Cystic Fibrosis Transmembrance Conductance Regulator (CFTR) Potentiators: Kalydeco (ivacaftor) Orkambi (lumacaftor/ivacaftor) Symdeko (tezacaftor/ivacaftor) Trikafta (elexacaftor/tezacaftor/ivacaftor) Effective 06/01/2022

Plan	☐ MassHealth ☒ MH UPPL ☐Commercial/Exchange	**Program Type**	☒ Prior Authorization ☒ Quantity Limit ☐ Step Therapy
Benefit	☒ Pharmacy Benefit ☐ Medical Benefit (NLX)		
Specialty Limitations	This medication has been designated specialty and must be filled at a contracted specialty pharmacy.		
Contact Information	**Specialty Medications**		
	All Plans	Phone: 866-814-5506	Fax: 866-249-6155
	Non-Specialty Medications		
	MassHealth	Phone: 877-433-7643	Fax: 866-255-7569
	Commercial	Phone: 800-294-5979	Fax: 888-836-0730
	Exchange	Phone: 855-582-2022	Fax: 855-245-2134
	Medical Specialty Medications (NLX)		
	All Plans	Phone: 844-345-2803	Fax: 844-851-0882
Exceptions			

Overview

CF is caused by genetic mutations in the CFTR protein. The CFTR protein is present in the respiratory epithelium and plays an important role in the regulation of airway surface liquid. Genetic mutations in the protein result in abnormal airway secretions, chronic endobronchial infection, and progressive airway obstruction. The CFTR potentiators treat the underlying cause of CF by targeting the defective CFTR protein to help facilitate increased chloride transport.

No PA	Drugs That Require PA
	Kalydeco® (ivacaftor)[PD]
	Orkambi® (lumacaftor/ivacaftor)[PD]
	Symdeko® (tezacaftor/ivacaftor)[PD]
	Trikafta® (elexacaftor/tezacaftor/ivacaftor)[PD]

PD = preferred drug. In general, a trial of the preferred drug or clinical rationale for prescribing a non-preferred drug within a therapeutic class.

Coverage Guidelines:

Kalydeco (ivacaftor)
Authorization may be reviewed on a case by case basis for members new to AllWays Health Partners are currently receiving treatment with Kalydeco for an FDA approved indication excluding when the product is obtained as samples or via manufacturer's patient assistance programs.
OR
Authorization may be granted when documentation is of ALL the following is provided:

1. The member has a diagnosis of Cystic Fibrosis with one mutation in the CFTR gene that is responsive to ivacaftor. (specific gene mutation MUST be documented) (see Appendix A)
2. The member is ≥ 4 months of age
3. Baseline body mass index (BMI) and percent predicted forced expiratory volume in one second ($ppFEV_1$) †
4. Request does not exceed 2 units per day
5. Kalydeco will not be used in combination with Symdeko, Orkambi, or Trikafta

Orkambi (lumacaftor/ivacaftor)
Authorization may be reviewed on a case by case basis for members new to AllWays Health Partners are currently receiving treatment with Orkambi for an FDA approved indication excluding when the product is obtained as samples or via manufacturer's patient assistance programs.
OR
Authorization may be granted when documentation is of ALL the following is provided:

1. The member has a diagnosis of Cystic Fibrosis with two copies (homozygous) of the F508del-CFTR mutation (specific gene mutation MUST be documented)
2. The member is ≥ 2 years of age.
3. Request does not exceed 4 tablets per day or 2 packets per day
4. Baseline BMI and $ppFEV_1$ †
5. Orkambi will not be used in combination with Kalydeco, Symdeko, or Trikafta.

Symdeko (tezacaftor/ivacaftor)
Authorization may be reviewed on a case by case basis for members new to AllWays Health Partners are currently receiving treatment with Symdeko for an FDA approved indication excluding when the product is obtained as samples or via manufacturer's patient assistance programs.
OR
Authorization may be granted when documentation is of ALL the following is provided:

1. The member has a diagnosis of Cystic Fibrosis with two copies (homozygous) of the F508del-CFTR mutation or at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor (specific gene mutation MUST be documented) (Appendix B)
2. The member ≥ 6 years of age
3. Request does not exceed 2 tablets per day
4. Baseline BMI and $ppFEV_1$ †
5. Symdeko will not be used in combination with Kalydeco, Orkambi, or Trikafta

Trikafta (elaxacaftor/tezacaftor/ivacaftor)
Authorization may be reviewed on a case by case basis for members new to AllWays Health Partners are currently receiving treatment with Trikafta for an FDA approved indication excluding when the product is obtained as samples or via manufacturer's patient assistance programs.
OR
Authorization may be granted when documentation is of ALL the following is provided:

1. The member has a diagnosis of Cystic Fibrosis with at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive to elexacaftor/tezacaftor/ivacaftor (specific gene mutation MUST be documented) (see Appendix C)
2. The member is ≥ 6 years of age
3. Request does not exceed 3 tablets per day
4. Baseline BMI and $ppFEV_1$ †
5. Trikafta will not be used in combination with Kalydeco, Symdeko, or Orkambi.

† *If member is ≤ 6 years of age, ppFEV1 does not have to be performed*

Continuation of Therapy

Reauthorization requires physician documentation of ALL of the following:

1. Provider provides documentation of positive response to therapy (e.g., improvement in BMI, $ppFEV_1$, decrease in clinical exacerbations, etc.)
2. Provider documentations continuation OR pharmacy claims confirms adherence

Limitations

1. Initial approvals will be granted for 6 months
2. Reauthorizations will be granted for 12 months
3. The following quantity limits apply:

Kalydeco 150mg tablets	56 tablets per 28 days
Kalydeco 25mg, 50mg, or 75mg packets	56 packets per 28 days
Orkambi 200-125mg tablets	112 tablets per 28 days
Orkambi 150-188mg granules	56 packets per 28 days
Symdeko 50-75mg tablets	56 tablets per 28 days
Symdeko 100-150mg tablets	56 tablets per 28 days
Trikafta 100-50-75mg tablets	84 tablets per 28 days

Appendix

Appendix A: List of CFTR gene that is responsive to Kalydeco

List of CFTR Gene Mutations that Produce CFTR Protein and are 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**	*S997F**
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*	*R993G*	*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.

Appendix B: List of CFTR Gene Mutations that are Responsive to Symdeko

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*
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.
^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.
† 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.

Appendix C: List of CFTR Gene Mutations that are Responsive to Trikafta

CFTR Gene Mutations Responsive to Trikafta					
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	*F508del* *	*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*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data.
† 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.

References

1. Kalydeco [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; April 2019.
2. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187:680-689.

3. Orkambi [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; August 2018.
4. Symdeko [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; June 2019.
5. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, Nair N, Simard C, Han L, Ingenito EP, McKee C, Lekstrom-Himes J, Davies JC. Tezacaftor-Ivacaftor in Residual Funtion Heterzygotes with Cystic Fibrosis. *N Engl J Med*. 2017; 377:2024-2035
6. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del *N Engl J Med* 2017; 377:2013-2023
7. Trikafta (elexacaftor/tezacaftor/ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Inc., January 2020.

Review History

05/19/2021 – Created and Reviewed May P&T Mtg; Matched MH UPPL; previously on same criteria with Comm/exch. Removed Kalydeco, Orkambi, and Symdeko use prior to Trikafta. Added all 4 drugs as preferred. Effective 7/1/2021
05/18/2022 – Reviewed and updated for May P&T; note added to Symdeko and Trikafta (similar to other CFTR modulators that if member is ≤ 6 years of age, ppFEV1 does not have to be performed); guideline updated to include FDA-expanded age indication for Trikafta to ≥ 6 years; matched MH UPPL; Effective 6/1/22.

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