

Attachment 1: Cystic Fibrosis (CF) Mutations Responsive to Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulator Therapy

Orkambi (lumacaftor/ivacaftor) is indicated for beneficiaries ages one year and older who have two copies of the F508del protein processing mutation.

Trikafta (elexacaftor, tezacaftor and ivacaftor; ivacaftor) is indicated for beneficiaries ages 6 years and older who have at least one copy of the F508del mutation. Trikafta is also approved for beneficiaries ages 6- and older who have certain mutations in the CFTR gene.

On December 21, 2020, the FDA approved new mutations that can be treated by each of the CFTR Modulator Therapy Drugs. The following is a listing of all the mutations approved for each drug.

List of CFTR Gene Mutations that are Responsive to Trikafta

(elexacaftor/tezacaftor/ivacaftor and ivacaftor) Bolded mutations are approved effective 12/21/2020

| Table 1: List of CFTR Gene Mutations That Are 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 | 1336K | P205S | R751L | V456F |
| D443Y;G576A;R668C† | G126D | 1502T | P574H | R792G | V562I |
| D579G | G178E | <i>l</i> 601F | Q98R | R933G | V754M |
| D614G | G178R | <i>l</i> 618T | Q237E | R1066H | V1153E |
| D836Y | G194R | 1807M | Q237H | R1070Q | V1240G |
| D924N | G194V | 1980K | Q359R | R1070W | V1293G |
| D979V | G314E | I1027T | Q1291R | R1162L | W361R |
| D1152H | G463V | I1139V | R31L | R1283M | W1098C |
| D1270N | G480C | I1269N | R74Q | R1283S | W1282R |

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State of California



Gavin Newsom, Governor

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| 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 | 7 |

**F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data [see Clinical Studies(14) in the TRIKAFTA full Prescribing Information (PI)].

†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.

List of CFTR Gene Mutations that are Responsive to Symdeko

(tezacaftor/ivacaftor and ivacaftor) Bolded mutations are approved effective 12/21/2020

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|--|----------------|-------------------|--------|--------|--------|--|
| Table 2: 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 | 1336K | Q98R | R553Q | V232D | |
| D192G | F1016S | <i>I601F</i> | Q237E | R668C | V562I | |
| D443Y | F1052V | l618T | Q237H | R751L | V754M | |
| D443Y;G576A;R668C† | F1074L | I807M | Q359R | R792G | V1153E | |
| D579G* | F1099L | 1980K | Q1291R | R933G | V1240G | |
| D614G | G126D | I1027T | R31L | R1066H | V1293G | |
| | | | | | | |

| D836Y | G178E | l1139V | R74Q | R1070Q | W1282R |
|---------|-------|--------|----------------------------|---------|--------|
| D924N | G178R | l1269N | R74W | R1070W* | Y109N |
| D979V | G194R | l1366N | R74W;D1270N† | R1162L | Y161S |
| D1152H* | G194V | K1060T | R74W;V201M† | R1283M | Y1014C |
| D1270N | G314E | L15P | <i>R74W;V201M;D1270N</i> † | R1283S | Y1032C |
| E56K | G551D | L206W* | R75Q | S549N | |
| E60K | G551S | L320V | R117C* | S549R | |

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*Clinical data for these mutations in Clinical Studies [see Clinical Studies (14.1 and 14.2) in the SYMDEKO full PI].

^A patient must have 2 copies of the F508del mutation or at least 1 copy of a responsive mutation presented in Table 2 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.

List of CFTR Gene Mutations that are Responsive to Kalydeco

| (ivacaftor) | | | | | | |
|--|---------------|----------|---------|---------|--|--|
| Bolded mutations are approved effective 12/21/2020 | | | | | | |
| Table 3: List of CFTR Gene Mutations That Produce CFTR Protein and Are Responsive to | | | | | | |
| | | Kalydeco | | | | |
| 711+3A→G* | F311del | l148T | R75Q | S589N | | |
| 2789+5G→A* | F311L | l175V | R117C* | S737F | | |
| 3272 - 26A→G* | F508C | I807M | R117G | S945L* | | |
| 3849+10kbC→T* | F508C;S1251N† | I1027T | R117H* | S977F* | | |
| A120T | F1052V | l1139V | 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 [see Clinical Studies (14) in the KALYDECO full PI]. †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.