

PHARMACY POLICY – 5.01.539


Pharmacologic Treatment of Cystic Fibrosis

Effective Date: May 1, 2025
Last Revised: Apr. 8, 2025
Replaces: N/A

RELATED MEDICAL POLICIES:
None

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

Introduction

Cystic fibrosis is a condition that causes thick, sticky mucus to build up in the lungs, digestive tract, and other areas of the body and is caused by change(s) to the *CFTR* gene. A child inherits one *CFTR* gene from each parent. If two faulty *CFTR* genes are inherited, it leads to cystic fibrosis. (If children inherit one problematic *CFTR* gene, they usually won't have symptoms of cystic fibrosis but can pass the changed gene to their children.) The change(s) in the *CFTR* gene results in problems with how salt moves in and out of cells. The end result is a buildup of sticky, thick mucus. Drugs have been developed that target specific changes on the *CFTR* gene. This policy describes when these drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Alyftrek (vanzacaftor/tezacaftor/deutivacaftor)	<p>Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) may be considered medically necessary for the treatment of cystic fibrosis (CF) when all the following criteria are met:</p> <ul style="list-style-type: none"> • The individual is aged 6 years and older <p>AND</p> <ul style="list-style-type: none"> • Has at least one <i>F508del</i> mutation in the <i>CFTR</i> gene OR another responsive mutation in the <i>CFTR</i> gene (Related Information) <p>AND</p> <ul style="list-style-type: none"> • Does not have liver function tests (LFT) above 3X upper limit of normal (ULN) <p>AND</p> <ul style="list-style-type: none"> • Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) will not be used in combination with Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor) <p>AND</p> <ul style="list-style-type: none"> • Dose is limited to three tablets of a fixed-dose combination containing vanzacaftor 4 mg, tezacaftor 20 mg, and deutivacaftor 50 mg OR two tablets of a fixed-dose combination containing vanzacaftor 10 mg, tezacaftor 50 mg, and deutivacaftor 125 mg daily
Kalydeco (ivacaftor)	<p>Kalydeco (ivacaftor) may be considered medically necessary for the treatment of cystic fibrosis (CF) when all the following criteria are met:</p> <ul style="list-style-type: none"> • The individual is aged 1 month and older <p>AND</p> <ul style="list-style-type: none"> • Has one of the following <i>CFTR</i> gene mutations listed in table below OR any <i>CFTR</i> gene mutation subsequently added to the FDA-approved indication as responsive to Kalydeco (Related Information) <p>AND</p> <ul style="list-style-type: none"> • Documentation of at least one copy of the <i>CFTR</i> gene mutation <p>AND</p> <ul style="list-style-type: none"> • Does not have liver function tests (LFT) above 3X upper limit of normal (ULN) <p>AND</p>



Drug	Medical Necessity
	<ul style="list-style-type: none"> Kalydeco (ivacaftor) will not be used in combination with Alyftrek (vanzacaftor/tezacaftor/deutivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/ tezacaftor/ivacaftor) <p>AND</p> <ul style="list-style-type: none"> Dose is limited to two tablets OR two packets daily <p>Note: Since <i>CFTR</i> is recessive, heterozygous individuals with one allele containing one of the above mutations are candidates for therapy; however, a minority of CF individuals carry these mutations. There is no demonstrated benefit in others, nor is any expected.</p> <p>Kalydeco (ivacaftor) is considered not medically necessary when used in individuals that have homozygous F508del, and in individuals that have G970R and do not have at least one copy of one of the above target mutations.</p>
Orkambi (lumacaftor/ivacaftor)	<p>Orkambi (lumacaftor/ivacaftor) may be considered medically necessary for the treatment of cystic fibrosis (CF) when all the following criteria are met:</p> <ul style="list-style-type: none"> The individual is aged 1 year and older <p>AND</p> <ul style="list-style-type: none"> Is homozygous for the F508del mutation in the <i>CFTR</i> gene <p>AND</p> <ul style="list-style-type: none"> Does not have liver function tests (LFT) above 3X upper limit of normal (ULN) <p>AND</p> <ul style="list-style-type: none"> Orkambi (lumacaftor/ivacaftor) will not be used in combination with Alyftrek (vanzacaftor/tezacaftor/deutivacaftor), Kalydeco (ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/ tezacaftor/ivacaftor) <p>AND</p> <ul style="list-style-type: none"> Dose is limited to four tablets or two packets daily
Symdeko (tezacaftor/ivacaftor)	<p>Symdeko (tezacaftor/ivacaftor) may be considered medically necessary for the treatment of cystic fibrosis (CF) when all the following criteria are met:</p> <ul style="list-style-type: none"> The individual is aged 6 years and older



Drug	Medical Necessity
	<p>AND</p> <ul style="list-style-type: none"> Is homozygous for the <i>F508del</i> mutation in the <i>CFTR</i> gene OR heterozygous for <i>F508del</i> with a residual function mutation <p>OR</p> <ul style="list-style-type: none"> Have at least one mutation in the <i>CFTR</i> gene that is responsive to Symdeko or subsequently added to the FDA-approved indication (Related Information) <p>AND</p> <ul style="list-style-type: none"> Does not have liver function tests (LFT) above 3X upper limit of normal (ULN) <p>AND</p> <ul style="list-style-type: none"> Symdeko (tezacaftor/ivacaftor) will not be used in combination with Alyftrek (vanzacaftor/tezacaftor/deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), or Trikafta (elexacaftor/ tezacaftor/ivacaftor) <p>AND</p> <ul style="list-style-type: none"> Dose is limited to two tablets daily
Trikafta (elexacaftor/tezacaftor/ivacaftor)	<p>Trikafta (elexacaftor/tezacaftor/ivacaftor) may be considered medically necessary for the treatment of cystic fibrosis (CF) when all the following criteria are met:</p> <ul style="list-style-type: none"> The individual is aged 2 years and older <p>AND</p> <ul style="list-style-type: none"> Has at least one <i>F508del</i> mutation in the <i>CFTR</i> gene OR a mutation in the <i>CFTR</i> gene that is responsive based on clinical and/or in vitro data (Related Information) <p>AND</p> <ul style="list-style-type: none"> Does not have liver function tests (LFT) above 3X upper limit of normal (ULN) <p>AND</p> <ul style="list-style-type: none"> Trikafta (elexacaftor/ tezacaftor/ivacaftor) will not be used in combination with Alyftrek (vanzacaftor/tezacaftor/deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), or Symdeko (tezacaftor/ivacaftor) <p>AND</p> <ul style="list-style-type: none"> Dose is limited to three tablets OR two packets daily

Drug	Medical Necessity

Drug	Investigational
<ul style="list-style-type: none"> • Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) • Kalydeco (ivacaftor) • Orkambi (lumacaftor/ivacaftor) • Symdeko (tezacaftor/ivacaftor) • Trikafta (elexacaftor/tezacaftor/ivacaftor) 	<p>All other uses of Alyftrek (vanzacaftor/ tezacaftor/ deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor) for conditions not outlined in this policy are considered investigational.</p> <p>The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.</p>

Length of Approval	
Approval	Criteria
Initial authorization	<p>Non-formulary exception reviews for Alyftrek (vanzacaftor/ tezacaftor/ deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor) may be approved up to 12 months.</p> <p>All other reviews for Alyftrek (vanzacaftor/ tezacaftor/ deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor) may be approved up to 6 months.</p>
Re-authorization criteria	<p>Non-formulary exception reviews and all other reviews for Alyftrek (vanzacaftor/ tezacaftor/ deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), or Trikafta (elexacaftor/tezacaftor/ivacaftor) may be approved up to 12 months in duration when documentation provided at the time of re-authorization show:</p>

Length of Approval

Approval	Criteria
	<ul style="list-style-type: none">The coverage criteria as outlined above are met AND <ul style="list-style-type: none">The individual has shown and continues to show improvement in FEV1, symptoms or stabilization of disease

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, results of *CFTR* gene mutation tests, physical evaluation and medication history

Coding

N/A

Related Information

Benefit Application

This policy is managed through the pharmacy benefit.

CFTR Gene Mutations Responsive to Alyftrek

CFTR Gene Mutations Responsive to Alyftrek Based on Clinical Data						
A455E	G551D	L1077P	R352Q	S549N	V754M	
D1152H	G85E	L206W	R75Q	S549R	W1098C	
F508del	H1054D	M1101K	S1159F	S945L	W1282R	



G1244E	I336K	R1066H	S1251N	V562I	Y563N	
--------	-------	--------	--------	-------	-------	--

CFTR Gene Mutations Responsive to Alyftrek Based on in vitro Data

1507_1515del9	E116Q	G424S	I556V	P140S	R334L	T1053I
2183A→G	E193K	G463V	I601F	P205S	R334Q	T1086I
3141del9	E292K	G480C	I618T	P499A	R347H	T1246I
3195del6	E403D	G480S	I807M	P5L	R347L	T1299I
3199del6	E474K	G551A	I980K	P574H	R347P	T338I
546insCTA	E56K	G551S	K1060T	P67L	R352W	T351I
A1006E	E588V	G576A	K162E	P750L	R516G	T604I
A1067P	E60K	G576A;R668C	K464E	P99L	R516S	V1153E
A1067T	E822K	G622D	L1011S	Q1100P	R553Q	V1240G
A107G	E92K	G628R	L102R	Q1291R	R555G	V1293G
A120T	F1016S	G91R	L1065P	Q1313K	R560S	V201M
A234D	F1052V	G970D	L1324P	Q237E	R560T	V232D
A309D	F1074L	G970S	L1335P	Q237H	R668C	V392G
A349V	F1099L	H1085P	L137P	Q359R	R709Q	V456A
A46D	F1107L	H1085R	L1480P	Q372H	R74Q	V456F
A554E	F191V	H1375P	L15P	Q452P	R74W	V520F
A559T	F200I	H139R	L165S	Q493R	R74W;D1270N	V603F
A559V	F311del	H199R	L320V	Q552P	R74W;V201M	W361R
A561E	F311L	H199Y	L333F	Q98R	R74W;V201M;D1270N	Y1014C



A613T	F508C	H609R	L333H	R1048G	R75L	Y1032C
A62P	F508C;S1251N	H620P	L346P	R1066C	R751L	Y109N
A72D	F575Y	H620Q	L441P	R1066L	R792G	Y161D
C491R	F587I	H939R	L453S	R1066M	R933G	Y161S
D110E	G1047R	H939R;H949L	L619S	R1070Q	S1045Y	Y301C
D110H	G1061R	I1027T	L967S	R1070W	S108F	Y569C
D1270N	G1069R	I105N	L997F	R1162L	S1118F	Y913C
D1445N	G1123R	I1139V	M1101R	R117C	S1159P	
D192G	G1247R	I1234Vdel6aa	M1137V	R117C;G576A;R668C	S1235R	
D443Y	G1249R	I125T	M150K	R117G	S1255P	
D443Y;G576A;R668C	G126D	I1269N	M152V	R117H	S13F	
D513G	G1349D	I331N	M265R	R117L	S341P	
D565G	G149R	I1366N	M952I	R117P	S364P	
D579G	G178E	I1398S	M952T	R1283M	S492F	
D614G	G178R	I148N	N1088D	R1283S	S549I	
D836Y	G194R	I148T	N1303I	R170H	S589N	
D924N	G194V	I175V	N1303K	R258G	S737F	
D979V	G27E	I502T	N186K	R297Q	S912L	
D993Y	G27R	I506L	N187K	R31C	S977F	
E116K	G314E	I506T	N418S	R31L	T1036N	

CFTR Gene Mutations Responsive to Alyftrek Based on Extrapolation



1341G→A	2789+2insA	3041-15T→G	3849+10kbC→T	3850-3T→G	5T;TG13	711+3A→G
1898+3A→G	2789+5G→A	3272-26A→G	3849+4A→G	4005+2T→C	621+3A→G	E831X
2752-26A→G	296+28A→G	3600G→A	3849+40A→G	5T;TG12		

CFTR Gene Mutations Responsive to Kalydeco

CFTR Gene Mutations Responsive to Kalydeco				
711+3A→G	F311del	I148T	R75Q	S589N
2789+5G→A	F311L	I175V	R117C	S737F
3272-26A→G	F508C	I807M	R117G	S945L
3849+10kbC→T	F508C;S1251N	I1027T	R117H	S977F
A120T	F1052V	I1139V	R117L	S1159F
A234D	F1074L	K1060T	R117P	S1159P
A349V	G178E	L206W	R170H	S1251N
A455E	G178R	L320V	R347H	S1255P
A1067T	G194R	L967S	R347L	T338I
D110E	G314E	L997F	R352Q	T1053I
D110H	G551D	L1480P	R553Q	V232D
D192G	G551S	M152V	R668C	V562I
D579G	G576A	M952I	R792G	V754M
D924N	G970D	M952T	R933G	V1293G
D1152H	G1069R	P67L	R1070Q	W1282R
D1270N	G1244E	Q237E	R1070W	Y1014C
E56K	G1249R	Q237H	R1162L	Y1032C
E193K	G1349D	Q359R	R1283M	

E822K	H939R	Q1291R	S549N	
E831X	H1375P	R74W	S549R	

CFTR Gene Mutations Responsive to Symdeko

CFTR Gene Mutations Responsive to Symdeko					
546insCTA	E92K	G576A	L346P	R117G	S589N
711+3A→G	E116K	G576A;R668C	L967S	R117H	S737F
2789+5G→A	E193K	G622D	L997F	R117L	S912L
3272-26A→G	E403D	G970D	L1324P	R117P	S945L
3849+10kbC→T	E403D	G1069R	L1335P	R170H	S977F
A120T	E822K	G1244E	L1480P	R258G	S1159F
A234D	E831X	G1249R	M152V	R334L	S1159P
A349V	F191V	G1349D	M265R	R334Q	S1251N
A455E	F311del	H939R	M952I	R347H	S1255P
A554E	F311L	H1054D	M952T	R347L	T338I
A1006E	F508C	H1375P	P5L	R347P	T1036N
A1067T	F508C;S1251N	I148T	P67L	R352Q	T1053I
D110E	F508del	I175V	P205S	R352W	V201M



D110H	F575Y	I336K	Q98R	R553Q	V232D
D192G	F1016S	I601F	Q237E	R668C	V562I
D443Y	F1052V	I618T	Q237H	R751L	V754M
D443Y;G576A;R668C	F1074L	I807M	Q359R	R792G	V1153E
D579G	F1099L	I980K	Q1291R	R933G	V1240G
D614G	G126D	I1027T	R31L	R1066H	V1293G
D836Y	G178E	I1139V	R74Q	R1070Q	W1282R
D924N	G178R	I1269N	R74W	R1070W	Y109N
D979V	G194R	I1366N	R74W;D1270N	R1162L	Y161S
D1152H	G194V	K1060T	R74W;V201M	R1283M	Y1014C
D1270N	G314E	L15P	R74W;V201M;D1270N	R1283S	Y1032C
E56K	G551D	L206W	R75Q	S549N	
E60K	G551S	L320V	R117C	S549R	

CFTR Gene Mutations Responsive to Trikafta

Mutations responsive to Trikafta based on clinical data

2789+5G→A	D1152H	L206W	R1066H	S945L
-----------	--------	-------	--------	-------



3272-26A→G	F508del	L997F	R117C	T338I
3849+10kbC→T	G85E	M1101K	R347H	V232D
A455E	L1077P	P5L	R347P	

Mutations responsive to Trikafta based on in vitro data

N1303K	F200I	I1139V	P574H	S1045Y
1507_1515del9	F311del	I125T	P67L	S108F
2183A→G	F311L	I1269N	P750L	S1118F
3141del9	F508C	I1366N	Q1291R	S1159F
546insCTA	F508C;S1251N	I148N	Q1313K	S1159P
A1006E	F575Y	I148T	Q237E	S1235R
A1067P	F587I	I175V	Q237H	S1251N
A1067T	G1047R	I331N	Q359R	S1255P



A107G	G1061R	I336K	Q372H	S13F
A120T	G1069R	I502T	Q493R	S341P
A234D	G1123R	I506L	Q552P	S364P
A309D	G1244E	I556V	Q98R	S492F
A349V	G1247R	I601F	R1048G	S549I
A46D	G1249R	I618T	R1070Q	S549N
A554E	G126D	I807M	R1070W	S549R
A62P	G1349D	I980K	R1162L	S589N
C491R	G178E	K1060T	R117C;G576A;R668C	S737F
D110E	G178R	K162E	R117G	S912L
D110H	G194R	K464E	R117H	S977F
D1270N	G194V	L1011S	R117L	T1036N
D1445N	G27E	L1324P	R117P	T1053I



D192G	G27R	L1335P	R1283M	T1086I
D443Y	G314E	L137P	R1283S	T1246I
D443Y;G576A;R668C	G424S	L1480P	R170H	T1299I
D565G	G463V	L15P	R258G	T351I
D579G	G480C	L165S	R297Q	V1153E
D614G	G480S	L320V	R31C	V1240G
D836Y	G551A	L333F	R31L	V1293G
D924N	G551D	L333H	R334L	V201M
D979V	G551S	L346P	R334Q	V392G
D993Y	G576A	L441P	R347L	V456A
E116K	G576A;R668C	L453S	R352Q	V456F
E116Q	G622D	L619S	R352W	V562I
E193K	G628R	L967S	R516S	V603F



E292K	G970D	M1137V	R553Q	V754M
E403D	G970S	M150K	R555G	W1098C
E474K	H1054D	M152V	R668C	W1282R
E56K	H1085P	M265R	R709Q	W361R
E588V	H1085R	M952I	R74Q	Y1014C
E60K	H1375P	M952T	R74W	Y1032C
E822K	H139R	N1088D	R74W;D1270N	Y109N
E92K	H199Y	N1303I	R74W;V201M	Y161D
F1016S	H620P	N186K	R74W;V201M;D1270N	Y161S
F1052V	H620Q	N187K	R751L	Y301C
F1074L	H939R	N418S	R75L	Y563N
F1099L	H939R;H949L	P140S	R75Q	
F1107L	I1027T	P205S	R792G	



F191V	I105N	P499A	R933G	
-------	-------	-------	-------	--

Mutations responsive to Trikafta based on in vitro data				
4005+2T→C	2789+2insA	3849+40A→G	5T;TG13	
1341G→A	296+28A→G	3849+4A→G	621+3A→G	
1898+3A→G	3041-15T→G	3850-3T→G	711+3A→G	
2752-26A→G	3600G→A	5T;TG12	E831X	

Evidence Review

Description

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive genetic disorder passed down through families that causes thick, sticky mucus to build up in the lungs, digestive tract, and other areas of the body. It is one of the most common chronic lung diseases in children and young adults and is considered a life-threatening disorder. Survival has increased for individuals with cystic fibrosis from the late teens to the mid-30s due in part to the many medical advances in diagnosis and treatment of the symptoms and sequelae of the disease. However, there is no cure.

CF is caused by a mutation in the gene cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, $\Delta F508$, is a deletion (Δ) of three nucleotides that results in a loss of the amino acid phenylalanine (F) at the 508th position on the protein. This mutation accounts for two-thirds (66-70%) of CF cases worldwide and 90% of cases in the United States; however, there are over 1500 other mutations that can produce cystic fibrosis. Although most

people have two working copies (alleles) of the CFTR gene, only one is needed to prevent cystic fibrosis. CF develops when neither allele can produce a functional CFTR protein. Thus, CF is considered an autosomal recessive disease.

Cystic fibrosis affects approximately 30,000 children and adults in the United States, and approximately 36,000 children and adults in Europe. Approximately one in 3,500 children in the United States is born with CF each year, and CF affects all ethnic and racial groups, although is most common in Caucasians. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is the mid-30's. In the United States, approximately 90% of individuals carry at least one $\Delta F508$ allele with 60-70% of individuals being homozygous for $\Delta F508$. Worldwide, ~4% of individuals carry the G551D mutation. Most of these are heterozygous, with the other allele having $\Delta F508$. Since CF is a recessive trait, these individuals would be expected to respond to treatment with ivacaftor.

The CFTR gene encodes an epithelial chloride channel, the CFTR protein, which is responsible for aiding in the regulation of salt and water absorption and secretion in multiple organ systems, including the lungs, pancreas, intestinal tract, biliary tract, sweat gland, and reproductive tract. Mutations in the CFTR gene that result in CF disease do so by reducing the quantity of CFTR protein channels that reach the cell surface or by reducing the chloride transport function of CFTR protein channels at the cell surface. CFTR protein channel dysfunction is the underlying cause of CF disease.

The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF. The majority of individuals with CF die from progressive lung disease. In the airways of individuals with CF, impaired chloride channel function results in a reduction of the height of the periciliary fluid layer. This occurs as a consequence of altered osmotic forces secondary to reduced CFTR-dependent chloride ion secretion and its associated sodium ion hyperabsorption into the epithelia. The reduced height of the periciliary fluid layer results in a reduced ability of the cilia to effectively clear mucus, trapped pathogens and particulates from the lungs. Mucus retention then leads to airway plugging, chronic infection of the lung passages, and inflammatory responses that in turn cause scarring of airway tissue and progressive and permanent loss of lung function.

While the clinical manifestations of CF vary between individuals, several studies indicate an association between the type of CFTR mutations present in an individual, the degree of residual CFTR protein function and the severity of CF pulmonary disease, pancreatic function, and mortality. Severe CF disease ("classical CF") is typically characterized by an early onset of clinical manifestations, a high incidence of pancreatic insufficiency, airway colonization with *Pseudomonas aeruginosa*, a more rapid rate of lung function decline, and shorter life expectancy. Most individuals with severe CF carry 2 CFTR mutations associated with minimal

CFTR protein function and therefore sweat chloride concentrations in individuals with severe disease are generally 90 mmol/L or greater. Most of the common CFTR mutations are associated with minimal CFTR protein channel function and therefore with a severe CF disease course. While reports of individual cases and small cohorts of individuals show variable phenotypes in individuals carrying the G551D mutation, the 3 largest genotype phenotype association studies that evaluated individuals from different geographical regions have classified the G551D mutation as being associated with severe CF disease, with rates of lung disease progression and mortality that are similar to other severe phenotypes.

The F508del mutation is the most common mutation in the CFTR gene associated with CF disease. It causes a defect in CFTR protein folding. F508del-CFTR proteins are generally retained and degraded within the cell instead of being trafficked to the apical cell membrane. The result is little to no CFTR protein reaching the cell surface and as a consequence severe reduction in CFTR-mediated chloride ion transport.

In contrast to mutations such as F508del, the G551D mutation in the CFTR gene does not impact the quantity of CFTR channels present at the cell membrane. The G551D mutation is an amino acid substitution located in the first of two nucleotide binding domains within the CFTR protein. The nucleotide binding domains bind and hydrolyze ATP to drive opening (or gating) of the CFTR channel pore, thereby allowing transport of chloride and other ions. The G551D substitution affects the ATP binding ability of the nucleotide binding domain, thereby greatly reducing channel gating activity and, as a consequence, CFTR-mediated chloride ion transport. G551D is the most prevalent CFTR gating mutation. Mutations in the CFTR gene that result in alterations of the CFTR channel pore structure can also limit or eliminate the rate of ion flow through the channel. Mutations of this type are referred to as "conductance" mutations.

There are societal, humanistic and economic burdens associated with cystic fibrosis.

- Individuals with CF experience severe progressive dysfunction primarily in the lungs and digestive system, resulting in life-threatening manifestations that persist over their lifetime and negatively impact quality of life.
- Rates of depression among CF individuals and their caregivers have consistently been shown to be higher than the general population.
- Maintenance therapy for CF places a significant burden on individuals with CF as well as caregivers
- The number of outpatient visits to health care providers is high, with adults averaging 12 doctor visits and children averaging 10 visits annually in a study of a large commercial/Medicaid U.S. health insurer.



- Comorbidities and manifestations of the disease increase treatment burden.

Alyftrek (vanzacaftor/ tezacaftor/ deutevacaftor)

The approval of Alyftrek was supported by results from the Phase 3 SKYLINE 102 and SKYLINE 103 trials, which compared once-daily Alyftrek with twice-daily Trikafta (elexacaftor, tezacaftor, and ivacaftor) in individuals ≥ 12 years of age. The trial met its primary and secondary endpoints, with Alyftrek demonstrating noninferiority in the absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) compared with Trikafta, and a superior reduction in sweat chloride (SwCl) levels through Week 24. Alyftrek was also evaluated in the single-arm, 24-week Phase 3 RIDGELINE 105 trial in children aged 6 to 11 years. The trial demonstrated a safety profile consistent with the SKYLINE trials, which was the primary endpoint. Additionally, it showed further reduced levels of SwCl compared with baseline treatment with Trikafta. The safety profile of Alyftrek is similar to that of Trikafta, and its labeling includes the same Boxed Warning for drug-induced liver injury and liver failure that was added to Trikafta's label on December 20, 2024.

Kalydeco (ivacaftor)

Kalydeco (ivacaftor) is a potentiator of the CFTR protein and is the first drug that directly targets the defective CFTR protein rather than cystic fibrosis symptoms. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor appears to increase the probability of CFTR channel opening (or gating) to enhance chloride transport, which allows chloride and bicarbonate flow across epithelial cell membranes present in individuals with the G551D mutation. Different testing panels might be employed for identification of CFTR mutations in individuals diagnosed with CF, in relatives of CF individuals, or in newborn screening. The minimum standard panel includes G551D and therefore would identify suitable candidates for ivacaftor therapy. Sensitivity for detection of G551D in generalized screening is 88%; specificity is greater than 99%.

Efficacy/Effectiveness

Efficacy of ivacaftor was demonstrated in cystic fibrosis individuals with a G551D mutation in two randomized, double-blind, placebo-controlled Phase 3 clinical trials of 48 weeks duration. Treatment with ivacaftor demonstrated improved lung function (absolute change in percent



predicted FEV1 from baseline to week 24) by 10 and 12% in trials in adolescents/adults, and in children 6 to 11 years of age, respectively. Secondary endpoints, including weight gain and time to first pulmonary exacerbation, also support efficacy. No evidence of real-world comparative effectiveness was available at the time of review. Ivacaftor is a first in class drug for which there is no approved CF therapy that could serve as an active comparator.

In 2014 the FDA approved ivacaftor for several other CFTR mutations: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R. The efficacy of ivacaftor in individuals with these polymorphisms was evaluated in a two-part double-blind placebo-controlled crossover RCT with 39 individuals ≥ 6 years old (mean age 23) with baseline FEV1 $\geq 40\%$ of predicted (mean 78%, range: 43% to 119%). Individuals received either 150 mg of ivacaftor or placebo every 12 hours for 8 weeks in addition to their routine meds. After a 4-8 week washout period they were crossed over to the other treatment for the second 8 weeks. Treatment with ivacaftor significantly improved percent predicted FEV1 (10.7% through Week 8, $P < 0.0001$). Improvements from baseline in sweat chloride and BMI, and improvement in CF symptoms (including cough, sputum production, and difficulty breathing) were also observed; however, there was a high degree of variability of efficacy responses among the 9 mutations. Based on clinical and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in individuals with the G970R mutation could not be established.

The deletion mutation at F508 in the CFTR gene is the most common in the U.S. population; however, a 16-week trial of ivacaftor in individuals with homozygous F508del failed to produce significant improvement.

The safety and tolerability of Kalydeco was assessed in phase 3, open-label study focusing on a subgroup of participants consisting of forty-three children between the ages of 1 month and less than 2 years, who had CF with ivacaftor response mutations. These children received Kalydeco as part of the study. The primary objective of the study was to evaluate the trough concentrations of ivacaftor, M1 ivacaftor, and M6 ivacaftor. As a secondary outcome, the study aimed to measure the absolute change in sweat chloride levels from baseline. Pharmacokinetics analysis indicated the exposure of ivacaftor in pediatric individuals aged 1 month to less than 24 months were within the range observed in individuals 6 years and older.

Safety/Tolerability

Ivacaftor was well-tolerated and demonstrated no major safety signals in clinical trials. No deaths were reported, AEs were generally those associated with cystic fibrosis (i.e., GI issues, exacerbations, pneumonia). Common adverse events included headache, upper respiratory tract

infection, nasal congestion, nausea, rash, rhinitis, dizziness, arthralgia, and bacteria in sputum, generally well-tolerated. Laboratory assessments suggest the possibility that ivacaftor may be associated with an increase in liver transaminases, but the increase was only slightly over those who received placebo treatment in the clinical trials. Transaminases are recommended to be monitored in individuals receiving the drug.

Orkambi (lumacaftor/ivacaftor)

Orkambi (lumacaftor/ivacaftor) is a combination of two drugs: a CFTR potentiator (ivacaftor) and a drug to increase the quantity of CFTR ion channels (lumacaftor). Together they provide a new approach to the treatment of cystic fibrosis in individuals homozygous for the F508del CFTR mutation by improving the quantity and function of the CFTR protein.

Efficacy/Effectiveness

Lumacaftor/ivacaftor displayed a modest improvement in individuals homozygous for the F508del CFTR mutation in measurable outcomes of lung function, BMI, quality of life and decreased pulmonary exacerbations in the two phase III trials (total n=1108), TRAFFIC and TRANSPORT. ppFEV1 increased +2.8%, BMI P&T Committee Agenda 126 September 2015 Vol. 16, No. 3 increased +0.24, CFQR-RD score increased +2.2 and the rate ratio of pulmonary exacerbations was 0.61 when compared to placebo. Results were based off of 24-week trials in individuals 6 years and older. The clinical significance in the absolute change in FEV1 as well as the change in the other outcomes is unknown.

Safety/Tolerability

Lumacaftor/ivacaftor displayed a safety profile similar to placebo in most adverse event types, with the primary exception in serious adverse events where LUM/IVA exhibited superior safety (rate of SAE 28.6% in placebo vs 17.3% in LUM/IVA). This was primarily a result of significantly decreased pulmonary exacerbations of CF, 24.1% placebo vs. 11.1% LUM/IVA.



Symdeko (tezacaftor/ivacaftor)

Symdeko (tezacaftor/ivacaftor) is a combination CFTR corrector and potentiator indicated for individuals with CF and are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence. Tezacaftor/ivacaftor provides a novel treatment option for individuals heterozygous for F508del and a residual mutation function while providing an alternative to Orkambi for those homozygous for F508del.

Efficacy/Effectiveness

Symdeko (tezacaftor/ivacaftor) was evaluated in two pivotal clinical trials assessing efficacy in individuals homozygous for the F508del mutation or heterozygous for F508del and a residual function mutation. These trials showed modest improvements in lung function and patient-centered quality of life measures.

EVOLVE was a phase III, double-blind, multicenter, placebo-controlled, parallel group RCT that randomized 510 individuals older than 12 years and homozygous for the F508del CFTR mutation and FEV1 between 40% and 90% to tezacaftor/ivacaftor or placebo. The primary endpoint of absolute change in predicted FEV1 through week 24 was 3.4% (2.7%, 4.0%) and -0.6% (-1.3%, 0.0%) and a difference of 4.0% (3.1%, 4.8%; $p < 0.001$) for TEZ/IVA and placebo respectively. There was also improvement in relative change from predicted FEV1 with a difference of 6.8% (5.3%, 8.3%; $p < 0.001$) from tezacaftor/ivacaftor over placebo. Quality of life measures related to lung function was also improved in the tezacaftor/ivacaftor group, with an improvement of 5.0 (3.5, 6.5) points in the CFQ-R respiratory domain score and a difference of 5.1 (3.2, 7.0) points over placebo. The EVOLVE trial is of good quality and demonstrates superiority of tezacaftor/ivacaftor over placebo.

EXPAND was a phase III, double-blind, placebo-controlled, crossover RCT that evaluated 244 individuals 12 years or older who are heterozygous for the F508del CFTR mutation and a second allele with a residual-function CFTR mutation. Absolute change in predicted FEV1 was 4.7% (3.7%, 5.8%; $p < 0.001$) for IVA vs PBO, 6.8% (4.7%, 7.8%; $p < 0.001$) for tezacaftor/ivacaftor vs PBO, and 2.1% (1.2%, 2.9%; $p < 0.001$) for tezacaftor/ivacaftor vs IVA. Tezacaftor/ivacaftor also increased CFQ-R scores by 11.1 (8.7, 13.6; $p < 0.001$) versus PBO. The crossover design of EXPAND is not optimal due to confounding by carryover effects, although the 8-week washout period is comparable to the treatment period of 8 weeks. The difficulty of obtaining individuals with rare mutations to power the study for a traditional parallel group design should also be noted.



Safety/Tolerability²²⁻²⁴

Tezacaftor/ivacaftor was well-tolerated in clinical trials and comparable to placebo or IVA alone. No individuals died in any clinical trials due to drug treatment and discontinuation rates were low. Overall, tezacaftor/ivacaftor did not show signals for major adverse events due to drug treatment alone and can be evaluated as safe within the clinical trial duration of 24 months.

EVOLVE evaluated 509 individuals for safety with 90.4% individuals in the tezacaftor/ivacaftor group and 95.0% in the placebo group reporting at least one adverse event. Most events were of mild severity (41.8%) or moderate severity (40.9%). Safety signals were consistent across all subgroups for tezacaftor/ivacaftor. Serious safety events were reported in 31 individuals (12.4%) in the tezacaftor/ivacaftor group and in 47 (18.2%) in the placebo group. 7 individuals in the tezacaftor/ivacaftor and 8 individuals in the placebo group discontinued the trial due to AEs. Only one individual in the placebo arm had coincident elevations in liver function tests (LFTs) 3x the upper limit of normal (ULN). Overall, the incidence of adverse events associated with elevated LFTs was low, occurring in 10 individuals (4.0%) in the tezacaftor/ivacaftor group and 15 (5.8%) in the placebo group. Common side effects (>10%) were infective pulmonary exacerbation, cough, headache, nasopharyngitis, and increased sputum production which are consistent with CF symptoms.

EXPAND had similar safety signals to EVOLVE with the majority of individuals having adverse events that were considered either mild or moderate in severity. Four individuals (2%) in the tezacaftor/ivacaftor group, eight (5%) in the IVA group, and nine (6%) in the placebo group had severe or life-threatening adverse events. The most common events were cough, infective pulmonary exacerbation of CF, headaches and hemoptysis. Adverse events that were associated with respiratory symptoms were less common in the tezacaftor/ivacaftor group than in the placebo group. No report of bronchoconstriction or acute reduction in FEV1 within 4 hours of treatment was noted.

Donaldson et al was a phase 2, placebo-controlled, double-blind, multicenter, RCT comparing tezacaftor/ivacaftor, TEZ and placebo in individuals homozygous for F508del mutation or compound heterozygous for F508del and G551D. 152 individuals homozygous for F508del (88.4%) had at least 1 adverse event, with an incidence of 30 (90.9%) individuals in the TEZ arm, 92 (86.8%) individuals in the tezacaftor/ivacaftor arm, and 30 (90.9%) individuals in the placebo arm. The majority (81.4%) of adverse events were mild to moderate in nature. The most common adverse events by subject were infective pulmonary exacerbation of CF, cough, increased sputum, nausea, diarrhea, headache, and fatigue.

Trikafta (elexacaftor/tezacaftor/ivacaftor)

Trikafta (elexacaftor/tezacaftor/ivacaftor) is a combination of three drugs: a CFTR potentiator (ivacaftor) and elexacaftor and tezacaftor which bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity.

Efficacy/Effectiveness

The efficacy of Trikafta in individuals with CF aged 12 years and older was evaluated in two Phase 3, double blind, controlled trials (Trials 1 and 2).

Trial 1 evaluated 403 individuals (200 Trikafta, 203 placebo) with CF aged 12 years and older (mean age 26.2 years). The mean percent predicted FEV1 (ppFEV1) at baseline was 61.4% (range: 32.3%, 97.1%). The primary endpoint assessed at the time of interim analysis was mean absolute change in ppFEV1 from baseline at Week 4. The final analysis tested all key secondary endpoints in the 403 individuals who completed the 24-week study participation, including absolute change in ppFEV1 from baseline through Week 24; absolute change in sweat chloride from baseline at Week 4 and through Week 24; number of pulmonary exacerbations through Week 24; absolute change in BMI from baseline at Week 24, and absolute change in CFQ-R Respiratory Domain Score (a measure of respiratory symptoms relevant to individuals with CF, such as cough, sputum production, and difficulty breathing) from baseline at Week 4 and through Week 24. Of the 403 individuals included in the interim analysis, the treatment difference between Trikafta and placebo for the mean absolute change from baseline in ppFEV1 at Week 4 was 13.8 percentage points (95% CI: 12.1, 15.4; $P < 0.0001$). The treatment difference between Trikafta and placebo for mean absolute change in ppFEV1 from baseline through Week 24 was 14.3 percentage points (95% CI: 12.7, 15.8; $P < 0.0001$). Mean improvement in ppFEV1 was observed at the first assessment on Day 15 and sustained through the 24-week treatment period.

Trial 2 evaluated 107 individuals with CF aged 12 years and older (mean age 28.4 years). The mean ppFEV1 at baseline, following the 4-week open-label run-in period with tezacaftor/ivacaftor was 60.9% (range: 35.0%, 89.0%). The primary endpoint was mean absolute change in ppFEV1 from baseline at Week 4 of the double-blind treatment period. The key secondary efficacy endpoints were absolute change in sweat chloride and CFQ-R Respiratory



Domain Score from baseline at Week 4. Treatment with Trikafta compared to tezacaftor/ivacaftor resulted in a statistically significant improvement in ppFEV1 of 10.0 percentage points (95% CI: 7.4, 12.6; $P < 0.0001$). Mean improvement in ppFEV1 was observed at the first assessment on Day 15.

Trial 3 evaluated 71 individuals with CF aged 6 years through 11 years of age. The mean ppFEV1 at baseline was 88.8%. The primary endpoint was to determine the safety and tolerability of Trikafta from baseline as measured by clinical laboratory values and adverse events. The secondary endpoint was the change in the ppFEV1, absolute change in sweat chloride and absolute change in CFQ-R Respiratory Domain score from baseline through week 24. The most frequently reported adverse effects in individuals treated with Trikafta included cough, headache, fever, upper respiratory tract infection, oropharyngeal pain, and nasal congestion. Approximately 10.6% of individuals experienced elevation of ALT/AST. Treatment with Trikafta demonstrated a significant improvement in ppFEV1 by 10.2 percentage points (95% CI: 7.9, 12.6). Additionally, Trikafta resulted in a reduction in sweat chloride by 60.9 mmol/L (95% CI: -63.7, -58.2), and an increase in CFQ-R Respiratory Domain Score by 7.0 points (95% CI: 4.7, 9.2).

Trial 4 evaluated individuals aged 2 years through 5 years of age with confirmed diagnosis of CF. the primary outcome of the study was to determine the safety and tolerability of Trikafta as determined by the adverse events and clinical laboratory assessments. The secondary endpoints are absolute change in the sweat chloride concentration from baseline through week 24. Treatment with Trikafta resulted in a reduction in sweat chloride concentration by 57.9 mmol/L.

Safety/Tolerability

The safety profile of Trikafta is based on data from 510 CF individuals in two double-blind, controlled, Phase 3 trials of 24 weeks and 4 weeks treatment duration (Trials 1 and 2). Eligible individuals were also able to participate in an open-label extension safety study (up to 96 weeks of Trikafta). In the two controlled Phase 3 trials, a total of 257 individuals aged 12 years and older received at least one dose of Trikafta. The top five most common adverse reactions in $\geq 5\%$ of Trikafta-treated individuals and higher than placebo by $\geq 1\%$ were headache (17%), upper respiratory tract infection (16%), abdominal pain (14%), diarrhea (13%) and rash (10%).

2013 Update

Search of recent literature found no new information that would modify this policy.



2014 Update

Added new CFTR mutations that now have evidence of ivacaftor efficacy and have been added to the labeled indication.

2015 Update

Added new combination product, Orkambi, approved by the FDA in 2015. A literature search from 7/1/14 through 10/31/15 did not find any other new evidence that would indicate the need to change the policy criteria.

2016 Update

Orkambi's age criteria has changed from 12 to 6 years of age and older.

The age stated in this policy for which Kalydeco (ivacaftor) is considered medically necessary for the treatment of cystic fibrosis is age 6 and above. This age is based on the FDA labeling. The age stated in this policy for which Orkambi (lumacaftor/ivacaftor) is considered medically necessary for the treatment of cystic fibrosis is age 6 years and older which is based on the FDA labeling.

2017 Update

Updated Kalydeco's age criteria from 6 years of age and older to 2 years of age and older. The age stated in this policy for which Kalydeco (ivacaftor) is considered medically necessary for the treatment of cystic fibrosis is age 2 and above, which is based on the revised FDA labeling.

Verification with bi-directional sequencing when recommended by the mutation test instructions for use is added to follow the CF mutation test.



2018 Update

Added Symdeko (tezacaftor/ivacaftor) as a treatment option along with evidence for safety and tolerability. The age listed in the Symdeko policy statement is based on FDA labeling. Updated Orkambi age to 2 years. Updated Kalydeko age to one year, per label changes. Added table of target mutations for Symdeko.

2019 Update

Reviewed prescribing information for all drugs and updated Symdeko (tezacaftor/ivacaftor) to age 6 years and older. No new evidence was identified that would require changes to other drugs listed in this policy.

2020 Update

Reviewed prescribing information for all drugs and updated Symdeko (tezacaftor/ivacaftor) to remove CFTR gene mutation R117H from list of mutations responsive to Symdeko. No new evidence was identified that would require changes to other drugs listed in this policy.

2021 Update

Reviewed prescribing information for all drugs and updated Trikafta (elexacaftor/tezacaftor/ivacaftor) approval for individuals age 6 years and older and added coverage for CFTR gene mutations that are responsive to Trikafta based on *in vitro* data as documented in the prescribing information in Section 12.1. Updated for Kalydeco (ivacaftor) the list of CFTR gene mutations that are responsive to Kalydeco. Updated for Symdeko (tezacaftor/ivacaftor) the list of CFTR gene mutations that are responsive to Symdeko.

2022 Update

Reviewed prescribing information for all drugs and updated Orkambi (ivacaftor/lumacaftor) approval for individuals age 1 year of age and older per the change to FDA labeling.



2023 Update

Reviewed prescribing information for all drugs and updated Kalydeco (ivacaftor) approval for individuals age 1 month of age and older per the change to FDA labeling. Updated Trikafta (elexacaftor/ tezacaftor/ivacaftor) approval for individuals age 2 years of age and older per the change to FDA labeling.

2024 Update

Reviewed prescribing information for all drugs. No changes to policy statements.

2025 Update

Reviewed prescribing information for all drugs. Updated Trikafta (elexacaftor/ tezacaftor/ivacaftor) coverage criteria to include treatment of certain individuals with cystic fibrosis who have a mutation that is responsive to Trikafta based on clinical and/or in vitro data. Added coverage criteria for Alyftrek (vanzacaftor/tezacaftor/ deutivacaftor). Clarified that the following cannot be used in combination: Alyftrek (vanzacaftor/tezacaftor/ deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor). Added a quantity limit per the prescribing information for Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated policy title from "Pharmacologic Treatment of Cystic Fibrosis with Ivacaftor Products" to "Pharmacologic Treatment of Cystic Fibrosis."

References

1. Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in Persons with Cystic Fibrosis and the G551D-CFTR Mutation. N Engl J med 2011; 365:1663-1672.
2. Center for Drug Evaluation and Research. Application No. 203188 Document: 203188Orig1s000 Medical Review. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203188Orig1s000MedR.pdf Accessed March 29, 2025.



3. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation. *N Engl J Med* 2011; 365:1663-1672.
4. Aherns R, Rodriguez S, Yen K, Davies JC. VX-770 in subjects 6 to 11 years with cystic fibrosis and the G551D-CFTR mutation (Abstract). *Pediatric Pulmonology*. 2011;46:283.
5. Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordonez CL, Geller DE and for the VX08-770-104 Study Group. Ivacaftor in Subjects with Cystic Fibrosis who are Homozygous for the F508del-CFTR Mutation. *Chest* 2012 Mar 1
6. Cystic Fibrosis Foundation (CFF) 2010 Cystic Fibrosis Patient Registry Annual Data Report (2011).
7. Kalydeco (Ivacaftor) Prescribing Information. Vertex Pharmaceuticals Incorporated; Boston, MA. Updated August 2023.
8. FDA Briefing Document. Pulmonary-allergy drugs advisory committee meeting, [lumicaftor/ivacaftor]. Updated May 2015 Available at: <https://wayback.archive-it.org/7993/20171102175528/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM446193.pdf> Accessed March 29, 2025.
9. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med*. 2015. doi: 10.1056/NEJMoa1409547 [doi].
10. Boyle MP, Bell SC, Konstan MW, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: A phase 2 randomised controlled trial. *Lancet Respir Med*. 2014;2(7):527-538. doi: 10.1016/S2213-2600(14)70132-8 [doi].
11. Vertex Pharmaceuticals Incorporated. A phase 3 rollover study of lumacaftor in combination with ivacaftor in subjects 12 years and older with cystic fibrosis. <https://clinicaltrials.gov/ct2/show/results/NCT01931839?term=809-105&rank=1> Updated 2017. Accessed March 29, 2025.
12. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365(18):1663-1672. doi: 10.1056/NEJMoa1105185 [doi].
13. Donohue JF. Minimal clinically important differences in COPD lung function. *COPD*. 2005;2(1):111-124.
14. Orkambi (lumacaftor/ivacaftor) prescribing information. Vertex Pharmaceuticals; Boston, MA. Updated December 2024.
15. National Institute for Health and Care Excellence. Proposed health technology appraisal: Lumacaftor in combination with ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [draft scope (pre-referral)]. <http://www.nice.org.uk/guidance/GID-TAG530/documents/cystic-fibrosis-f508del-mutation-lumacaftor-with-ivacaftor-id786-draft-scope2> Accessed March 29, 2025.
16. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: A systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2014;18(18):1-106. doi: 10.3310/hta18180 [doi].
17. Sawicki GS, McKone EF, Pasta DJ, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and CF patient registry data. *Am J Respir Crit Care Med*. 2015. doi: 10.1164/rccm.201503-0578OC [doi].
18. Taylor-Cousar JL, Munck A, McKone EF, Ent CKVD, Moeller A, Simard C, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *New England Journal of Medicine*. 2017;377(21):2013-23.
19. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *New England Journal of Medicine*. 2017;377(21):2024-35.
20. Donaldson SH, Pilewski JM, Griese M, Cooke J, Viswanathan L, Tullis E, et al. Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. *American Journal of Respiratory and Critical Care Medicine*. 2018;197(2):214-24.
21. Symdeko (tezacaftor/ivacaftor) tablets; (ivacaftor) tablets prescribing information. Vertex Pharmaceuticals; Boston, MA. Updated January 2025.
22. Trikafta (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets) prescribing information. Vertex Pharmaceuticals; Boston, MA. Updated December 2024.



23. Jennifer G, Jordana E, et al. Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2 Through 5 Years with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med. Available at: Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2 Through 5 Years with Cystic Fibrosis and at Least One F508del Allele - PubMed (nih.gov). Accessed March 29, 2025.
24. Edith Z, Jennifer T, et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med. Available at: A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele - PubMed (nih.gov). Accessed March 29, 2025.
25. Davies JC, Wainwright CE, Sawicki GS, et al. Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation: results of a 2-part phase 3 clinical trial. Am J Respir Crit Care Med. 2020; doi: 10.1164
26. Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor tablets) prescribing information. Vertex Pharmaceuticals Incorporated; Boston, MA. Updated January 2025.

History

Date	Comments
06/12/12	New policy, add to Prescription Drug section.
07/08/13	Minor Update – Clarification was added to the policy that it is managed through the member’s pharmacy benefit; this is now listed in the header and within the coding section.
10/14/13	Replace policy. Policy updated with literature review; no change to policy statement.
12/08/14	Annual Review. Policy updated with additional gene mutations within the medically necessary policy statement; a not medically necessary policy statement is added addressing specific patient pools, with clarification added that all other uses of ivacaftor are investigational when policy criteria are not met. Reference 7 removed (duplicate of #2); reference 10 added.
01/13/15	Annual Review. Medically necessary policy statement updated with the addition gene mutation R117H, recently approved by the FDA; additional language added to include “any mutation subsequently added to the FDA-approved indication”.
12/08/15	Interim Review. Policy updated with literature review. Policy title expanded to match the scope of policy which now includes Lumacaftor/Ivacaftor (Orkambi). Medically necessary policy statement added to address Orkambi to treat CF in patients 12 and older when criteria are met.
02/09/16	Annual Review. Medically necessary policy statement for ivacaftor now includes documentation of at least on copy of the listed mutations; CF mutation testing required if genotype is unknown.



Date	Comments
12/01/16	Interim Review, approved November 8, 2016. Orkambi's age criteria has changed from 12 to 6 years of age and older. Information added to explain the application of age for this policy is based on FDA-labelled indication.
10/01/17	Annual Review, approved September 12, 2017. Kalydeco's age criteria has changed from 6 to 2 years of age and older. The age stated in this policy for which Kalydeco (ivacaftor) is considered medically necessary for the treatment of cystic fibrosis is age 2 and above, which is based on the FDA labeling. Verification with bi-directional sequencing when recommended by the mutation test instructions for use is added to follow the CF mutation test.
03/01/18	Interim Review, approved February 13, 2018. Added Symdeko (tezacaftor/ivacaftor) as a treatment option along with evidence for safety and tolerability. References 23, 24, and 25 added. Title updated from "Kalydeco (ivacaftor) and Orkambi (lumacaftor / ivacaftor) " to "Kalydeco (ivacaftor) ,Orkambi (lumacaftor / ivacaftor), and Symdeko (tezacaftor / ivacaftor)"
06/01/18	Interim Review, approved May 3, 2018. Removed criteria requiring sputum cultures free of Burkholderia cenocepacia, dolosa, or Mycobacterium abscessus.
09/01/18	Minor update. Under the 2018 update, added a statement that the age for Symdeko is based on FDA labeling.
11/01/18	Annual Review, approved October 26, 2018. Orkambi age updated. Kalydeco age updated. Added table of updated target mutations for Symdeko.
07/01/19	Interim Review, approved June 20, 2019. Kalydeco age updated.
08/01/19	Annual Review, approved July 25, 2019. Symdeko age updated.
02/01/20	Interim Review, approved January 14, 2020. Added coverage criteria for Trikafta (elexacaftor/tezacaftor/ivacaftor). Changed policy title to "Pharmacologic Treatment of Cystic Fibrosis with Ivacaftor Products" from "Kalydeco (ivacaftor), Orkambi (lumacaftor / ivacaftor), and Symdeko (tezacaftor / ivacaftor)".
10/01/20	Annual Review, approved September 17, 2020. For Symdeko (tezacaftor/ivacaftor) updated coverage criteria removing CFTR gene mutation R117H from list of mutations responsive to Symdeko based on FDA labeling.
12/01/20	Interim Review, approved November 19, 2020. Updated Kalydeco (ivacaftor) age to 4 months and older.
08/01/21	Annual Review, approved July 9, 2021. Updated Trikafta (elexacaftor/tezacaftor/ivacaftor) criteria for age to 6 years and older and added coverage for CFTR gene mutations that are responsive to Trikafta. Updated the tables on CFTR gene mutations responsive to Kalydeco (ivacaftor) and Symdeko (tezacaftor/ivacaftor).



Date	Comments
11/01/22	Annual Review, approved October 24, 2022. Updated Orkambi (ivacaftor/lumacaftor) approval for patients age 1 year of age and older per the change to FDA labeling. Changed the wording from "patient" to "individual" throughout the policy for standardization.
07/01/23	Annual Review, approved June 26, 2023. Updated Kalydeco (ivacaftor) approval for individuals age 1 month of age and older per the change to FDA labeling. Updated Trikafta (elexacaftor/ tezacaftor/ivacaftor) approval for individuals age 2 years of age and older per the change to FDA labeling.
06/01/24	Annual Review, approved May 24, 2024. No changes to policy statements.
05/01/25	Annual Review, approved April 8, 2025. Updated Trikafta (elexacaftor/ tezacaftor/ivacaftor) coverage criteria to include treatment of certain individuals with cystic fibrosis who have a mutation that is responsive to Trikafta based on clinical and/or in vitro data. Added coverage criteria for Alyftrek (vanzacaftor/tezacaftor/ deutivacaftor). Clarified that the following cannot be used in combination: Alyftrek (vanzacaftor/tezacaftor/ deutivacaftor), Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor). Added a quantity limit per the prescribing information for Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Updated policy title from "Pharmacologic Treatment of Cystic Fibrosis with Ivacaftor Products" to "Pharmacologic Treatment of Cystic Fibrosis."

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

