KALYDECO® (ivacaftor): treating the underlying cause of CF in patients 4 months and older

An overview of clinical trial data in patients with cystic fibrosis (CF) age 4 to 24 months

**Indications and Usage**

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Please click for Important Safety Information and full Prescribing Information for KALYDECO.
KALYDECO® (ivacaftor) Important Safety Information

Transaminase (ALT or AST) Elevations
- Elevated transaminases have been reported in patients with CF receiving KALYDECO. Transaminase elevations were more common in patients with a history of transaminase elevations or in patients who had abnormal transaminases at baseline. ALT and AST should be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, consider more frequent monitoring of liver function tests.
- Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO.

Concomitant Use With CYP3A Inducers
- Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort is not recommended.

Cataracts
- Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating KALYDECO treatment.

Pediatric Use
- The safety and effectiveness of KALYDECO in patients with CF younger than 4 months of age have not been studied. The use of KALYDECO in children under the age of 4 months is not recommended.

Serious Adverse Reactions
- Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in patients treated with KALYDECO included abdominal pain, increased hepatic enzymes, and hypoglycemia.

Most Common Adverse Reactions
- The most common adverse reactions in patients with a G551D mutation in the CFTR gene (Trials 1 and 2) with an incidence of ≥8% and at a higher incidence for patients treated with KALYDECO (N=109) than for placebo (N=104) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness.
- The safety profiles for patients with additional approved mutations enrolled in Trials 4, 5, and 7; and for patients aged 2 to less than 6 years enrolled in Trial 6; and for patients aged 4 months to less than 24 months enrolled in Trial 8; were similar to that observed in Trials 1 and 2.

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Indications and Usage

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.
TRIAL 8 (ARRIVAL): Patients with CF age 4 to less than 24 months
KALYDECO® (ivacaftor) in patients as young as 4 months

Trial design
- Trial 8 was a Phase 3, 24-week, open-label, 2-part study of KALYDECO that included the following cohorts of patients with CF: patients age 4 to <6 months (n=6), patients age 6 to <12 months (n=11), and patients age 12 to <24 months (n=19).
- Patients were eligible to enroll in this study if they had a G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, or S549R mutation.
- Patients in this trial received KALYDECO every 12 hours with fat-containing food, in addition to their prescribed CF therapies. In the 4 to <6 months cohort, patients received 25 mg of KALYDECO. Patients 6 months and older received KALYDECO based on weight: 5 kg to <7 kg: one 25 mg packet of oral granules; 7 kg to <14 kg: one 50 mg packet of oral granules; ≥14 kg: one 75 mg packet of oral granules.
- Instruction was provided to administer KALYDECO oral granules mixed with 5 mL of an age-appropriate soft food or liquid, either orally with a syringe or with a spoon, every 12 hours along with fat-containing food. Bottle use was not recommended.

Primary endpoint: Safety, assessed by adverse events (AEs) and clinical laboratory assessments.
Select secondary endpoint: Absolute change from baseline in sweat chloride concentration through Week 24.

Trial 8 limitations
- The study was open label and not placebo controlled; therefore, causality cannot be attributed to KALYDECO.
- All patients in the study knew they were on active drug, which may have introduced bias related to awareness of treatment.

Discontinuations and serious AEs
- 4 to <6 months cohort:
  - No treatment discontinuations
  - 1 serious AE of bronchiolitis
- 6 to <12 months cohort:
  - There was 1 treatment interruption and no permanent discontinuations due to AEs
  - Serious AEs included viral respiratory tract infection (1), viral rash (1), and cough (1)
- 12 to <24 months cohort:
  - 1 patient discontinued due to withdrawal of consent
  - 4 serious AEs occurred in 2 patients
    - 1 patient had constipation, distal intestinal obstruction syndrome (DIOS), and eczema herpeticum
    - The serious AE of constipation was considered possibly related to ivacaftor by the investigator
  - 1 patient had persistent cough

All other serious AEs in all cohorts were considered unrelated or unlikely to be related to ivacaftor.

The safety profile of patients in this trial was similar to that observed in patients age 2 years and older.

*Patients with the R117H mutation were eligible to enroll in this study only in the United States.

Please click for full Prescribing Information for KALYDECO.
### Transaminase Elevations

#### INCIDENCE OF TRANSMAMINASE ELEVATIONS

<table>
<thead>
<tr>
<th>ELEVATED ALT OR AST</th>
<th>4 TO &lt;6 MONTHS COHORT n/N (%)</th>
<th>6 TO &lt;12 MONTHS COHORT n/N (%)</th>
<th>12 TO &lt;24 MONTHS COHORT n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 x ULN</td>
<td>0/6 (0.0)</td>
<td>1/11 (9.1)</td>
<td>5/18 (27.8)</td>
</tr>
<tr>
<td>&gt;5 x ULN</td>
<td>0/6 (0.0)</td>
<td>0/11 (0.0)</td>
<td>2/18 (11.1)</td>
</tr>
<tr>
<td>&gt;8 x ULN</td>
<td>0/6 (0.0)</td>
<td>0/11 (0.0)</td>
<td>2/18 (11.1)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

- No patients in any of the cohorts had elevations in total bilirubin, or discontinued ivacaftor treatment due to transaminase elevations
- **4 to <6 months cohort:** During the course of this study, no patient interrupted treatment because of transaminase elevations
- **6 to <12 months cohort:** During the course of this study, no patient interrupted treatment because of AEs of elevated liver function tests
- **12 to <24 months cohort:** 2 patients had study drug interrupted because of AEs of elevated liver function tests
  - Both patients resumed treatment following a period of study drug interruption with no further elevations

### IMPORTANT SAFETY INFORMATION

#### Transaminase (ALT or AST) Elevations

- Elevated transaminases have been reported in patients with CF receiving KALYDECO. Transaminase elevations were more common in patients with a history of transaminase elevations or in patients who had abnormal transaminases at baseline. ALT and AST should be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, consider more frequent monitoring of liver function tests
- Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO

Please click for full Prescribing Information for KALYDECO.
TRIAL 8 (ARRIVAL): Patients with CF age 4 to less than 24 months

KALYDECO® (ivacaftor) pharmacodynamic results

Reduction in sweat chloride from baseline with KALYDECO in:

<table>
<thead>
<tr>
<th>Patients age 4 to less than 6 months</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>-50.0 mmol/L *</td>
<td></td>
</tr>
<tr>
<td>In the 4 to &lt;6 months cohort (n=3), the mean absolute change from baseline in sweat chloride was -50.0 mmol/L (95% CI: -93.1, -6.9) at Week 24 (secondary endpoint)</td>
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</table>

<table>
<thead>
<tr>
<th>Patients age 6 to less than 12 months</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>-58.6 mmol/L *</td>
<td></td>
</tr>
<tr>
<td>In the 6 to &lt;12 months cohort (n=6), the mean absolute change from baseline in sweat chloride was -58.6 mmol/L (95% CI: -75.9, -41.3) at Week 24 (secondary endpoint)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Patients age 12 to less than 24 months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-73.5 mmol/L *</td>
<td></td>
</tr>
<tr>
<td>In the 12 to &lt;24 months cohort (n=10), the mean absolute change from baseline in sweat chloride was -73.5 mmol/L (95% CI: -86.0, -61.0) at Week 24 (secondary endpoint)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There was no direct correlation between decreases in sweat chloride levels and improvement in lung function (FEV1).1

*Calculated from children with data available at both baseline and Week 24.1
CI, confidence interval; FEV1, forced expiratory volume in 1 second.

IMPORTANT SAFETY INFORMATION

Concomitant Use With CYP3A Inducers

- Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort is not recommended

Cataracts

- Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating KALYDECO treatment

Please click for full Prescribing Information for KALYDECO.
Overall KALYDECO® (ivacaftor) safety profile established in clinical trials

The overall safety profile for KALYDECO is based on Trials 1, 2, and 3

- The overall safety profile for KALYDECO is based on pooled data from 3 placebo-controlled clinical trials conducted in 353 patients age 6 years and older with CF who had a G551D mutation in the CFTR gene (Trials 1 and 2) or who were homozygous for the F508del mutation (Trial 3)
- KALYDECO is not indicated in patients with CF who are homozygous for the F508del mutation

Pooled safety data from Trials 1, 2, and 3

- The proportion of patients who prematurely discontinued study drug due to adverse reactions (ARs) was 2% for patients treated with KALYDECO and 5% for patients treated with placebo

- Serious ARs that occurred more frequently in patients treated with KALYDECO included:
  - ABDOMINAL PAIN
  - INCREASED HEPATIC ENZYMES
  - HYPOGLYCEMIA

- The most common ARs in patients treated with KALYDECO in Trials 1, 2, and 3 (N=221) were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%)

Most common ARs in Trials 1 and 2

- The safety profile for the patients with CF enrolled in the other clinical trials (Trials 3-8) was similar to that observed in the 48-week placebo-controlled trials (Trials 1 and 2)

### ADVERSE REACTION (PREFERRED TERM)

<table>
<thead>
<tr>
<th></th>
<th>KALYDECO N=109 n (%)</th>
<th>PLACEBO N=104 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>26 (24)</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>24 (22)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24 (22)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>22 (20)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>17 (16)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>16 (15)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (13)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (13)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (12)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (9)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Trials 1 and 2 were 48-week, Phase 3, randomized, double-blind, placebo-controlled trials in 213 patients with a G551D mutation. Trial 1 patients were age 12 years and older; Trial 2 patients were age 6 to 11 years.

*Trials 3-8 were 16-week, randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the F508del mutation. KALYDECO is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.

*Trial 4 was an 8-week, crossover design trial involving patients between the ages of 12 and 72 years who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be responsive to ivacaftor. A total of 156 patients were randomized to and received KALYDECO.

*Trial 7 was an 8-week crossover design trial involving patients between the ages of 12 and 72 years who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be responsive to ivacaftor. A total of 156 patients were randomized to and received KALYDECO.

*Trials 8-9 were 24-week, open-label trials in 191 patients age 12 months to <24 months, a cohort of 11 patients age 6 months to <12 months, and a cohort of 6 patients age 4 months to <6 months who could have a G551D, G1244E, G1349D, G178R, G551S, G970R, S1255P, S549R, or S549N mutation. Of the 156 patients enrolled, 32 had a G551D mutation and 2 had a S549N mutation. Trial 6 patients were 2 to <6 years of age.

*Trials 10-12 were 24-week, open-label trials in a cohort of 19 patients age 12 months to <24 months, a cohort of 11 patients age 6 months to <12 months, and a cohort of 6 patients age 4 months to <6 months who could have a G551D, G1244E, G1349D, G178R, G551S, R117H (eligible for this study only in the US), S1255P, S549R, or S549N mutation.
Overall KALYDECO® (ivacaftor) safety profile established in clinical trials (cont’d)

Transaminase elevations in patients age 6 years and older\textsuperscript{1ab}

- In Trials 1, 2, and 3, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN was 2%, 2%, and 6% in patients treated with KALYDECO and 2%, 2%, and 8% in patients treated with placebo, respectively.
- The proportion of patients who permanently discontinued treatment for elevated transaminases, all >8 x ULN, was 0.5% for patients treated with KALYDECO and 2% for patients treated with placebo.
- 2 patients treated with KALYDECO were reported to have serious ARs of elevated liver transaminases compared with none on placebo.
- Transaminase elevations were more common in patients with a history of transaminase elevations.

Transaminase elevations in patients age 4 months to less than 6 years\textsuperscript{1cd}

- In Trial 6, the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 14.7% (5/34). All 5 patients had maximum ALT or AST levels >8 x ULN, which returned to baseline levels following interruption of KALYDECO dosing.
  - Transaminase elevations were more common in patients who had abnormal transaminases at baseline.
  - KALYDECO was permanently discontinued in 1 patient.
- In Trial 8, the incidence of patients experiencing transaminase elevations (ALT or AST) >3, >5, and >8 x ULN in the cohort of patients age 12 to <24 months was 27.8%, 11.1%, and 11.1%, respectively. In the cohort of patients age 6 to <12 months, 1 patient (9.1%) had elevated ALT of >3 to ≤5 x ULN. In the cohort of patients age 4 to <6 months, no patients experienced transaminase elevations.
  - No patients had elevations in total bilirubin or discontinued treatment due to transaminase elevations.

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\textsuperscript{a}Trials 1 and 2 were 48-week, Phase 3, randomized, double-blind, placebo-controlled trials in 213 patients with a G551D mutation. Trial 1 patients were age 12 years and older; Trial 2 patients were age 6 to 11 years.\textsuperscript{1}

\textsuperscript{b}Trial 3 was a 16-week, randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the F508del mutation. KALYDECO is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.\textsuperscript{1}

\textsuperscript{c}Trial 6 was a 24-week, open-label trial in 34 patients who could have had a G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation. Of the 34 patients enrolled, 32 had a G551D mutation and 2 had a S549N mutation. Trial 6 patients were 2 to <6 years of age.\textsuperscript{1}

\textsuperscript{d}Trial 8 was a 24-week, open-label trial in a cohort of 19 patients age 12 months to <24 months, a cohort of 11 patients age 6 months to <12 months, and a cohort of 6 patients age 4 months to <6 months who could have a G551D, G1244E, G1349D, G178R, G551S, R117H (eligible for this study only in the US), S1251N, S1255P, S549N, or S549R mutation.\textsuperscript{1,3,4,6,7}
KALYDECO® (ivacaftor) oral granules should be taken with fat-containing food.

Recommended dosing for KALYDECO® (ivacaftor)

**KALYDECO DOSING**

**DOSAGE FORMS**

- **25 mg**
- **50 mg**
- **75 mg**

**RECOMMENDED DOSE BASED ON WEIGHT AND AGE**

**For patients age 4 to <6 months**
- ≥5 kg: One 25 mg packet every 12 hours

**For patients age 6 months to <6 years**
- 5 kg to <7 kg: One 25 mg packet every 12 hours
- 7 kg to <14 kg: One 50 mg packet every 12 hours
- ≥14 kg: One 75 mg packet every 12 hours

**Patients should continue taking all of their prescribed CF therapies with KALYDECO**

- The safety and efficacy of KALYDECO for patients <4 months have not been established. The use of KALYDECO in children <4 months is not recommended.
- See page 12 for more information on administration of KALYDECO oral granules.

Please click for full Prescribing Information for KALYDECO.
### Dosage adjustments for KALYDECO® (ivacaftor)

**KALYDECO DOSAGE ADJUSTMENTS**

<table>
<thead>
<tr>
<th>DOSAGE ADJUSTMENTS FOR PATIENTS AGE 4 TO &lt;6 MONTHS</th>
<th>DOSE AND ADMINISTRATION FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEPATIC IMPAIRMENT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Any</strong> impairment</td>
<td>Use is not recommended</td>
</tr>
<tr>
<td><strong>CYP3A INHIBITORS</strong></td>
<td></td>
</tr>
<tr>
<td>Co-administration with <strong>strong</strong> or <strong>moderate</strong> CYP3A inhibitors&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>Concomitant use is not recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DOSAGE ADJUSTMENTS FOR PATIENTS AGE ≥6 MONTHS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEPATIC IMPAIRMENT</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Severe</strong> impairment (Child-Pugh Class C)</td>
<td>Use with caution after weighing the risks and benefits of treatment. One dose once daily, or less frequently&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Moderate</strong> impairment (Child-Pugh Class B)</td>
<td>One dose once daily&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Mild</strong> impairment (Child-Pugh Class A)</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td><strong>CYP3A INHIBITORS</strong></td>
<td></td>
</tr>
<tr>
<td>Co-administration with <strong>strong</strong> CYP3A inhibitors&lt;sup&gt;a&lt;/sup&gt;</td>
<td>One dose twice a week&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Co-administration with <strong>moderate</strong> CYP3A inhibitors&lt;sup&gt;b&lt;/sup&gt;</td>
<td>One dose once daily&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Missed dose of oral granules**

- If ≤6 hours have passed: Advise patient to take the dose with fat-containing food
- If >6 hours have passed: Advise patient to skip that dose and resume the normal schedule for the following dose. A double dose should NOT be taken to make up for the forgotten dose

*Use of KALYDECO with a strong CYP3A inhibitor significantly increased ivacaftor exposure. Examples include ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin.¹
*Use of KALYDECO with a moderate CYP3A inhibitor increased ivacaftor exposure. Examples include fluconazole and erythromycin. Food containing grapefruit should be avoided.¹
Use of KALYDECO with strong CYP3A inducers significantly decreases the exposure of ivacaftor. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort is not recommended.¹
*For patients age 6 years and older, one dose is one tablet. For patients age 6 months to less than 6 years, one dose is one weight-based packet of oral granules.²
**PREPARATION**

1. Caregiver should hold the packet with the cut line on top, shake the packet gently to settle the granules, and tear or cut the packet open along the cut line.
2. Caregiver should mix all granules into 1 teaspoon (5 mL) of age-appropriate soft food or liquid.
3. Food or liquid should be at or below room temperature.

**EXAMPLES OF SOFT FOODS AND LIQUIDS TO MIX WITH KALYDECO GRANULES FOR CHILDREN:**

- Breast milk or infant formula
- Puréed vegetables or fruits
- Applesauce
- Milk or yogurt
- Water
- Juice

**ADMINISTRATION**

1. After mixing, caregiver should give within 1 hour.
2. Caregiver should make sure the child finishes the dose completely.
3 GIVE WITH FAT-CONTAINING FOOD

- Food that contains fat must be taken just before or just after the oral granules dose

EXAMPLES OF FAT-CONTAINING FOODS FOR CHILDREN:

- Breast milk or infant formula
- Cheese
- Whole milk

- Yogurt
- Butter
- Eggs
- Cheese pizza
- Peanut butter

Keep your patients’ age in mind when recommending fat-containing foods to caregivers.

a Be sure that cheeses and yogurts are made with whole milk.

Your patients can visit www.everyday-cf.com/cf-kitchen for examples of fat-containing food ideas.


Food containing grapefruit may increase exposure of ivacaftor, and should be avoided during treatment with KALYDECO.

Please click for full Prescribing Information for KALYDECO.