaftor 125 mg in evening
C	Maximum dose of lumacaftor 200 mg/ivacaftor 125 mg as tablets o granules every 12 hours (or less frequently); use with caution

Table 10. Lumacaftor / Ivacaftor Dosing in Hepatic Impairment (Pediatric Patients 2 to 5 Years)

Child-Pugh Class	Recommendation
A	No dosage adjustment
B	Lumacaftor 150 mg/ivacaftor 188 mg (greater than or equal to 14 kg) or lumacaftor 100 mg/ivacaftor 125 mg (less than 14 kg) as or granules in morning, and lumacaftor 150 mg/ivacaftor 188 mg (greater than or equal to 14 kg) or lumacaftor 100 mg/ivacaftor 12 mg (less than 14 kg) as oral granules in the evening every other da
C	Lumacaftor 150 mg/ivacaftor 188 mg (greater than or equal to 14 kg) or lumacaftor 100 mg/ivacaftor 125 mg (less than 14 kg) as ora granules in morning (or less frequently); no dose should be given ir evening (use with caution)

Tables 11 and 12 summarize tezacaftor/ivacaftor dosing recommendations in adults and pediatric patients 6 years and older with hepatic impairment.

Table 11. Tezacaftor/Ivacaftor Dosing in Hepatic Impairment [Adults, Pediatric Patients 6 to 11 Years (greater than or equal to 30 kg) and Children/Adolescents greater than or equal to 12 Years]

Child-Pugh Class	Recommendation
A	No dosage adjustment
B	Tezacaftor/ivacaftor 100 mg/150 once daily in morning; the evenin ivacaftor 150 mg dose should not be given
C	Tezacaftor/ivacaftor 100 mg/150 once daily in morning (or less frequently); the evening ivacaftor 150 mg dose should not be given use with caution – not studied in severe hepatic impairment)

Table 12. Tezacaftor/Ivacaftor Dosing in Hepatic Impairment (Pediatric Patients 6 to 11 Years (less than 30 kg)

Child-Pugh Class	Recommendation
A	No dosage adjustment
B	Tezacaftor/ivacaftor 50 mg/75 once daily in morning; the evening ivacaftor 75 mg dose should not be given
C	Tezacaftor/ivacaftor 50 mg/75 once daily in morning (or less frequently); the evening ivacaftor 75 mg dose should not be given; use with caution – not studied in severe hepatic impairment)

Table 13 summarizes elexacaftor/tezacaftor/ivacaftor dosing recommendations in adults and pediatric patients greater than or equal to 12 years with hepatic impairment.

Table 13. Elexacaftor/Tezacaftor/Ivacaftor Dosing in Hepatic Impairment (Adults, Pediatric Patients greater than or equal to 12 Years)

Child-Pugh Class	Recommendation
A	No dosage adjustment
B	2 tablets (elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg) in morning twice weekly once daily, with no evening ivacaftor 150 mg dose (not studied)
C	Not recommended for use

2 Duration of Therapy[1-14]

There is no basis for limiting the duration of ivacaftor in CF patients who have a GG551D mutation of the CFTR gene. Randomized, double-blind, placebo-controlled trials have shown a significant increase in pulmonary function following ivacaftor therapy in patients with GG551D mutations, with maintenance of effect and safety data through 48 weeks.

While treatment duration in the available clinical trial lasted only 16 weeks, CF patients with G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R mutations may benefit from long-term ivacaftor therapy provided that improved treatment response is observed. R117H mutations were studied until week 24 but may benefit from longer therapy. Lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor combination product efficacy has been demonstrated in randomized, double-blind, placebo-controlled, 24-week trials. Although not directly studied beyond 24 weeks, CF patients with F508del mutations may benefit from long-term therapy with these combination agents.

3 Duplicative Therapy

Gabapentin dosage formulations are not interchangeable due to variations in chemical forms and pharmacokinetic properties. Concurrent administration of two or more gabapentin formulations is not recommended due to lack of additional therapeutic benefit and increased risk of adverse effects. Patient profiles containing concomitant prescriptions for two or more gabapentin dosage formulations for more than two months will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for ivacaftor are summarized in Table 14. Only those drug-drug

interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 14. Ivacaftor and Lumacaftor/Ivacaftor Drug-Drug Interactions[1-9]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
ivacaftor, lumacaftor/ ivacaftor, tezacaftor/ ivacaftor, elexacaftor/ tezacaftor/ ivacaftor	strong CYP3A inhibitors (e.g., ketoconazole, voriconazole, posaconazole, telithromycin, clarithromycin)	concurrent use significantly increased ivacaftor exposu (8.5-fold ↑ in AUC with ketoconazole); adjunctive administration may significantly increase elexacaftor, tezacaftor and ivacaftor concentrations an ↑ potential for enhanced pharmacologic/adverse effects	reduce elexacaftor, ivacaftor, tezacaftor dosag and monitor for efficacy ar adverse events	2-major (CP) major (DrugReax)
ivacaftor, lumacaftor/ ivacaftor, tezacaftor/ ivacaftor, elexacaftor/ tezacaftor/ ivacaftor	moderate CYP3A inhibitors (e.g., fluconazole)	concurrent use increased ivacaftor exposure (3-fold ↑ AUC with fluconazole); adjunctive administration ma significantly increase tezacaf and ivacaftor concentrations and ↑ potential for enhanced pharmacologic/adverse effec	reduce elexacaftor, ivacaftor, tezacaftor dosages and monitor for efficacy and adverse even	2-major (CP) moderate (DrugRe
ivacaftor, lumacaftor/ ivacaftor, tezacaftor/ ivacaftor, elexacaftor/ tezacaftor/ ivacaftor	strong CYP3A inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort)	concurrent use decreased ivacaftor exposure [9-fold ↓ AUC with rifampin (57% ↓)]; adjunctive administration ma significantly reduce elexacaftor, tezacaftor and ivacaftor concentrations (CYP3A substrates) and ↓ efficacy	strong CYP3A inducers should be avoided while taking ivacaftor, lumacaftor/ ivacaftor, tezacaftor/ ivacaftor, and elexacaftor/ tezacaftor/ ivacaftor	2-major (CP) major (DrugReax)
ivacaftor, lumacaftor/ ivacaftor, tezacaftor/ ivacaftor, elexacaftor/ tezacaftor/ ivacaftor	CYP3A and/or P-glycoprotein (P-gp) substrates (e.g., midazolam, alprazolam, cyclosporine, tacrolimus)	ivacaftor is weak CYP3A and gp transport inhibitor; concurrent use with midazola ↑ midazolam AUC 1.5-fold an ↑ digoxin AUC 1.3-fold	use with caution and moni drug- related side effects and/or monitor therapeuti levels	tacrolimus: 2-maj others - 3-modera (CP) moderate (DrugRe
lumacaftor/ ivacaftor	CYP3A substrates (e.g antibiotics, antifungals antivirals)	lumacaftor is strong CYP3A inducer; concurrent use may result in reduced efficacy of CYP3A substrates	consider alternative antibiotics such as azithromycin, ciprofloxacir or levofloxacin whenever possible; if an antifungal is required, monitor for breakthrough fungal infection; consider alternative treatment with fluconazole whenever possible; may also adjust lumacaftor/ivacaftor dosages or avoid combination, if possible	major (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
lumacaftor/ ivacaftor	hormonal contraceptives	concurrent administration ma reduce hormonal contraceptiv exposure and efficacy and m increase menstruation-associated adverse events (e.g., menorrhagia)	avoid concurrent use; use alternate methods of birth control	major (DrugReax) 2-major (CP)
ivacaftor, lumacaftor/ ivacaftor, tezacaftor/ ivacaftor, elexacaftor/ tezacaftor/ ivacaftor	warfarin	warfarin exposure may be modified with adjunctive lumacaftor/ ivacaftor administration, as lumacaftor ivacaftor is a CYP3A4 inducer the enzyme that metabolizes warfarin, and ivacaftor is a weak CYP2C9 inhibitor, the primary enzyme that metabolizes S-warfarin	monitor international normalized ratio and adjus warfarin dosages as neede	moderate (DrugRe 3-moderate (CP)

- *CP = Clinical Pharmacology
- AUC = area under the curve

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