MASSACHUSETTS

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Pharmacy Medical Policy
Drugs for Cystic Fibrosis

Table of Contents

Policy Number: 408

BCBSA Reference Number: None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Note: All requests for outpatient retail pharmacy for indications listed and not listed on the medical policy guidelines may be submitted to BCBSMA Clinical Pharmacy Operations by completing the Prior Authorization Form on the last page of this document. Physicians may also call BCBSMA Pharmacy Operations department at (800)366-7778 to request a prior authorization/formulary exception verbally. Physicians may also submit requests for retail pharmacy exceptions via the web using Express PAth which can be found on the BCBSMA provider website or directly on the web at https://provider.express-path.com. Patients must have pharmacy benefits under their subscriber certificates.

Prior Authorization Information

<table>
<tr><td colspan="2">☒ Prior Authorization
☐ Step Therapy
☐ Quality Care Dosing</td><td>Pharmacy Operations:
Tel: 1-800-366-7778
Fax: 1-800-583-6289
Policy last updated | 4/2025</td></tr>
<tr><td>Pharmacy (Rx) or Medical (MED) benefit coverage</td><td>☒ Rx
☐ MED</td><td rowspan="2">To request for coverage: Physicians may call, fax, or mail the attached form (Formulary Exception/Prior Authorization form) to the address below.
Blue Cross Blue Shield of Massachusetts
Pharmacy Operations Department
25 Technology Place
Hingham, MA 02043

Individual Consideration: Policy for requests that do not meet clinical criteria of this policy, see section labeled Individual Consideration</td></tr>
<tr><td colspan="2">Policy applies to Commercial Members:
Managed Care (HMO and POS),
PPO and Indemnity
MEDEX with Rx plan
Managed Major Medical with Custom BCBSMA Formulary
Comprehensive Managed Major Medical with Custom BCBSMA Formulary
Managed Blue for Seniors with Custom BCBSMA Formulary</td></tr>
</table>

Please refer to the chart below for the formulary and step status of the medications affected by this policy.

Drug	Formulary Information
	Standard
	Formulary Status
Alyftrek™ (vanzacaftor / tezacaftor / deutivacaftor)	PA Required
Kalydeco ™ (ivacaftor)	PA Required
Orkambi ™ (lumacaftor / ivacaftor**)**	PA Required
Symdeko ™ (tezacaftor / ivacaftor)	PA Required
Trikafta ™ (elexacaftor / tezacaftor / ivacaftor)	PA Required

We may cover Alyftrek ™ (vanzacaftor / tezacaftor / deutivacaftor) for the treatment of cystic fibrosis when **all** of the following criteria are met:

- Age 6 years of age or older, **AND**
- Concurrent use of **Symdeko ™** or **Kalydeco ™** or **Orkambi ™ or Trikafta™** must be discontinued, **AND**
- Documentation for at least one F508del mutation in the CFTR gene as confirmed by an FDA- cleared cystic fibrosis mutation test **OR**
- Documentation of one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to vanzacaftor / tezacaftor / deutivacaftor based on in vitro data and/or clinical evidence as noted in table 1 below:

- Table 1 lists *CFTR* mutations responsive to ALYFTREK based on clinical response, and/or in vitro data in FRT or HBE cells, or based on extrapolation of efficacy

Table 1: List of *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*†	
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;D 1270N*§	*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; R 668C*	*S1235R*	
D443Y	*G1249R*	*I125T*	*M150K*	*R117G*	*S1255P*	
D443Y;G576A; R 668C§	*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*	
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*		

* Clinical data is obtained from Trials 1 and 2.
† This mutation is also predicted to be responsive by FRT assay with ALYFTREK.
‡ The *N1303K* mutation is predicted to be responsive only by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay.
§ Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.
¶ Efficacy is extrapolated to certain non-canonical splice mutations because clinical trials in all mutations in this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.

We may cover Kalydeco ™ (ivacaftor) for the treatment of cystic fibrosis when **all** of the following criteria are met[1]:

- Age 4 months of age or older **AND**
- Concurrent use of **Alyftrek ™ or Symdeko™ or Trikafta ™ or Orkambi™** must be discontinued. **AND**
- Documentation of a mutation of the CFTR gene as confirmed by an FDA- cleared cystic fibrosis mutation test. In Table 2 below.

Table 2 (Kalydeco Mutations)

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* *	

*Clinical data exist for these mutations.
†Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

We may cover Orkambi ™ (lumacaftor and ivacaftor**)** for the treatment of cystic fibrosis when **all** of the following criteria are met:

- Age 1 years of age or older **AND**
- Documentation of **TWO** copies of the F508del mutation in the CFTR gene as confirmed by an FDA- cleared cystic fibrosis mutation test **AND**
- Concurrent use of **Alyftrek ™ or Symdeko™ or Trikafta ™ or Kalydeco™** must be discontinued.

We may cover Symdeko ™ (tezacaftor and ivacaftor**)** for the treatment of cystic fibrosis when **all** of the following criteria are met:

- Age 6 years of age or older, **AND**
- Documentation of Homozygous for the F508del mutation in the CFTR gene as confirmed by an FDA- cleared cystic fibrosis mutation test

OR

- Documentation of one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence as noted in table 3 below:

AND

- Concurrent use of **Kalydeco ™** or **Orkambi ™ or Alyftrek ™ or Trikafta ™** must be discontinued.

Table 3: List of CFTR Gene Mutations that Produce CFTR Protein and are 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 *	E588V	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
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	

* Clinical data for these mutations in Clinical Studies *[see CLINICAL STUDIES (14.1 and 14.2)]*.

† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

‡ A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 6 to be indicated.

We may cover Trikafta ™ (elexacaftor**,** tezacaftor and ivacaftor**)** for the treatment of cystic fibrosis when **all** of the following criteria are met[1]:

- Age 2 years of age or older, **AND**
- Concurrent use of **Symdeko ™** or **Kalydeco ™** or **Orkambi ™ or Alyftrek ™** must be discontinued, **AND**
- Documentation for at least one F508del mutation in the CFTR gene as confirmed by an FDA- cleared cystic fibrosis mutation test in table 4below.

Table 4: List of 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 extrapolation from Trial 5[§]				
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*	

[*] Clinical data obtained from Trials 1, 2, and 5.

[†] This mutation is also predicted to be responsive by FRT assay.

[‡] The N1303K mutation is predicted to be responsive by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay.

[§] Efficacy is extrapolated from Trial 5 to non-canonical splice mutations because clinical trials in all mutations of this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.

We do not cover the above drugs for other conditions not listed above.

Other Information
Blue Cross Blue Shield of Massachusetts (BCBSMA*) members (other than Medex®; Blue MedicareRx, Medicare Advantage plans that include prescription drug coverage) will be required to fill their prescriptions for the above medications at one of the providers in our retail specialty pharmacy network, see link below:

Link to Specialty Pharmacy List

Individual Consideration
All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. Physicians may send relevant clinical information for individual patients for consideration to:

Blue Cross Blue Shield of Massachusetts
Pharmacy Operations Department
25 Technology Place
Hingham, MA 02043
Tel: 1-800-366-7778
Fax: 1-800-583-6289

Policy History
Date	Action
6/2025	Updated to add Alyftrek
5/2023	Updated additional mutations for Trikafta
7/2023	Updated Age for Trikafta.
11/2022	Updated new age for Orkambi ™ for homozygous F508del mutation criteria.
7/2021	Updated to include age update for Trikafta ™
2/2021	Updated to add New eligible mutations to the policy.
10/2020	Updated to include new age edit for Kalydeco ™.
2/2020	Updated to add Trikafta™ to the policy.
8/2019	Updated to include new age range for Symdeko ™.
9/2018	Updated to include new age range for Orkambi ™ & Kalydeco ™.

6/2018	Updated to include Symdeko™ and to add Specialty Pharmacy Link.
10/2017	Updated to change Walgreens Specialty Name.
7/2017	Updated to include additional genes and add AllCare to Specialty pharmacy list.
6/2017	Updated address for Pharmacy Operations.
11/2016	Updated to include new age indication for Orkambi ™.
4/2016	Updated to include Orkambi™ & add Walgreens Specialty.
4/2015	Updated for new FDA approved ages.
2/2015	Updated new gene types which were FDA approved.
4/2014	Updated new gene types which were FDA approved.
2/2014	Removal of Curascript from Specialty Pharmacy section.
1/2014	Updated to remove Blue Value.
1/2013	New Policy, effective 1/1/2013.

References

1. Kalydeco ™ [package insert]. Cambridge, MA: Vertex Pharmaceuticals, Inc.: 2012.
2. Yu H, Burton B, Huang CJ, et al. Ivacaftor potentiation of multiple CFTR channels with gating mutations. *J Cyst Fibros.* Jan 30 2012.
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Endnotes

1. Based on BCBSA Technology Evaluation Center Specialty Pharmacy Combined Capacity (SPCC) Report #3-2012 Ivacaftor (Kalydeco™), reviewed March 2012.

To request prior authorization using the Massachusetts Standard Form for Medication Prior Authorization Requests (eForm), click the link below:

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