



Drug and Biologic Coverage Policy

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Coverage Policy Number 1207

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators

Table of Contents

Overview	1
Coverage Policy.....	1
FDA Approved Indications and Dosing.....	4
General Background.....	8
Coding/Billing Information.....	10
References	11

Related Coverage Resources

[Genetic Testing for Hereditary and Multifactorial Conditions](#)
[Pharmacogenetic Testing](#)
[Quantity Limitations](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators addressed within this policy include the following products:

- **Kalydeco®** (ivacaftor tablets)
- **Orkambi®** (lumacaftor/ivacaftor tablets)
- **Symdeko®** (tezacaftor/ivacaftor and ivacaftor tablets)
- **Trikafta™** (elexacaftor/tezacaftor/ivacaftor tablets and ivacaftor tablets)

Coverage Policy

Kalydeco

Ivacaftor (Kalydeco®) is considered medically necessary when ALL of the following criteria are met:

- Individual is 4 months of age or older
- Documented diagnosis of cystic fibrosis (CF)
- Individual has at least ONE of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q,

A455E, D579G, S945L, S977F, F1052V, K1060T, A1067T, G1069R, R1070Q, R1070W, F1074L, D1152H, D1270N, G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, 2789+5G → A, 3272-26A → G, 3849+10kbC → T, 711+3A → G, E831X, R117H, A120T, A234D, A349V, D192G, D924N, E882K, F311L, F311delF508C, F508C;S1251N, G178E, G194R, G314E, G576A, G970D, G1249R, H939R, H1375P, I148T, I175V, I807M, I1027T, I1139V, L320V, L967S, L997F, L1480P, M152V, M952I, M952T, Q237E, Q237H, Q359R, Q1291R, R75Q, R117G, R117L, R117P, R170H, R347L, R553Q, R668C, R792G, R933G, R1162L, R1283M, S589N, S737F, S1159F, S1159P, T338I, T1053I, V232D, V562I, V754M, V1293G, W1282R, Y1014C, or Y1032C

- Prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis

Ivacaftor (Kalydeco®) is considered experimental, investigational, or unproven for ANY other use including the following (this list may not be all-inclusive):

- Diagnosis of CF with homozygous F508del mutations in the CFTR gene (i.e. 2 copies of the F508del mutation)
- Cystic fibrosis with an unknown CFTR gene mutation
- CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis)
- CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID)
- Combination therapy with Orkambi (lumacaftor/ivacaftor tablets), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor).

Orkambi

Lumacaftor/ivacaftor (Orkambi®) is considered medically necessary when ALL of the following criteria are met:

- Individual is 2 years of age or older
- Documented diagnosis of cystic fibrosis (CF)
- Documentation the individual is homozygous for the F508del mutation in the CFTR gene (i.e. 2 copies of the F508del mutation)
- Prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis

Lumacaftor/ivacaftor (Orkambi®) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all-inclusive):

- Diagnosis of CF with heterozygous F508del mutations in the CFTR gene. (i.e. 1 copy of the F508del mutation)
- Cystic fibrosis patients with an unknown CFTR gene mutation
- CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis)
- CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID)
- Combination therapy with Kalydeco (ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor)

Symdeko

Tezacaftor/ivacaftor (Symdeko®) is considered medically necessary when ALL of the following criteria are met:

- Individual is 6 years of age or older
- Documented diagnosis of cystic fibrosis (CF)
- **EITHER** of the following:
 - Documentation the individual is homozygous for the F508del mutation in the CFTR gene (i.e. 2 copies of the F508del mutation)
 - Individual has at least one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A → G, S945L, S977F, F1052V, E831X, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G → A, 3272-26A → G,

3849 + 10kbc → T, 546insCTA, A120T, A234D, A349V, A554E, A1006E, D192G, D443Y, D443Y;G57A;R668C, D614G, D836Y, D924N, D979V, I618T, I807M, I980K, I1027T, I1139V, I1269N, I1366N, L15P, L320V, R170H, R258G, R334L, R334Q, R347L, R347P, R352W, R553Q, R668C, R751L, V1293G, E60K, E92K, E116K, E403D, E558V, E822K, F191V, F311del, F311L, F508C, F508C;S1251N, F575Y, L346P, L967S, L997F, L1324P, L1335P, L1480P, M152V, M265R, M952I, R1066H, R1070Q, R1162L, R1283M, R1283S, S549N, S549R, S589N, S737F, S912L, F1016S, F1099L, G126D, G178E, G178R, G194R, G194V, G314E, G551D, G551S, G576A, G576A;R668C, M952T, P5L, P205S, Q98R, Q237E, Q237H, Q359R, Q1291R, R31L, S1251N, S1255P, T338I, T1036N, T1053I, V201M, V232D, V562I, V754M, V1153E, G622D, G970D, G1069R, G1244E, G1249R, G1349D, H939R, H1054D, H1375P, I148T, I175V, I336K, I601F, R74Q, R74W;D1270N, R74W;V201M, R74W;V201M;D1270N, R75Q, R117G, R117H, R117L, R117P, W1282R, Y109N, Y161S, Y1014C, Y1032C, R792G, R933G, S1159F, S1159P, or V1240G

- Prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis

Tezacaftor/ivacaftor (Symdeko®) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all-inclusive):

- Cystic fibrosis patients with an unknown CFTR gene mutation
- CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis)
- CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID)
- Combination therapy with Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor)

Trikafta

Elexacaftor/tezacaftor/ivacaftor (Trikafta™) is considered medically necessary when the following criteria are met:

- Individual is 6 years of age or older
- Documented diagnosis of cystic fibrosis (CF)
- Individual has at least one copy of one of the following mutations in the cystic fibrosis conductance regulator (CFTR) gene: F508del, 3141del9, E822K, G1069R, L967S, R117L, S912L, 546insCTA, F191V, G1244E, L997F, R117P, S945L, A46D, F311del, G1249R, L1077P, R170H, S977F, A120T, F311L, G1349D, L1324P, R258G, S1159F, A234D, F508C, H139R, L1335P, R334L, S1159P, A349V, F508C;S1251N, H199Y, L1480P, R334Q, S1251N, A455E, H939R, M152V, R347H, S1255P, A554E, F575Y, H1054D, M265R, R347L, T338I, A1006E, F1016S, H1085P, M952I, R347P, T1036N, A1067T, F1052V, H1085R, M952T, R352Q, T1053I, D110E, F1074L, H1375P, M1101K, R352W, V201M, D110H, F1099L, I148T, P5L, R553Q, V232D, D192G, G27R, I175V, P67L, R668C, V456A, D443Y, G85E, I336K, P205S, R751L, V456F, D443Y;G576A;R668C, G126D, I502T, P574H, R792G, V562I, D579G, G178E, I601F, Q98R, R933G, V754M, D614G, G178R, I618T, Q237E, R1066H, V1153E, D836Y, G194R, I807M, Q237H, R1070Q, V1240G, D924N, G194V, I980K, Q359R, R1070W, V1293G, D979V, G314E, I1027T, Q1291R, R1162L, W361R, D1152H, G463V, I1139V, R31L, R1283M, W1098C, D1270N, G480C, I1269N, R74Q, R1283S, W1282R, E56K, G551D, I1366N, R74W, S13F, Y109N, E60K, G551S, K1060T, R74W;D1270N, S341P, Y161D, E92K, G576A, L15P, R74W;V201M, S364P, Y161S, E116K, G576A;R668C, L165S, R74W;V201M;D1270N, S492F, Y563N, E193K, G622D, L206W, R75Q, S549N, Y1014C, E403D, G628R, L320V, R117C, S549R, Y1032C, E474K, G970D, L346P, R117G, S589N, E588V, G1061R, L453S, R117H, or S737F
- Prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis

Elexacaftor/tezacaftor/ivacaftor (Trikafta™) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all-inclusive):

- Cystic Fibrosis with an unknown CFTR gene mutation

- CFTR-related disorder (for example, congenital absence of the vas deferens (CAVD), isolated pancreatitis, recurrent sinusitis or bronchitis)
- CFTR-related metabolic syndrome, CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID)
- Combination therapy with Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), or Symdeko (tezacaftor/ivacaftor)

Coverage for CFTR modulators varies across plans. Refer to the customer's benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following will apply in addition to criteria listed above:

For Cigna Total Savings Plan

Kalydeco® (ivacaftor tablets)	ONE of the following: <ul style="list-style-type: none"> • Documented failure, inadequate response, contraindication per FDA label, intolerance or not a candidate for elexacaftor/tezacaftor/ivacaftor (Trikafta™) • Individual has previously been started on, or is currently receiving Kalydeco®
Orkambi® (lumacaftor/ivacaftor tablets)	ONE of the following: <ul style="list-style-type: none"> • Documented failure, inadequate response, contraindication per FDA label, intolerance or not a candidate for elexacaftor/tezacaftor/ivacaftor (Trikafta™) • Individual has previously been started on, or is currently receiving Orkambi®
Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets)	ONE of the following: <ul style="list-style-type: none"> • Documented failure, inadequate response, contraindication per FDA label, intolerance or not a candidate for elexacaftor/tezacaftor/ivacaftor (Trikafta™) • Individual has previously been started on, or is currently receiving Symdeko®

Initial and reauthorization for CFTR modulator therapy (Kalydeco®, Orkambi®, Symdeko® or Trikafta™) is up to 12 months.

CFTR modulator therapy (Kalydeco®, Orkambi®, Symdeko® or Trikafta™) is considered medically necessary for continued use when initial criteria are met and ONE of the following:

- For individuals who already have measureable lung disease or end organ involvement, documentation of beneficial clinical response (for example, improvement in, stabilization of, or a decrease in the rate of decline of FEV1, reduced number of pulmonary exacerbations, improvement in body mass index [BMI], or improvement on the patient reported Cystic Fibrosis Questionnaire-Revised respiratory domain score).
- For individuals who are previously asymptomatic, or have mild clinical manifestations, there is no evidence of clinical decline.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

FDA Approved Indications and Dosing

FDA Approved Indication

	Indications	Dosing	Availability
Kalydeco® (ivacaftor tablets and oral granules)	<p>KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the <i>CFTR</i> gene that is responsive to ivacaftor potentiation based on clinical and/or <i>in vitro</i> assay data [see <i>Clinical Pharmacology</i> (12.1) and <i>Clinical Studies</i> (14)].</p> <p>If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a <i>CFTR</i> mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.</p>	<p>Oral granules: 4 months to less than 6 months (weight based see package insert (5kg or greater)): One 25 mg packet Q12 H.</p> <p>≥ 6 years of age: One 150 mg tablet Q12H.</p> <p>≥ 6 months to < 6 years of age and ≥ 5 kg to < 7 kg: One 25 mg packet mixed with 1 tsp of soft food or liquid Q12H.</p> <p>≥ 6 months to < 6 years of age and ≥ 7 kg to < 14 kg: One 50 mg packet mixed with 1 tsp of soft food or liquid Q12H.</p> <p>≥ 6 months to < 6 years of age and ≥ 14 kg: One 75 mg packet mixed with 1 tsp of soft food or liquid Q12H.</p> <p>A fat-containing meal or snack should be consumed just before or just after dosing for all formulations.</p> <p>Reduce dose in patients with moderate and severe hepatic impairment. Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors.</p>	<p>Oral granules containing 25 mg, 50 mg, or 75 mg per packet.</p> <p>Tablets containing 150 mg ivacaftor.</p>
Orkambi® (lumacaftor/ivacaftor tablets)	<p>Treatment of CF in patients ≥ 2 years of age who are homozygous for F508del mutation in the <i>CFTR</i> gene.</p> <p><u>Limitation of use:</u> The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the F508del mutation.</p>	<p>≥ 12 years of age: Two 200/125 mg tablets Q12H.</p> <p>≥ 6 to ≤ 11 years of age: Two 100/125 mg tablets Q12H.</p> <p>≥ 2 to ≤ 5 years of age weighing < 14 kg: One 100/125 mg packet of granules Q12H.</p> <p>≥ 2 to ≤ 5 years of age weighing ≥ 14 kg: One 150/188 mg packet of granules Q12H.</p> <p>A fat-containing meal or snack should be consumed just before or just after dosing for all formulations.</p> <p>Reduce the dose in patients with moderate or severe hepatic impairment.</p> <p>When initiating Orkambi in patients taking strong CYP3A inhibitors,</p>	<p>Oral granules containing 100 mg lumacaftor and 125 mg ivacaftor per packet.</p> <p>Oral granules containing 150 mg lumacaftor and 188 mg ivacaftor per packet.</p> <p>Tablets containing 100 mg lumacaftor and 125 mg ivacaftor.</p> <p>Tablets containing 200 mg lumacaftor and 125 mg ivacaftor.</p>

	Indications	Dosing	Availability
		reduce Orkambi dose for the first week of treatment.	
Symdeko® (tezacaftor/ ivacaftor and ivacaftor tablets)	<p>SYMDEKO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the <i>F508del</i> mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>) gene that is responsive to tezacaftor/ivacaftor based on <i>in vitro</i> data and/or clinical evidence [see <i>Clinical Pharmacology</i> (12.1) and <i>Clinical Studies</i> (14)].</p> <p>If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a <i>CFTR</i> mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.</p>	<p>≥ 12 years of age: One tablet (tezacaftor 100 mg/ivacaftor 150 mg) taken in the morning and one tablet (ivacaftor 150 mg) taken in the evening, approximately 12 hours apart.</p> <p>≥ 6 to ≤ 12 years of age weighing < 30 kg: One tablet (tezacaftor 50 mg/ivacaftor 75 mg) taken in the morning and one tablet (ivacaftor 75 mg) taken in the evening, approximately 12 hours apart.</p> <p>≥ 6 to ≤ 12 years of age weighing ≥ 30 kg: One tablet (tezacaftor 100 mg/ivacaftor 150 mg) taken in the morning and one tablet (ivacaftor 150 mg) taken in the evening, approximately 12 hours apart.</p> <p>There are dose modifications for moderate or severe hepatic impairment and for use with moderate or strong CYP3A inhibitors.</p>	<p>Symdeko is co-packaged as a fixed-dose combination tablet and an ivacaftor tablet.</p> <p>Tablets containing 100 mg tezacaftor and 150 mg ivacaftor and tablets containing 150 mg of ivacaftor.</p> <p>Tablets containing 50 mg tezacaftor and 75 mg ivacaftor and tablets containing 75 mg of ivacaftor.</p>
Trikafta™ (elexacaftor/ tezacaftor/ ivacaftor and ivacaftor tablets)	<p>TRIKAFTA is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one <i>F508del</i> mutation in the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>) gene or a mutation in the <i>CFTR</i> gene that is responsive based on <i>in vitro</i> data [see <i>Clinical Pharmacology</i> (12.1)].</p> <p>If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one <i>F508del</i> mutation or a mutation that is responsive based on <i>in vitro</i> data.</p>	<p><u>6 to less than 12 years weighing less than 30 kgs</u> Morning dose: Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg Evening dose: One tablet of ivacaftor 75 mg</p> <p><u>6 to less than 12 years weighing 30 kgs or more</u> Morning dose: Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg Evening dose: One tablet of ivacaftor 150 mg</p> <p><u>12 years and older</u> Morning dose: Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg Evening dose: One tablet of ivacaftor 150 mg</p>	<p><u>Tablets</u> Fixed-dose combination containing elexacaftor 50 mg, tezacaftor 25 mg, and ivacaftor 37.5 mg co-packaged with ivacaftor 75 mg</p> <p>Fixed-dose combination containing elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg co-packaged with ivacaftor 150 mg</p>

CF – Cystic fibrosis; CFTR – Cystic fibrosis transmembrane conductance regulator; Q12H – Once every 12 hours; CYP – Cytochrome P450.

List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko.

(Symdeko Prescribing Information, 12/2020)

E56K	E193K	S945L	F1074L
P67L	L206W	S977F	D1152H
R74W	R347H	F1052V	D1270N
D110E	R352Q	E831X	2789+5G→A
D110H	A455E	K1060T	3272-26A→G
R117C	D579G	A1067T	3849 + 10kbC→T
F508del	711+3A→G	R1070W	G622D
A120T	E60K	F1016S	G970D
A234D	E92K	F1099L	G1069R
A349V	E116K	G126D	G1244E
A554E	E403D	G178E	G1249R
A1006E	E558V	G178R	G1349D
D192G	E822K	G194R	H939R
D443Y	F191V	G194V	H1054D
D443Y;G57A; R668C	F311del	G314E	H1375P
D614G	F311L	G551D	I148T
D836Y	F508C	G551S	I175V
D924N	F508C;S1251N	G576A	I336K
D979V	F575Y	G576A;R668C	I601F
I618T	L346P	M952T	R74Q
I807M	L967S	P5L	R74W;D1270N
I980K	L997F	P205S	R74W;V201M
I1027T	L1324P	Q98R	R74W;V201M;D1270N
I1139V	L1335P	Q237E	R75Q
I1269N	L1480P	Q237H	R117G
I1366N	M152V	Q359R	R117H
L15P	M265R	Q1291R	R117L
L320V	M952I	R31L	R117P
R170H	R1066H	S1251N	W1282R
R258G	R1070Q	S1255P	Y109N
R334L	R1162L	T338I	Y161S
R334Q	R1283M	T1036N	Y1014C
R347L	R1283S	T1053I	Y1032C
R347P	S549N	V201M	R792G
R352W	S549R	V232D	R933G
R553Q	S589N	V562I	S1159F
R668C	S737F	V754M	S1159P
R751L	S912L	V1153E	V1240G
V1293G	546insCTA		

CFTR – Cystic fibrosis transmembrane regulator; * A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation presented in Table 1 to be indicated

List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco.

(Kalydeco Prescribing Information, 12/2020)

2789+5G→A	F311del	I148T	R75Q	S549N
3272-26A→G	F311L	I175V	R1070Q	S549R
3849+10kbC→T	F508C	I807M	R1070W	S945L
711+3A→G	F508C;S1251N	I1027T	R117C	S977F
A120T	F1052V	I1139V	R117H	S589N
A234D	F1074L	K1060T	R347H	S737F
A349V	G1069R	L206W	R352Q	S1159F
A1067T	G1244E	L320V	R117G	S1159P
A455E	G1349D	L967S	R117L	T338I
D110E	G178R	L997F	R117P	T1053I
D1152H	G551D	L1480P	R170H	V232D
D110H	G551S	M152V	R347L	V562I
D192G	G194R	M952I	R553Q	V754M
D1270N	G314E	M952T	R668C	V1293G

D924N	G576A	P67L	R792G	W1282R
D579G	G970D	Q237E	R933G	Y1014C
E193K	Y1032C	Q237H	R1162L	G178E
E882K	G1249R	Q359R	R1283M	
E56K	H939R	Q1291R	S1251N	
E831X	H1375P	R74W	S1255P	

CFTR – Cystic fibrosis transmembrane regulator.

**List of CFTR Gene Mutations that are Responsive to Trikafta.
(Trikafta Prescribing Information, 12/2020)**

3141del9	A349V	D110E	D579G	D1152H	G576A;R668C
E822K	F508C;S1251N	F1074L	G178E	G463V	R74W;V201M;D1270N
G1069R	H199Y	H1375P	I601F	I1139V	S492F
L967S	L1480P	M1101K	Q98R	R31L	Y563N
R117L	R334Q	R352W	R933G	R1283M	E193K
S912L	S1251N	V201M	V754M	W1098C	G622D
546insCTA	A455E	D110H	D614G	D1270N	L206W
F191V	F508del	F1099L	G178R	G480C	R75Q
G1244E	H939R	I148T	I618T	I1269N	S549N
L997F	M152V	P5L	Q237E	R74Q	Y1014C
R117P	R347H	R553Q	R1066H	R1283S	E403D
S945L	S1255P	V232D	V1153E	W1282R	G628R
A46D	A554E	D192G	D836Y	E56K	L320V
F311del	F575Y	G27R	G194R	G551D	R117C
G1249R	H1054D	I175V	I807M	I1366N	S549R
L1077P	M265R	P67L	Q237H	R74W	Y1032C
R170H	R347L	R668C	R1070Q	S13F	E474K
S977F	T338I	V456A	V1240G	Y109N	G970D
A120T	A1006E	D443Y	D924N	E60K	L346P
F311L	F1016S	G85E	G194V	G551S	R117G
G1349D	H1085P	I336K	I980K	R74W;D1270N	S589N
L1324P	M952I	P205S	Q359R	S341P	E588V
R258G	R347P	R751L	R1070W	Y161D	G1061R
S1159F	T1036N	V456F	V1293G	E92K	L453S
A234D	A1067T	D443Y;G576A;R668C	D979V	G576A	R117H
F508C	F1052V	G126D	G314E	L15P	S737F
H139R	H1085R	I502T	I1027T	R74W;V201M	L165S
L1335P	M952T	P574H	Q1291R	S364P	K1060T
R334L	R352Q	R792G	R1162L	Y161S	
S1159P	T1053I	V562I	W361R	E116K	

CFTR – Cystic Fibrosis Transmembrane Regulator.

General Background

Disease Overview

Cystic fibrosis (CF) is an autosomal recessive disease of epithelial chloride transport.⁷ In the US, there are approximately 29,887 individuals with CF; 53.5% of individuals are ≥ 18 years of age and the remainder are < 18 years of age (46.5%). CF is caused by mutations in the gene encoding the CFTR protein. To date, > 1,800 mutations have been found in the CFTR gene. Some mutations result in almost no CFTR function and the others are associated with some residual function. In general, CFTR mutations cause reduced quantity or quality of CFTR protein at the cell surface, but the specific mechanisms leading to CFTR deficiency are distinct among different classes of mutations. The malfunctioning CFTR leads to an accumulation of unusually thick and sticky mucus in the lungs, pancreas, and other organs. The most common CFTR mutation is F508del. In the CF Registry (2017) 85.8% of patients had at least one copy of F508del; 45.3% of patients had two copies of F508del (homozygous), 40.9% of patients had one copy of F508del (heterozygous), and the remaining 13.9% of patients had no copies of F508del or their mutation status was unknown. (Farrel, 2017; CFF Patient Registry, 2017)

Pulmonary function is one of the two key measures of health in patients with CF (the other is nutritional outcome). For children, the goal is a percent predicted forced expiratory volume in 1 second (ppFEV1) \geq 100% and body mass index (BMI) percentile \geq 50th percentile. For adults, the goal is ppFEV1 \geq 75% and BMI \geq 22 kg/m² or 23 kg/m² for women and men, respectively. The majority of patients who are 18 years of age (a typical age of transition to adult care) have a ppFEV1 \geq 70%. The proportion of individuals with CF who are \geq 18 years of age with normal/mild CF (ppFEV1 \geq 70%) has increased over time to 74%. The proportion of patients in the severe category (ppFEV1 $<$ 40%) has decreased over time to 4%. Although pulmonary function in individuals with CF has improved over time, the pattern of decreasing pulmonary function beginning in adolescence persists. Research shows that people with CF of all ages, including infants, have some lung damage, even when ppFEV1 is within the normal range. This damage to the lungs is primarily the result of mucus buildup and lung infections. (Farrel, 2017; CFF Patient Registry, 2017)

Pulmonary exacerbations are associated with morbidity, mortality, and decreased quality of life in patients with CF. Despite notable improvements in pulmonary function and nutritional status over the years, there has been a minimal reduction in the proportion of individuals with CF who are treated with intravenous antibiotics for pulmonary exacerbations. (CFF Patient Registry, 2017)

There are four targeted therapies for patients with CF. All of the targeted therapies have different age indications; however, some general indications overlap. Approximately 80% of patients with CF are eligible for treatment with at least one of the four approved CFTRs. It is estimated that Kalydeco is indicated in 16% of patients (n = 4,600), Orkambi in 44% of patients (n = 12,600), Symdeko in 46% of patients (n = 13,300), and Trikafta in 60% of patients (n = 17,300).

Symdeko and Kalydeco are indicated in patients with similar non-F508del CFTR mutations (E56K, P67L, R74W, D110ED110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3AàG, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5GàA, 3849+10kbCàT); Symdeko is indicated in patients \geq 6 years of age and Kalydeco is indicated for those \geq 6 month of age. Kalydeco is uniquely indicated in patients with the following mutations: R117H, G178R, S549N, S549R, G551D, G551S, G1069R, R1069R, R1070Q, G1244E, S1251N, and S1255P. According to the CF patient registry data, only two of these mutations are among the top 25 mutations identified in individuals with CF (R117H in 2.9% of patients and G551D in 4.5% of patients); the other mutations unique to Kalydeco occur in $<$ 0.5% of the total CF population. Trikafta is the only targeted product with data to support use in patients with one F508del mutation a minimal function mutation. A minimal function mutation is defined as a mutation in which there is complete absence of protein production or lack of in vitro responsiveness to ivacaftor and tezacaftor/ivacaftor. (CFF Patient Registry, 2017; Middleton, 2019)

Professional Societies/Organizations Guidelines

Cystic Fibrosis Foundation Pulmonary Guidelines. Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Symdeko and Trikafta are not addressed in published guidelines at this time.

For adults and children (aged 6 years and older) that have Cystic Fibrosis that is due to gating mutations other than G551D or R117H, the guidelines conditionally recommended treatment with Ivacaftor. For those CP patients with a R117H mutation, the guidelines conditionally recommend treatment with Ivacaftor for the following:

- 1) Adults aged 18 years or older
- 2) Children aged 6–17 years and a forced expiratory volume in 1 second (FEV₁) that is less than 90% predicted

For those with the R117H mutation, the guidelines conditionally recommend against treatment with Ivacaftor for the following:

- 1) Children aged 12–17 years with an FEV₁ that is greater than 90% predicted

2) Children less than 6 years of age

Among those patients with two copies of the F508del, the guidelines made a strong recommendation for treatment with Ivacaftor/Lumacaftor for adults and children aged 12 years and older with an FEV₁ less than 90% predicted. Additionally, the guidelines conditionally recommend treatment with Ivacaftor/Lumacaftor for the following:

- 1) Adults and children aged 12 years or older with an FEV₁ greater than 90% predicted
- 2) Children aged 6–11 years. (Ren et al, 2018)

American College of Medical Genetics (ACMG)

Regarding genetic testing for CF, ACMG (2004, reaffirmed 2013) recommends a pan-ethnic carrier screening panel (ACMG-23) that analyzes 23 core mutations of the *CFTR* gene. The ACMG-23 includes the following mutations, listed in descending order of their occurrence: delF508, G542X, W1282X, G551D, 621+1G>T, N1303K, R553X, dell507, 3849+10kbC>T, 3120+1G>T, R117H, 1717-1G>T, 2789+5G>A, R334W, R560T, R1162X, 3569delC, A455E, G85E, 2184delA, 1898+aG>A, 1148T, 1078delT. These genes represent 84% of the mutations that occur in this subpopulation. The pan-ethnic population includes: non-Hispanic Caucasians, Hispanic Caucasians, African Americans, Asian Americans, and Ashkenazi Jewish. (Watson, 2004)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:

No recommendations are available for CFTR modulator therapy (Kalydeco,® Orkambi,® Symdeko® or Trikafta™).

Other Uses with Supportive Evidence

AHFS Drug Information 2020 Edition does not support any off-label uses of Kalydeco,® Orkambi,® Symdeko® or Trikafta™

Other Uses without Supportive Evidence

- **Kalydeco Use in Cystic Fibrosis Individuals with Homozygous F508del CFTR Mutation** - Efficacy results from a double-blind, placebo controlled trial in patients with CF who were homozygous for the phe508del mutation in the CFTR gene showed no statistically significant difference in FEV₁ over 16 weeks of Kalydeco treatment compared with placebo. In a Phase II trial in patients homozygous for the F508del (n = 112) Kalydeco did not result in an improvement in FEV₁ relative to placebo. (Flume, 2012)
- **Cystic Fibrosis (CF) Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** According to the prescribing information for all of the CFTR modulators a Food and Drug Administration (FDA)-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of any CFTR modulator therapy.
- **Combination Therapy with other CFTR modulators** - Orkambi, Symdeko, and Trikafta contain ivacaftor, the active agent in Kalydeco and therefore are not indicated in combination with Kalydeco or with each other. Symdeko also contains tezacaftor, part of Trikafta.
- **Orkambi use in Cystic Fibrosis Individuals Heterozygous for the F508del Mutation in the CFTR Gene.** Orkambi is not indicated for patients with only one copy of the F508del mutation in the CFTR gene. (Vertex [Orkambi PI], 2018) Patients who are heterozygous for the F508del mutation and have one of the following mutations are potential candidates for Kalydeco therapy: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D, or R117H. (Vertex [Kalydeco PI], 2019)

Coding/Billing Information

Note: Kalydeco, Orkambi, Symdeko, and Trikafta are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

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