What is KALYDEC\textsuperscript{O}?

KALYDEC\textsuperscript{O} is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have at least one mutation in their CF gene that is responsive to KALYDEC\textsuperscript{O}.

Talk to your doctor to learn if you have an indicated CF gene mutation.

It is not known if KALYDEC\textsuperscript{O} is safe and effective in children under 6 months of age.

Please see Important Safety Information on pages 8-9 and full Prescribing Information for KALYDEC\textsuperscript{O}, including Patient Information.
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Please see Important Safety Information on pages 8-9 and full Prescribing Information for KALYDECO, including Patient Information.
What is KALYDECO® (ivacaftor) for?

KALYDECO is for the treatment of cystic fibrosis (CF) in people age 6 months and older who have one of the following 38 CF gene mutations:

- The following mutations were not included in the clinical studies but are predicted to respond based on results from a laboratory setting: A1067T, D110E, D110H, D1270N, E56K, E193K, F1052V, F1074L, G1069R, K1060T, R74W, and R1070Q
- F508del and 26 other mutations are not responsive to KALYDECO based on clinical and/or laboratory data

What is KALYDECO?

KALYDECO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have at least one mutation in their CF gene that is responsive to KALYDECO.

Talk to your doctor to learn if you have an indicated CF gene mutation.

It is not known if KALYDECO is safe and effective in children under 6 months of age.

Approved since 2012

KALYDECO was initially approved in 2012 for people age 6 years and older with the G551D mutation.

38 mutations

Through 2017, approval for KALYDECO had expanded to include 38 specific mutations based on studies with KALYDECO in clinical and/or laboratory settings.

Age 6+

As of 2019, KALYDECO has been approved to treat people as young as 6 months who have at least one mutation in the CF gene that is responsive to KALYDECO.

Important Safety Information

Who should not take KALYDECO?

Do not take KALYDECO if you take certain medicines or herbal supplements, such as:
- the antibiotics rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medicines such as phenobarbital, carbamazepine (Tegretol®, Carbatrol®, and Equetro®), or phenytoin (Dilantin®, Phenytek®)
- St. John’s wort (Hypericum perforatum)

Talk to your doctor before taking KALYDECO if you take any of the medicines or supplements listed above.

Please see Important Safety Information on pages 8-9 and full Prescribing Information for KALYDECO, including Patient Information.
How does KALYDECO® (ivacaftor) work?

What is the underlying cause of cystic fibrosis (CF)?

CF is caused by CFTR protein defects. A mutation in the genes of a person with CF may make defective CFTR proteins that:

- Don’t open correctly
- Don’t get to the cell surface, where they are normally located

A person with CF may make CFTR proteins that have one of these defects.

Because of these defects, chloride ions cannot flow freely into or out of the cells as they should. This can lead to thick, sticky mucus in the lungs.

How does KALYDECO® (ivacaftor) work?

KALYDECO works on a certain defect of the CFTR protein at the cellular level in people age 6 months and older with a mutation that is responsive to KALYDECO.

The Cell of Someone With CF

KALYDECO allows more chloride ions to pass into and out of the cells, helping to keep a balance of salt and water in certain organs, such as the lungs.

What is known about how KALYDECO works was learned from studies conducted in a lab. Keep in mind that results from laboratory studies do not always match how these medicines work in a person. If you have any questions about your KALYDECO treatment, please speak with your healthcare provider.

See how KALYDECO works
Watch the video at kalydeco.com/HowItWorks
What is the Important Safety Information for KALYDECO® (ivacaftor)?

Who should not take KALYDECO?
Do not take KALYDECO if you take certain medicines or herbal supplements, such as:
- the antibiotics rifampin (Rifamcat®, Rifater®) or rifabutin (Mycobutin®)
- seizure medicines such as phenobarbital, carbamazepine (Tegetrol®, Carbtropl®, and Equetro®), or phenytoin (Dilantin®, Phenytek®)
- St. John’s wort (Hypericum perforatum)

Talk to your doctor before taking KALYDECO if you take any of the medicines or supplements listed above.

What should I tell my doctor before taking KALYDECO?
Before you take KALYDECO, tell your doctor if you:
- have liver or kidney problems
- drink grapefruit juice, or eat grapefruit or Seville oranges
- are pregnant or plan to become pregnant. It is not known if KALYDECO will harm your unborn baby.
- are breastfeeding or planning to breastfeed. It is not known if KALYDECO passes into your breast milk.
- are taking KALYDECO while you are breastfeeding.

KALYDECO may affect the way other medicines work, and other medicines may affect how KALYDECO works.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements, as the dose of KALYDECO may need to be adjusted when taken with certain medications.

Especially tell your doctor if you take:
- antifungal medications such as ketoconazole (e.g., Nizoral®), itraconazole (e.g., Sporanox®), posaconazole (e.g., Noxafil®), voriconazole (e.g., Vfend®), or fluconazole (e.g., Diflucan®)
- antibiotics such as telithromycin (e.g., Ketek®), clarithromycin (e.g., Biaxin®), or erythromycin (e.g., Ery-Tab®)

What should I avoid while taking KALYDECO?
- KALYDECO can cause dizziness in some people who take it. Do not drive a car, use machinery, or do anything that needs you to be alert until you know how KALYDECO affects you
- You should avoid food containing grapefruit or Seville oranges while you are taking KALYDECO

What are the possible side effects of KALYDECO® (ivacaftor)?
KALYDECO can cause serious side effects.

High liver enzymes in the blood have been reported in patients receiving KALYDECO.
Your doctor will do blood tests to check your liver:
- before you start KALYDECO
- every 3 months during your first year of taking KALYDECO
- every year while you are taking KALYDECO

For patients who have had high liver enzymes in the past, the doctor may do blood tests to check the liver more often.

Call your doctor right away if you have any of the following symptoms of liver problems:
- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark, amber-colored urine

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO. Your doctor should perform eye examinations prior to and during treatment with KALYDECO to look for cataracts.

The most common side effects include:
- headache
- upper respiratory tract infection (common cold), including sore throat, nasal or sinus congestion, runny nose
- stomach (abdominal) pain
- diarrhea
- rash
- nausea
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of KALYDECO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You are encouraged to report side effects to FDA at 1-800-FDA-1088.
How was KALYDECO® (ivacaftor) studied?

The effect of KALYDECO on several different measures has been studied in the trials covered in the following pages.

- **Lung function (FEV₁)**
  - Lung function can be measured with an FEV₁ test, which measures how much air a person can exhale in a forced breath in 1 second.

- **Sweat chloride levels**
  - Sweat chloride is a measure of the amount of salt in your sweat. People with cystic fibrosis (CF) have high levels of sweat chloride.

- **Body mass index (BMI)**
  - BMI is a measure of someone’s weight in relation to his or her height.

- **CF respiratory symptoms**
  - Respiratory symptoms are measured by the CFQ-R Respiratory Domain score, which is a tool used to measure respiratory symptoms, including coughing, mucus, and trouble breathing.

- **Pulmonary exacerbations**
  - Pulmonary exacerbations are defined as changes in certain symptoms requiring changes in the use of oral, IV, or inhaled antibiotics.

Keep in mind that not all studies evaluated the same measures, and results shown on the following pages are an average of all people studied and differed among individuals and mutations. Your experience may be different.

Review the results of studies of KALYDECO® (ivacaftor)

Each study below lists the mutations that were evaluated in clinical trials.

- **Age 6 months to less than 1 year old**
  - Study 8: G551D, G178R.

- **Age 1 to less than 2 years old**
  - Study 8: G178R, G551D, S549N.

- **Age 2 to less than 6 years old**
  - Study 6: G551D, S549N.

- **Age 6 years and older**
  - Study 2 (age 6 through 11): G551D.
  - Study 5 (age 6 years and older): R117H.

- **Age 12 years and older**
  - Study 1: G551D.

- **Important Safety Information**
  - 8-9, 18-19, and 26-27

*KALYDECO is not indicated for people with CF who have the G970R mutation.

A note for patients and caregivers

Keep in mind that not all mutations were evaluated in clinical studies, and those that were evaluated were not studied in all age groups. However, KALYDECO is approved for people age 6 months and older with any of the 38 indicated mutations on page 4.

Talk to your healthcare provider to learn more about how these mutations were approved.

Please see Important Safety Information on pages 8 and 9 and full Prescribing Information for KALYDECO, including Patient Information.
Children with CF age 6 months to less than 1 year old

**Study 8** (children 6 months to less than 1 year old)

Study 8 was a 24-week safety study of KALYDECO® (ivacaftor) in children less than 2 years old. Nineteen children age 1 to less than 2 years old and 11 children age 6 months to less than 1 year old with cystic fibrosis (CF) were evaluated in this study. All patients enrolled took KALYDECO. No one in the study took placebo. The primary purpose of this study was to determine the safety and tolerability of KALYDECO.

**Mutations eligible to enroll in this study were:**

**Mutations included in this study:**
10 children had the G551D mutation, and 1 had the G178R mutation.

**How KALYDECO was given**

All children took KALYDECO oral granules mixed with 1 teaspoon of age-appropriate soft food or liquid every 12 hours with fat-containing food. All children continued to take their other CF treatments.

**Please note:** A 25-mg dose is available for children who weigh ~11 pounds (5 kg) to less than ~15 pounds (7 kg).

See page 32 to learn more about how to give your child KALYDECO.

Study results

**Safety**

The safety of KALYDECO® (ivacaftor), observed in this study, was similar to what was observed in KALYDECO studies in people with CF age 2 and older.

For safety information and side effects of KALYDECO, see pages 8-9.

**Sweat chloride**

After taking KALYDECO:

Sweat chloride decreased on average by -58.6 mmol/L at Week 24.

(average mmol/L at beginning of study was 101.5)

Sweat chloride is the amount of salt in your child’s sweat. A decrease in sweat chloride levels does not mean there will be an improvement in lung function (FEV).

**Study limitations**

Because no one in this study took placebo, it is not known if changes in sweat chloride were due to KALYDECO.

KALYDECO was approved in people age 6 months to less than 1 year old based on the benefits shown in studies of KALYDECO in older people as well as the safety assessment in this study.

Talk to your healthcare provider to learn more about how KALYDECO was approved in this age group.

Please see Important Safety Information on pages 8-9 and full Prescribing Information for KALYDECO, including Patient Information.
Study 8 was a 24-week safety study of KALYDECO® (ivacaftor) in children less than 2 years old. Nineteen children age 1 to less than 2 years old and 11 children age 6 months to less than 1 year old with cystic fibrosis (CF) were evaluated in this study. All patients enrolled took KALYDECO. No one in the study took placebo. The primary purpose of this study was to determine the safety and tolerability of KALYDECO.

Mutations eligible to enroll in this study were:

Mutations included in this study:
16 children had the G551D mutation, 2 had the S549N mutation, and 1 had the G178R mutation.

How KALYDECO was given

Children who weighed ~15 pounds (7 kg) to less than ~31 pounds (14 kg) received 50 mg of KALYDECO oral granules.

Children who weighed ~31 pounds (14 kg) or more received 75 mg of KALYDECO oral granules.

All children took KALYDECO oral granules mixed with 1 teaspoon of age-appropriate soft food or liquid every 12 hours with fat-containing food. All children continued to take their other CF treatments.

To learn how to give your child KALYDECO oral granules, see page 32.

Safety results

The safety of KALYDECO® (ivacaftor), observed in this study, was similar to what was observed in KALYDECO studies in people with CF age 2 and older. For safety information and side effects of KALYDECO, see pages 8-9.

Sweat chloride

After taking KALYDECO:
Sweat chloride decreased on average by -73.5 mmol/L at Week 24.
(average mmol/L at beginning of study was 104.1)

Sweat chloride is the amount of salt in your child’s sweat. A decrease in sweat chloride levels does not mean there will be an improvement in lung function (FEV1).

Study limitations

Because no one in this study took placebo, it is not known if changes in sweat chloride were due to KALYDECO.

KALYDECO was approved in people age 1 to less than 2 years old based on the benefits shown in studies of KALYDECO in older people as well as the safety assessment in this study.

Talk to your healthcare provider to learn more about how KALYDECO was approved in this age group.
Study 6 was a 24-week study in which the safety of KALYDECO® (ivacaftor) was studied in 34 children age 2 to less than 6 years old with cystic fibrosis (CF). All children in this study took KALYDECO. No one in this study took placebo. The primary purpose of this study was to determine the safety and tolerability of KALYDECO.

Mutations eligible to enroll in this study were:
*KALYDECO is not indicated for people with CF who have the G970R mutation.

Mutations included in this study:
32 children had the G551D mutation and 2 had the S549N mutation.

How KALYDECO was given

Children who weighed less than ~31 pounds (14 kg) received 50 mg of KALYDECO oral granules.

Children who weighed ~31 pounds (14 kg) or more received 75 mg of KALYDECO oral granules.

All children took KALYDECO oral granules mixed with 1 teaspoon of soft food or liquid every 12 hours with fat-containing food. All children continued to take their other CF treatments.

To learn how to give your child KALYDECO oral granules, see page 32.

Study results

Safety

The type and frequency of side effects for children in the study were similar to those seen in KALYDECO® (ivacaftor) studies in people with CF age 6 years and older.

High liver enzymes were more common in children who had abnormal liver enzymes before starting KALYDECO.

For safety information and side effects of KALYDECO, see pages 8-9.

Sweat chloride

After taking KALYDECO:
Sweat chloride decreased on average by ~45 mmol/L at Week 24.

Sweat chloride is the amount of salt in your child’s sweat. A decrease in sweat chloride levels does not mean there will be an improvement in lung function (FEV1).

Study limitations

Because no one in this study took placebo, it is not known if changes in sweat chloride were due to KALYDECO.

KALYDECO was approved in people age 2 to less than 6 years old based on the benefits shown in studies of KALYDECO in older people as well as the safety assessment in this study.

Talk to your healthcare provider to learn more about how KALYDECO was approved in this age group.
What is the Important Safety Information for KALYDECO® (ivacaftor)?

Who should not take KALYDECO?
Do not take KALYDECO if you take certain medicines or herbal supplements, such as:

- the antibiotics rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medicines such as phenobarbital, carbamazepine (Tegretol®, Carbatrol®, and Equetro®), or phenytoin (Dilantin®, Phenytek®)
- St. John’s wort (Hypericum perforatum)

Talk to your doctor before taking KALYDECO if you take any of the medicines or supplements listed above.

What should I tell my doctor before taking KALYDECO?
Before you take KALYDECO, tell your doctor if you:

- have liver or kidney problems
- drink grapefruit juice, or eat grapefruit or Seville oranges
- are pregnant or plan to become pregnant. It is not known if KALYDECO will harm your unborn baby. You and your doctor should decide if you will take KALYDECO while you are pregnant
- are breastfeeding or planning to breastfeed. It is not known if KALYDECO passes into your breast milk. You and your doctor should decide if you will take KALYDECO while you are breastfeeding

KALYDECO may affect the way other medicines work, and other medicines may affect how KALYDECO works.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements, as the dose of KALYDECO may need to be adjusted when taken with certain medications.

Especially tell your doctor if you take:

- antifungal medications such as ketoconazole (e.g., Nizoral®), itraconazole (e.g., Sporanox®), posaconazole (e.g., Noxafil®), voriconazole (e.g., Vfend®), or fluconazole (e.g., Diflucan®)
- antibiotics such as telithromycin (e.g., Ketek®), clarithromycin (e.g., Biaxin®), or erythromycin (e.g., Ery-Tab®)

What should I avoid while taking KALYDECO?

- KALYDECO can cause dizziness in some people who take it. Do not drive a car, use machinery, or do anything that needs you to be alert until you know how KALYDECO affects you
- You should avoid food containing grapefruit or Seville oranges while you are taking KALYDECO

What are the possible side effects of KALYDECO® (ivacaftor)?

KALYDECO can cause serious side effects.

High liver enzymes in the blood have been reported in patients receiving KALYDECO.

Your doctor will do blood tests to check your liver:

- before you start KALYDECO
- every 3 months during your first year of taking KALYDECO
- every year while you are taking KALYDECO

For patients who have had high liver enzymes in the past, the doctor may do blood tests to check the liver more often.

Call your doctor right away if you have any of the following symptoms of liver problems:

- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark, amber-colored urine

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO. Your doctor should perform eye examinations prior to and during treatment with KALYDECO to look for cataracts.

The most common side effects include:

- headache
- upper respiratory tract infection (common cold), including sore throat, nasal or sinus congestion, runny nose
- stomach (abdominal) pain
- diarrhea
- rash
- nausea
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of KALYDECO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You are encouraged to report side effects to FDA at 1-800-FDA-1088.
**Study 2**

**Study 2** was a 48-week study in which 52 people **age 6 to less than 12 years old** with a G551D mutation took KALYDECO® (ivacaftor) (150-mg tablets) or placebo with fat-containing food every 12 hours. Results were measured at different time points including 24 and 48 weeks. All people took their other cystic fibrosis (CF) treatments except for hypertonic saline through the entire length of the study (48 weeks). This study evaluated lung function (FEV₁). Other results studied were CF respiratory symptoms, weight, and sweat chloride. The study also evaluated the safety of KALYDECO.

**Mutation eligible to enroll and included in this study was:**
G551D.

**Study results**

<table>
<thead>
<tr>
<th>Lung function (FEV₁)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung function increased</strong></td>
</tr>
<tr>
<td>12.5 percentage points greater average improvement, compared to placebo through 24 weeks.</td>
</tr>
<tr>
<td>10.0 percentage points greater average improvement, compared to placebo through 48 weeks.</td>
</tr>
</tbody>
</table>

Lung function was measured as FEV₁, or forced expiratory volume exhaled in 1 second.

To learn how to give your child KALYDECO tablets, see page 32.

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**CF respiratory symptoms**

**No difference was seen in respiratory symptoms**
Compared to placebo through Week 48.

Respiratory symptoms are measured by the CFQ-R Respiratory Domain score, which is a tool used to measure respiratory symptoms, including coughing, mucus, and trouble breathing.

**Weight**

**Weight increased**
About 6 pounds (2.8 kg) on average, compared to placebo at Week 48.

**Sweat chloride**

After taking KALYDECO:
Sweat chloride decreased on average by -53 mmol/L, compared to placebo at Week 48.

Sweat chloride is the amount of salt in your sweat. A decrease in sweat chloride levels does not mean there will be an improvement in lung function (FEV₁).

KALYDECO® (ivacaftor) has also been studied in people age 12 and older who have the G551D mutation. Be sure to review the information on this study on pages 26-29.
People with CF age 6 years and older

Study 4

In Study 4, 39 people age 6 and older who had an eligible cystic fibrosis (CF) mutation (listed below) took KALYDECO® (ivacaftor) (150-mg tablets) or placebo with fat-containing food every 12 hours. All people took all their other CF treatments except for hypertonic saline. Each person had an 8-week treatment period with KALYDECO and an 8-week treatment period with placebo. This study evaluated lung function (FEV₁). Other results studied were CF respiratory symptoms, body mass index (BMI), and sweat chloride. The study also evaluated the safety of KALYDECO.

Mutations eligible to enroll and included in this study were:

*KALYDECO is not indicated for people with CF who have the G970R mutation.

Important considerations
- Results for the mutations studied varied by mutation. Not all mutations showed the same level of benefit when taking KALYDECO
- Some people experienced less improvement compared to the average for all the people in the study. Others experienced more improvement
- Talk to your healthcare provider to learn more about your specific mutation

Study results

Lung function (FEV₁)

Lung function increased

In the overall population for the 9 mutations studied, people had a 10.7 percentage points average improvement in lung function compared to placebo, from the start of the study through Week 8.

Results varied by mutation.

Sweat chloride

Sweat chloride decreased

In the overall population for the 9 mutations studied, people had a -50 mmol/L average decrease in sweat chloride compared to placebo, from the start of the study through Week 8.

Results varied by mutation.

CF respiratory symptoms

CF respiratory symptoms improved

In the overall population for the 9 mutations studied, people had a 9.6 point average improvement in CF respiratory symptoms compared to placebo, from the start of the study through Week 8.

Results varied by mutation.

Body mass index (BMI)

BMI increased

In the overall population for the 9 mutations studied, people had a 0.66 kg/m² on average increase in BMI compared to placebo at Week 8.

Results varied by mutation.

BMI is a measure of someone's weight in relation to his or her height. For example, for a 5'4", 110-lb adult, a 0.66 kg/m² increase in BMI would be a gain of about 4 lb; for a 4'6", 65-lb child, this would be a gain of about 3 lb.

Sweat chloride is the amount of salt in your sweat. A decrease in sweat chloride levels does not mean there will be an improvement in lung function (FEV₁).
Study 5

Study 5 was a 24-week study in which 69 people age 6 and older with an R117H mutation took either KALYDECO® (ivacaftor) (150-mg tablets) or placebo with fat-containing food every 12 hours, along with their other cystic fibrosis (CF) treatments. This study evaluated lung function (FEV1). Other results studied were sweat chloride, CF respiratory symptoms, body mass index (BMI), and pulmonary exacerbations. The study also evaluated the safety of KALYDECO.

Mutation eligible to enroll and included in this study was:
R117H.

What was studied?

**Lung function (FEV1)** was the main measure of this study.

Lung function was measured as FEV1, or forced expiratory volume exhaled in 1 second.

- **Sweat chloride**
- **CF respiratory symptoms** (cough, mucus, and trouble breathing)
- **Body mass index (BMI)**
- **Pulmonary exacerbations**
- **Safety**

Some people in this study showed improvement in these measures, but others did not.

- Please talk to your healthcare provider if you’d like to learn about the results of this study.

To learn how to give your child KALYDECO tablets, see page 32.

Kristen, Makson’s mom

Makson, Age 7, R117H
Who should not take KALYDECO?

Do not take KALYDECO if you take certain medicines or herbal supplements, such as:

- the antibiotics rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medicines such as phenobarbital, carbamazepine (Tegretol®, Carbatrol®, and Equetro®), or phenytoin (Dilantin®, Phenytek®)
- St. John’s wort (Hypericum perforatum)

Talk to your doctor before taking KALYDECO if you take any of the medicines or supplements listed above.

What should I tell my doctor before taking KALYDECO?

Before you take KALYDECO, tell your doctor if you:

- have liver or kidney problems
- drink grapefruit juice, or eat grapefruit or Seville oranges
- are pregnant or plan to become pregnant. It is not known if KALYDECO will harm your unborn baby. You and your doctor should decide if you will take KALYDECO while you are pregnant
- are breastfeeding or planning to breastfeed. It is not known if KALYDECO passes into your breast milk. You and your doctor should decide if you will take KALYDECO while you are breastfeeding

KALYDECO may affect the way other medicines work, and other medicines may affect how KALYDECO works.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements, as the dose of KALYDECO may need to be adjusted when taken with certain medications.

Especially tell your doctor if you take:

- antifungal medications such as ketoconazole (e.g., Nizoral®), itraconazole (e.g., Sporanox®), posaconazole (e.g., Noxafil®), voriconazole (e.g., Vfend®), or fluconazole (e.g., Diflucan®)
- antibiotics such as telithromycin (e.g., Ketek®), clarithromycin (e.g., Biaxin®), or erythromycin (e.g., Ery-Tab®)

What should I avoid while taking KALYDECO?

- KALYDECO can cause dizziness in some people who take it. Do not drive a car, use machinery, or do anything that needs you to be alert until you know how KALYDECO affects you.
- You should avoid food containing grapefruit or Seville oranges while you are taking KALYDECO.

What are the possible side effects of KALYDECO® (ivacaftor)?

KALYDECO can cause serious side effects.

High liver enzymes in the blood have been reported in patients receiving KALYDECO. Your doctor will do blood tests to check your liver:

- before you start KALYDECO
- every 3 months during your first year of taking KALYDECO
- every year while you are taking KALYDECO

For patients who have had high liver enzymes in the past, the doctor may do blood tests to check the liver more often.

Call your doctor right away if you have any of the following symptoms of liver problems:

- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark, amber-colored urine

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO. Your doctor should perform eye examinations prior to and during treatment with KALYDECO to look for cataracts.

The most common side effects include:

- headache
- upper respiratory tract infection (common cold), including sore throat, nasal or sinus congestion, runny nose
- stomach (abdominal) pain
- diarrhea
- rash
- nausea
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of KALYDECO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You are encouraged to report side effects to FDA at 1-800-FDA-1088.
Study 1

Study 1 was a 48-week study in which 161 people age 12 and older with a G551D mutation took KALYDECO® (ivacaftor) (150-mg tablets) or placebo with fat-containing food every 12 hours, along with their other cystic fibrosis (CF) treatments. Results were measured at different time points including 24 and 48 weeks. All people took all their other cystic fibrosis (CF) treatments except for hypertonic saline through the entire length of the study (48 weeks). The study evaluated lung function (FEV₁). Other results studied were CF respiratory symptoms, pulmonary exacerbations, weight, and sweat chloride. The study also evaluated the safety of KALYDECO.

Mutation eligible to enroll and included in this study was: G551D.

Study results

<table>
<thead>
<tr>
<th>Lung function (FEV₁)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung function increased</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.6 percentage points greater average improvement, compared to placebo through 24 weeks.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.5 percentage points greater average improvement, compared to placebo through 48 weeks.</td>
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</tbody>
</table>

To learn how to take KALYDECO tablets, see page 32.

- **CF respiratory symptoms**
  - CF respiratory symptoms improved
    - 8.6 points on average compared to placebo, from the start of the study through Week 48.
    - Respiratory symptoms are measured by the CFQ-R Respiratory Domain score, which is a tool used to measure respiratory symptoms, including coughing, mucus, and trouble breathing.

- **Pulmonary exacerbations**
  - Pulmonary exacerbations decreased
    - Nearly 7 out of 10 people who took KALYDECO® (ivacaftor) did not have a pulmonary exacerbation, compared to around 4 out of 10 people who took placebo at Week 48.
    - Pulmonary exacerbations are defined as changes in certain symptoms requiring changes in the use of oral, IV, or inhaled antibiotics.

- **Weight**
  - Weight increased
    - About 6 pounds (2.7 kg) on average, compared to placebo at Week 48.

- **Sweat chloride**
  - After taking KALYDECO:
    - Sweat chloride decreased on average by -48 mmol/L, compared to placebo at Week 48.
    - Sweat chloride is the amount of salt in your sweat. A decrease in sweat chloride levels does not mean there will be an improvement in lung function (FEV₁).
Study 7

Study 7 was an 8-week study in which people age 12 and older with 1 copy of the F508del mutation and a second mutation predicted to respond to KALYDECO® (ivacaftor) took either KALYDECO (150-mg tablets) or placebo with fat-containing food every 12 hours. All people took all their other cystic fibrosis (CF) treatments except for hypertonic saline. The study evaluated lung function (FEV₁). CF respiratory symptoms and safety were also studied.

In this study, 156 people took KALYDECO (150-mg tablets) and 161 people took placebo.

Mutations enrolled in this study were:

Study results

Lung function (FEV₁)

Lung function increased
4.7 percentage points on average in the overall population studied compared to placebo, from the start of the study to the average of Week 4 and Week 8. Results varied by mutation.

Lung function was measured as FEV₁, or forced expiratory volume exhaled in 1 second.

CF respiratory symptoms

CF respiratory symptoms improved
9.7 points on average in the overall population studied compared to placebo, from the start of the study to the average of Week 4 and Week 8. Results varied by mutation.

Respiratory symptoms are measured by the CFQ-R Respiratory Domain score, which is a tool used to measure respiratory symptoms, including coughing, mucus, and trouble breathing.

Important considerations

- Lung function and respiratory results varied by mutation. Not all mutations showed the same level of benefit when taking KALYDECO
- Some people experienced less improvement compared to the average for all the people in the study. Others experienced more improvement
- This is not intended to represent the full study design or results
- Talk to your healthcare provider for more information

To learn how to take KALYDECO tablets, see page 32.
Taking KALYDECO oral granules and tablets

KALYDECO oral granules are prescribed based on weight for people age 6 months to less than 6 years old and come in 3 different strengths.

<table>
<thead>
<tr>
<th>WEIGHT-BASED DOSE</th>
<th>EACH DOSE</th>
<th>TOTAL DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>~11 pounds to less than 15 pounds (5 kg to &lt;7 kg)</td>
<td>25-mg packet (1 packet every 12 hours)</td>
<td>50 mg (2 packets per day)</td>
</tr>
<tr>
<td>~15 pounds to less than 31 pounds (7 kg to &lt;14 kg)</td>
<td>50-mg packet (1 packet every 12 hours)</td>
<td>100 mg (2 packets per day)</td>
</tr>
<tr>
<td>~31 pounds or more (14 kg or more)</td>
<td>75-mg packet (1 packet every 12 hours)</td>
<td>150 mg (2 packets per day)</td>
</tr>
</tbody>
</table>

KALYDECO tablets are prescribed for people age 6 years and older.

<table>
<thead>
<tr>
<th>EACH DOSE</th>
<th>TOTAL DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>150-mg tablet (1 tablet every 12 hours)</td>
<td>300 mg (2 tablets per day)</td>
</tr>
</tbody>
</table>

Your or your child’s dose may be different. Your healthcare provider will tell you how much KALYDECO you or your child should take and when to take it.

How to give your child KALYDECO® (ivacaftor) oral granules

STEP 1: Preparation

- Hold 1 packet of KALYDECO oral granules with the cut line on top
- Shake the packet gently to settle the KALYDECO granules
- Tear or cut the packet open along the cut line
- Carefully pour all of the KALYDECO granules into 1 teaspoon (5 mL) of age-appropriate soft food or liquid such as puréed fruits or vegetables, yogurt, applesauce, water, breast milk, prepared infant formula, milk, or juice
  - Food or liquid should be at or below room temperature
- Then, mix the granules with the 1 teaspoon of food or liquid

STEP 2: Administration

- Within 1 hour of mixing, give KALYDECO to your child
- Make sure the entire medicine mixture is taken

STEP 3: Fat-containing food before or after the dose

Always take KALYDECO with fat-containing food

- Give your child fat-containing food just before or after the dose of KALYDECO granules. This helps the body absorb KALYDECO better
- Examples of fat-containing food include:
  - Eggs
  - Peanut butter
  - Cheese pizza
  - Whole milk
  - Whole-milk cheese
  - Whole-milk yogurt
- Your doctor can help you choose healthy fat-containing meals and snacks

Learn additional important information about how to take KALYDECO oral granules and tablets on the next page.
How should KALYDECO® (ivacaftor) be taken? (cont.)

Avoid foods or drinks that contain grapefruit or Seville oranges—these may affect the amount of KALYDECO in the body.

What to do if a dose of KALYDECO is missed?

If a dose of KALYDECO is missed and it is within 6 hours of when it is usually taken, take that dose of KALYDECO as prescribed with fat-containing food as soon as possible.

If a dose of KALYDECO is missed and it is more than 6 hours after the time the dose is usually taken, skip that dose only and take the next dose with fat-containing food when it is usually taken. Do not take 2 doses at the same time to make up for a missed dose.

Remember:

- Taking KALYDECO every 12 hours is not the same as taking it twice a day
- Take KALYDECO, plus all other CF therapies, exactly as your healthcare provider tells you
- Tell your healthcare provider before starting, changing, or stopping any medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements
Frequently asked questions about KALYDECO® (ivacaftor) oral granules

**Q:** How should KALYDECO oral granules be stored?

KALYDECO should be stored at 68°F to 77°F (20°C to 25°C). Do not use KALYDECO after the expiration date on the package. Keep KALYDECO and all medicines out of the reach of children.

**Q:** Are the oral granules packets child proof?

The packets are child-resistant.

**Q:** Can I mix KALYDECO oral granules in breast milk or prepared infant formula?

Yes, KALYDECO oral granules can be mixed with 1 teaspoon (5 mL) of breast milk or prepared infant formula at or below room temperature. Be sure that the entire mixture is taken by the child within 1 hour. Remember your child should always take KALYDECO with a fat-containing food.

**Q:** Can I mix KALYDECO oral granules in soft food or liquid that contains fat? If so, do I still need to give fat-containing food to my child?

Yes, you can mix KALYDECO granules with fat-containing food, for example 1 teaspoon (5 mL) of whole-milk yogurt or milk, to give to your child. But your child should still eat fat-containing food just before or after taking the spoonful of the mixture.

**Q:** Do breast milk and prepared infant formula qualify as fat-containing foods that my child can take with KALYDECO?

Yes, breast milk and prepared infant formula qualify as fat-containing foods.

**Q:** Can my child swallow the granules without mixing them in soft food or liquid?

The entire contents of each packet should be mixed with 1 teaspoon (5 mL) of age-appropriate soft food or liquid. The mixture should be taken within 1 hour of being mixed. Make sure all medicine is taken.

**Q:** Can I give my child KALYDECO® (ivacaftor) oral granules using a bottle?

You should not use a bottle to give your child KALYDECO oral granules. You can use a spoon to give KALYDECO oral granules mixed with 1 teaspoon (5 mL) of age-appropriate soft food or liquid.

**Q:** Do the granules have a taste?

The granule formulation is sweetened but unflavored.

**Q:** Does the temperature of the food that I mix with KALYDECO oral granules matter? Can the granules be mixed in foods that are hot or cold?

The granules should be mixed with soft food or liquid at room temperature or below. The granules should not be mixed in items that are frozen or hot.

For more information about how to take KALYDECO oral granules, visit KALYDECO.com

Please see Important Safety Information on pages 8-9 and full Prescribing Information for KALYDECO, including Patient Information.
**Frequently asked questions about KALYDECO® (ivacaftor) tablets**

**Q:** How should KALYDECO tablets be stored?
KALYDECO should be stored at 68°F to 77°F (20°C to 25°C). Do not use KALYDECO after the expiration date on the package. Keep KALYDECO and all medicines out of the reach of children.

**Q:** What do KALYDECO tablets look like?
For people 6 years and older, KALYDECO tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor. Each tablet is printed with the characters “V 150” on one side and plain on the other.

**Q:** Can I separate the doses on the blister cards?
You may cut along the dotted line to separate your doses from the blister card.

For more information about how to take KALYDECO tablets, visit KALYDECO.com
Explore how Vertex GPS™: Guidance and Patient Support can help

Vertex GPS provides eligible patients with reimbursement support, information about financial resources, refill reminders, and ongoing educational materials.

If you are currently enrolled and want to learn more about how Vertex GPS can support you, you can speak to your Case Manager at 1-877-752-5933 (press 2), Monday through Friday from 8:30 AM to 7:00 PM ET. If you have been prescribed KALYDECO® (ivacaftor) and are not enrolled, please speak with your healthcare provider.

To find out more about Vertex GPS and the support resources available to you, including Delicious Dishes, visit VertexGPS.com.

Please see full Prescribing Information for KALYDECO, including Patient Information.