



# Understanding your treatment

A diagnosis of metastatic breast cancer can be overwhelming. This guide has been designed to help you understand your type of metastatic breast cancer. Read more to learn what you can expect from treatment.

Images in this brochure do not depict actual patients.

## What is Itovebi™?

Itovebi (inavolisib) is a prescription medicine used in combination with the medicines palbociclib and fulvestrant to treat adults who have hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has an abnormal phosphatidylinositol-3-kinase catalytic subunit alpha (*PIK3CA*) gene, and has spread to nearby tissue or lymph nodes (locally advanced), or to other parts of the body (metastatic), and has come back after hormone (endocrine) therapy.

Your healthcare provider will test your cancer for abnormal *PIK3CA* genes to make sure that Itovebi is right for you.

It is not known if Itovebi is safe and effective in children.

Please see Important Safety Information on pages 24-25 and the full [Prescribing Information](#), including [Patient Information](#).

## Important Safety Information

### What are the possible side effects of Itovebi?

**Itovebi may cause serious side effects, including:**

- **High blood sugar levels (hyperglycemia).** High blood sugar is common with Itovebi and may be severe. Your healthcare provider will monitor your blood sugar levels before you start and during treatment with Itovebi. Your blood sugar levels may be monitored more often if you have a history of Type 2 diabetes. Your healthcare provider may also ask you to self-monitor and report your blood sugar levels at home. This will be required more frequently in the first 4 weeks of treatment. If you are not sure how to test your blood sugar levels, talk to your healthcare provider. You should stay well-hydrated during treatment with Itovebi.



## Questions?

For additional information and downloadable resources, please visit [Itovebi.com](https://www.itovebi.com).

### PATIENT RESOURCE CENTER

Genentech is dedicated to providing patients and caregivers with financial support and other resources.

**1 (877) GENENTECH (436-3683)**  
Monday-Friday, 6 AM-5 PM PT

Please see Important Safety Information on pages 24-25 and the full [Prescribing Information](#), including [Patient Information](#).



# What's inside

- **Understanding your diagnosis** ..... 4-5

Learn more about HR+/HER2- metastatic breast cancer with a *PIK3CA* mutation.
- **About Itovebi** ..... 6-8

Find out more about Itovebi, including how it works and how it performed in a clinical study.
- **Taking Itovebi** ..... 9-11

Understand how to take your treatment.
- **Possible side effects and tips** ..... 12-17

Learn about potential side effects and tips that can help.
- **Additional resources** ..... 18-23

Keep track of questions to ask your healthcare team, connect with Genentech Patient Support Services, and find community support.
- **Important Safety Information** ..... 24-25

Review the Indication and Important Safety Information for Itovebi.

# Understanding your diagnosis



## What does it mean if I have metastatic breast cancer (mBC)?

If your breast cancer is metastatic, it means it has spread from where it started to another part of your body.

The goal of treatments for metastatic breast cancer is to stop cancer from spreading further and help maintain quality of life, with acceptable side effects.

## What is hormone receptor-positive HER2-negative breast cancer (BC)?

If your doctor refers to your breast cancer as hormone-receptor positive (HR+), this means the cancer cells have a high number of hormone (estrogen or progesterone) receptors. Cancer cells with more hormone receptors make copies of themselves more often, making the tumor grow.

Breast cancers are also categorized by a protein called HER2. If your breast cancer is HER2 negative (HER2-), it means the cancer cells don't have many HER2 receptors.

## Important Safety Information

### Itovebi may cause serious side effects, including high blood sugar levels (hyperglycemia) (cont'd)

Tell your healthcare provider right away if you develop symptoms of high blood sugar, including:

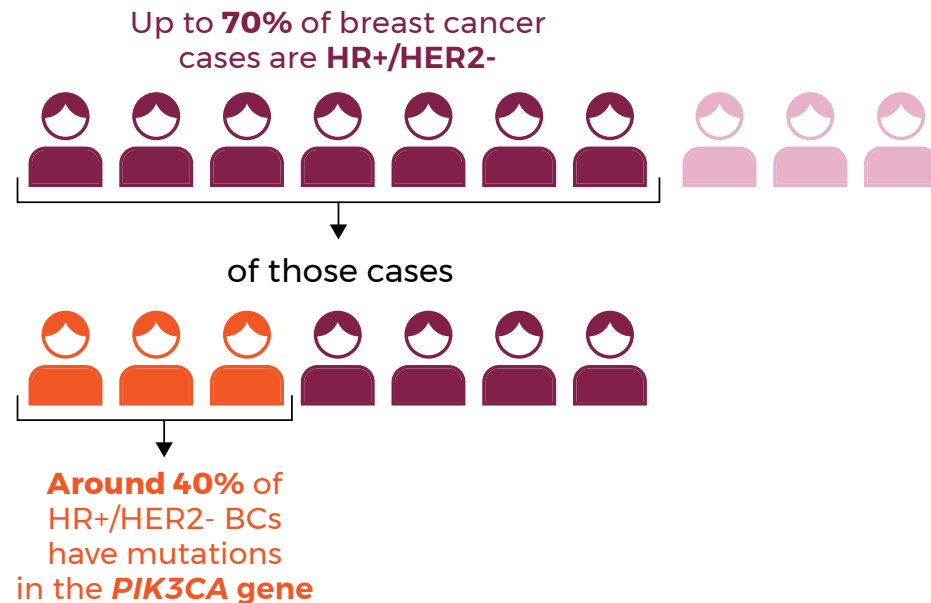
- difficulty breathing
- nausea and vomiting (lasting more than 2 hours)
- stomach pain
- excessive thirst
- dry mouth
- more frequent urination than usual or a higher amount of urine than normal
- blurred vision
- unusually increased appetite
- weight loss
- fruity-smelling breath
- flushed face and dry skin
- feeling unusually sleepy or tired
- confusion

Please see Important Safety Information on pages 24-25 and the full [Prescribing Information](#), including [Patient Information](#).

# Understanding your diagnosis

## What does it mean if I have BC that is *PIK3CA*-mutated?

Around 40% of people with HR+/HER2- breast cancer have one or more mutations in the *PIK3CA* gene. The mutations lead to an altered protein that can cause cancer cells to grow and spread.



## Itovebi is specifically designed to target cells with the *PIK3CA* mutation

Itovebi is a treatment for patients who have been diagnosed with but not yet treated for HR+/HER2- mBC with mutations in the *PIK3CA* gene.

*PIK3CA* mutations occur spontaneously. They are not inherited, and cannot be passed on to children.

## Important Safety Information

Itovebi may cause serious side effects, including:

- **Mouth sores (stomatitis).** Mouth sores are common with Itovebi and may be severe. Tell your healthcare provider if you develop any of the following in your mouth:
  - pain
  - redness
  - swelling
  - ulcers

## About Itovebi

Your doctor prescribed **Itovebi** because they believe it is the most appropriate treatment for your type of breast cancer at this stage of treatment.

### Itovebi is not chemotherapy

It is an oral prescription medicine that is used together with the oral medicine palbociclib and a type of hormone therapy injection called fulvestrant.

### Important Safety Information

**Itovebi may cause serious side effects, including:**

- **Diarrhea.** Diarrhea is common with Itovebi and may be severe. Severe diarrhea can lead to the loss of too much body water (dehydration) and kidney injury. Tell your healthcare provider right away if you develop diarrhea, stomach-area (abdominal) pain, or see mucus or blood in your stool during treatment with Itovebi. Your healthcare provider may tell you to drink more fluids or take medicines to treat your diarrhea.

Your healthcare provider may tell you to decrease your dose, temporarily stop your treatment, or completely stop your treatment with Itovebi if you develop certain serious side effects.

Please see **Important Safety Information** on pages 24-25 and the full **Prescribing Information**, including **Patient Information**.

 **itovebi**™  
inavolisib 3 mg · 9 mg  
tablets



# About Itovebi



## Who is Itovebi for?

Your doctor may have prescribed Itovebi if you have metastatic breast cancer that:

- Is HR+ and HER2-, and
- Has come back during or after endocrine therapy you received following breast surgery, and
- A test showed that your cancer has a mutation in the *PIK3CA* gene

## Important Safety Information

**The most common side effects and abnormal blood test results of Itovebi when used in combination with palbociclib and fulvestrant include:**

- decreased white blood cell counts, red blood cell counts, and platelet counts
- decreased blood levels of calcium, potassium, sodium, and magnesium
- increased creatinine blood levels
- tiredness
- increased blood levels of the liver enzyme alanine transaminase (ALT)
- nausea
- rash
- loss of appetite
- COVID-19 infection
- headache

Itovebi may affect fertility in males and in females who are able to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of Itovebi. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). You may also report side effects to Genentech at (877) 436-3683.

# About Itovebi



## About the Itovebi study

- In a clinical trial that included 325 adults who had HR+/HER2- mBC with a *PIK3CA* mutation, Itovebi + palbociclib + fulvestrant was studied in 161 patients
- The trial participants had received endocrine therapy for early breast cancer, but their cancer came back during or within 12 months of stopping that treatment
- The adults in this study had not previously been treated for mBC
- About half of the people in the study were given Itovebi + palbociclib + fulvestrant, and the other half were given placebo + palbociclib + fulvestrant until their disease worsened (progressed) or they stopped due to side effects

## Itovebi study results

Adults who took Itovebi + palbociclib + fulvestrant had **more than double the time without their cancer growing or spreading** compared to those who took placebo + palbociclib + fulvestrant.

**7 months**

Placebo + palbociclib + fulvestrant

**15 months**

Itovebi + palbociclib + fulvestrant

MORE THAN  
**2X**  
AS LONG



# ➤ Taking Itovebi



Itovebi is a once-a-day pill you can take wherever is convenient for you.

## Important Safety Information

**Before you take Itovebi, tell your healthcare provider about all of your medical conditions, including if you:**

- have a history of diabetes or high blood sugar
- have kidney problems
- are pregnant or plan to become pregnant. Itovebi can harm your unborn baby.


### Females who are able to become pregnant:


- Your healthcare provider will check to see if you are pregnant before you start treatment with Itovebi.
- You should use effective non-hormonal birth control (contraception) during treatment with Itovebi and for 1 week after your last dose. Talk to your healthcare provider about what birth control method is right for you during this time.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with Itovebi.


### Males with female partners who are able to become pregnant:

- You should use effective birth control (contraception) during treatment with Itovebi and for 1 week after your last dose.
- are breastfeeding or plan to breastfeed. It is not known if Itovebi passes into your breastmilk. Do not breastfeed during treatment with Itovebi and for 1 week after your last dose. Talk to your healthcare provider about the best way to feed your baby during treatment with Itovebi.

## Itovebi-based treatment:

 **Itovebi** is a tablet you take once per day.

 **Palbociclib** is a tablet you take once a day for 3 weeks, followed by a week of no tablets.

 **Fulvestrant** is given as 2 injections, one in each buttock muscle. You'll receive the injections when you first start treatment, 2 weeks after you start, 4 weeks after you start, and then once a month. You will be given these injections by your healthcare provider.

## Important Safety Information

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

# Taking Itovebi



## What will my treatment schedule look like?

### First month

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1							
Week 2							
Week 3							
Week 4							

Itovebi - Itovebi is usually taken as one tablet, but depending on your dose, you might need to take more than one tablet.

palbociclib

fulvestrant

Actual Itovebi and palbociclib tablets appear different. Itovebi is available in 3-mg and 9-mg tablets.

### After first month

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1							
Week 2							
Week 3							
Week 4							

# Taking Itovebi



## How should I take Itovebi?

- **Take Itovebi exactly as directed by your healthcare provider.**
- Do not change your dose or stop taking Itovebi unless your healthcare provider tells you.

## Take Itovebi:



Once daily  
by mouth



With or  
without food



Ideally at the same  
time each day

- Swallow Itovebi tablet(s) whole. Do not chew, crush, or split the tablet(s).

## Make Itovebi a part of your daily routine.

Set a daily reminder so you always remember when it's time to take your medicine.

- If you miss your dose of Itovebi, you may still take it within 9 hours from the time you usually take it. If more than 9 hours, skip your dose for the day. The next day, take your dose at your usual time.
- If you vomit after taking Itovebi, do not take an extra dose. Take your regular dose at your usual time the next day.
- For women who have not reached menopause or are just starting menopause, your healthcare provider will prescribe a medicine called luteinizing hormone-releasing hormone (LHRH) agonist. For men, your healthcare provider may prescribe a LHRH agonist.
- Store Itovebi at room temperature (68°F to 77°F).
- Keep Itovebi and all medicines out of reach of children.

**Tell your healthcare provider if you experience any side effects while taking Itovebi.** The symptoms of some of the common side effects are listed in this brochure.

## Possible side effects and tips

### What possible side effects might I experience while taking Itovebi?

Like all medicines, Itovebi can cause side effects. Be sure to tell your healthcare provider if you experience any changes in your body or health, as they may be signs of a side effect.

To manage side effects, your doctor may:



**TREAT**  
SIDE EFFECTS



**DELAY**  
YOUR DOSE



**LOWER**  
YOUR DOSE



**STOP**  
YOUR TREATMENT

### 6% of people in the clinical trial completely stopped Itovebi treatment because of side effects.

The majority were able to stay on treatment for the duration of the trial.

### The most common side effects and abnormal blood test results of Itovebi-based treatment include:

- decreased white blood cell counts, red blood cell counts, and platelet counts
- decreased blood levels of calcium, potassium, sodium, and magnesium
- increased creatinine blood levels
- tiredness
- increased blood levels of the liver enzyme alanine transaminase (ALT)
- nausea
- rash
- loss of appetite
- COVID-19 infection
- headache

Itovebi may affect fertility in males and in females who are able to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of Itovebi.

**Call your doctor if you experience these or any other side effects.**

#### Carry the Wallet Card with you at all times.

- Show it to any healthcare provider involved in your care.
- The card can be downloaded on [Itovebi.com](https://www.itovebi.com)



# Possible side effects and tips (cont'd)

Itovebi may cause serious side effects, including:



## High blood sugar levels (Hyperglycemia)

Higher than normal amount of sugar in the blood

- Hyperglycemia is common with Itovebi and may be severe
- Your healthcare provider will monitor your blood sugar levels before you start and during treatment with Itovebi
- They may also ask you to self-monitor and report your blood sugar levels at home
- If you are self-monitoring, talk to your healthcare provider about how and when to test your blood sugar levels

Notes from my healthcare team:

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## Tell your healthcare provider right away if you develop symptoms of high blood sugar, including:

- difficulty breathing
- nausea and vomiting (lasting more than 2 hours)
- stomach pain
- excessive thirst
- dry mouth
- more frequent urination than usual or a higher amount of urine than normal
- blurred vision
- unusually increased appetite
- weight loss
- fruity-smelling breath
- flushed face and dry skin
- feeling unusually sleepy or tired
- confusion

## Support is only a call away.

- Contact your healthcare provider if you experience any side effects
- Genentech also offers no-cost, virtual 1:1 Itovebi Patient Education where you can discuss topics including possible side effects, what to ask your healthcare provider, and tips that can help



Visit [Itovebi.com/patient-support](https://www.itovebi.com/patient-support) to sign up.

## ➤ Possible side effects and tips (cont'd)

Hyperglycemia **occurred early\*** in half of the patients who developed it during the clinical study, and later in the other half.

**Talk to your doctor about any side effects you may be experiencing. Continue to the next page to learn more.**

\*Within the first 7 days. The time to first onset of hyperglycemia ranged from 2 to 955 days.

Please see Important Safety Information on pages 24-25 and the full [Prescribing Information](#), including [Patient Information](#).



## ➤ Possible side effects and tips (cont'd)

### Managing hyperglycemia

- If you experience hyperglycemia, your doctor may change or pause your dose, prescribe medication, or suggest some lifestyle modifications (like dietary changes) to help with the symptoms
- You should stay well-hydrated during treatment with Itovebi
- Monitoring hyperglycemia is especially important in the first three months after starting Itovebi treatment

**In the Itovebi study, some patients with high blood sugar levels were treated with antihyperglycemic medication.**

Of the 162 adults taking Itovebi-based treatment, 1.2% stopped treatment completely because of hyperglycemia.

### Monitoring for hyperglycemia

#### Fasting glucose level

<b>Once</b>	before starting Itovebi
<b>Week 1</b>	every 3 days
<b>Weeks 2-4</b>	once a week
<b>Weeks 5-12</b>	once every 2 weeks
<b>After Week 12</b>	once every 4 weeks and when your doctor feels it's needed

#### Hemoglobin A<sub>1c</sub>

<b>Once</b>	before starting Itovebi
<b>Once</b>	every 3 months and when your doctor feels it's needed

**If you have a history of Type 2 diabetes, your blood sugar level monitoring may be more frequent.**



# Possible side effects and tips (cont'd)

Itovebi may cause serious side effects, including:



## Diarrhea

Frequent and watery bowel movements

- Diarrhea is common with Itovebi and may be severe
- No patients in the clinical study completely stopped taking Itovebi because of diarrhea

### Managing diarrhea

- Tell your healthcare provider right away if you develop diarrhea, stomach-area (abdominal) pain, or see mucus or blood in your stool during treatment with Itovebi
- Your healthcare provider may tell you to drink more fluids or take medicines to treat your diarrhea

Notes from my healthcare team:

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If you develop diarrhea, ask your doctor which foods and drinks you should try or avoid.



### Foods and drinks you may want to try:

- Water
- Drinks containing electrolytes (eg, sugar-free sports drinks)
- Caffeine-free, sugar-free teas
- Clear, fat-free broths
- Gelatin, plain yogurt, and eggs
- Toast, saltine crackers, and rice (however, if you have hyperglycemia, you may need to limit carbohydrates)
- Skinless meats that can be broiled or baked (for example, turkey, chicken, and fish)



### Foods and drinks you may want to avoid:

- Juices or foods that have a laxative effect, such as prunes or prune juice
- Alcoholic beverages
- Milk and other dairy products (except for yogurt)
- Coffee and other caffeinated drinks
- Spicy foods and sauces
- Greasy and fried foods
- High-fiber foods, such as cooked dried beans, raw vegetables and fruits, nuts, and whole-grain breads and cereals

The general information above is for reference only.



Your **Itovebi Treatment Tracker**, available at [Itovebi.com](https://www.itovebi.com), helps you track side effects in a format you can easily share with your healthcare team.



## ➤ Possible side effects and tips (cont'd)

Itovebi may cause serious side effects, including:



### Mouth sores (stomatitis)

Inflammation or irritation of the lining of the mouth

- Mouth sores are common with Itovebi and may be severe
- Fewer than 1% of patients in the clinical study completely stopped taking Itovebi because of mouth sores

#### Managing stomatitis

- To lower the chances of mouth sores, your doctor may recommend a medicated daily mouthwash
- Check your mouth daily, and report any pain, redness, swelling, or ulcers to your healthcare team as soon as you notice them
- Practice good mouth care, such as using an extra-soft toothbrush to gently brush your teeth. Ask your healthcare team if you should floss
- Be sure to discuss dietary options with your healthcare team if you develop stomatitis

Notes from my healthcare team:

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### Rash

An area of the skin that has changes in texture or color and may look inflamed or irritated. The skin may be red, warm, scaly, bumpy, dry, itchy, swollen, painful, cracked, or blistered

- No patients in the clinical study completely stopped taking Itovebi because of a rash

#### Managing rash

- Try to take quick showers or sponge baths instead of long, hot ones
- Clean skin gently with warm water and mild, moisturizing soap; rinse and pat dry
- Apply a fragrance- and alcohol-free moisturizer while skin is still damp
- Wear soft, loose-fitting clothing
- Avoid being in the sun as much as possible. If you need to be outside during the day, wear a hat and long-sleeved clothing and apply broad-spectrum sunscreen of at least SPF 30
- Be sure to get skin care advice from your healthcare team if you develop a rash



For a digital version of your Itovebi Treatment Tracker, please visit [Itovebi.com](https://www.itovebi.com)

# Questions to ask your healthcare team



## Starting treatment

What should I do to prepare for treatment?

Will I need any tests during treatment?  
What are they, and how often will I have them?

How will we know if the treatment is working?

How might I feel while on treatment?

How long will I stay on treatment?

## Managing side effects

What side effects should I watch for? When might they start, and how long could they last?

What should I do if I have side effects?

Which side effects should I report, and who should I contact?

What should I do if side effects are severe or occur after hours?

How can I tell the difference between side effects and cancer symptoms?

Notes from my healthcare team:

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## Important Safety Information

### Females who are able to become pregnant:

- Your healthcare provider will check to see if you are pregnant before you start treatment with Itovebi.
- You should use effective non-hormonal birth control (contraception) during treatment with Itovebi and for 1 week after your last dose. Talk to your healthcare provider about what birth control method is right for you during this time.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with Itovebi.

# Questions to ask your healthcare team (cont'd)

## Other topics

Are there any lifestyle changes I need to make during treatment?

Can I exercise?

Do I need to avoid alcohol or certain foods?

Can I continue working?

Will I be able to travel?

Should I change anything about my diet or meal times?  
Can you recommend a dietitian or nutritionist?

Do I need to adjust any of my other medications, including vitamins, supplements, laxatives, and over-the-counter medicines?

Can you suggest resources for financial, emotional, and practical support?

Can you recommend a mental health professional who works with cancer patients?

## Important Safety Information

**Itovebi may cause serious side effects, including:**

- **High blood sugar levels (hyperglycemia).** High blood sugar is common with Itovebi and may be severe. Your healthcare provider will monitor your blood sugar levels before you start and during treatment with Itovebi. Tell your healthcare provider right away if you develop symptoms of high blood sugar, including excessive thirst, urinating more often, blurred vision, mental confusion, difficulty breathing, or increased appetite with weight loss.
- **Mouth sores (stomatitis).** Mouth sores are common with Itovebi and may be severe. Tell your healthcare provider right away if you develop painful redness, swelling, or sores in your mouth.
- **Diarrhea.** Diarrhea is common with Itovebi and may be severe. Tell your healthcare provider right away if you develop diarrhea, stomach-area (abdominal) pain, or see mucus or blood in your stool during treatment with Itovebi.

# Genentech Patient Support Services

We may be able to help you get the Itovebi you need, even if you can't pay for it.



 **itovebi**<sup>™</sup>  
inavolisib 3 mg · 9 mg  
tablets



## Not sure where to start?

The **Genentech Patient Resource Center** connects you to all the help we offer to people prescribed Itovebi.

Call **(877) GENENTECH (436-3683)**

Monday-Friday, 6 AM - 5 PM PST

# ➤ Genentech Patient Support Services (cont'd)

No matter what type of health insurance you have, and even if you have none at all, there may be some potential options available to help you afford your medicine.

## Genentech Co-pay Assistance Program\*

Can help you if you have commercial health insurance and meet other eligibility criteria:



Eligible patients pay as little as \$0 for their Itovebi.\*



The program covers the rest of your co-pay, up to a \$25,000 annual benefit.

### For more information or to get started:

- Visit [copayassistancenow.com](https://www.copayassistancenow.com)
- Call **(855) MY-COPAY (855-692-6729)**

### Independent Co-pay Assistance Foundations†

- Help patients with public or commercial health insurance
- You can visit [Genentech-Access.com](https://www.Genentech-Access.com) to view a list of independent co-pay assistance foundations or call **(888) 249-4918** to get help

### Genentech Patient Foundation‡

The Genentech Patient Foundation gives free Itovebi to people who have been prescribed this medicine and don't have insurance, or who have financial concerns and meet certain eligibility criteria.

### Not sure if you're eligible?

- Call **(888) 941-3331** to speak with a live **Foundation Specialist**
- You can also visit [GenentechPatientFoundation.com](https://www.GenentechPatientFoundation.com) for more information

\*Eligibility criteria apply. Not valid for patients using federal or state government programs to pay for their medicine and/or administration of their Genentech medicine. Patients must be taking the Genentech medicine for an FDA-approved indication. Please visit the Co-pay Program website for the full list of Terms and Conditions.

†Independent co-pay assistance foundations have their own rules for eligibility. Genentech has no involvement or influence in independent foundation decision-making or eligibility criteria and does not know if a foundation will be able to help you. We can only refer you to a foundation that supports your disease state. Genentech does not endorse or show preference for any particular foundation. The foundations we refer you to may not be the only ones that might be able to help you.

‡If you have health insurance, you should try to get other types of financial assistance, if available. You also need to meet income requirements. If you do not have insurance, or if your insurance does not cover your Genentech medicine, you must meet a different set of income requirements. Genentech reserves the right to modify or discontinue the program at any time and to verify the accuracy of information submitted.

## ➤ Advocacy groups: Resources and support

Information for people living with cancer, as well as families, friends, and survivors

### **Breastcancer.org** | [www.breastcancer.org](http://www.breastcancer.org)

This website is dedicated to providing educational content and research news coverage about treatment options, symptoms, diagnosis, and prevention.

### **Living Beyond Breast Cancer** | [www.lbbc.org](http://www.lbbc.org)

Support and information for people who are newly diagnosed, in treatment, years beyond treatment, or living with breast cancer.

### **Metastatic Breast Cancer Network** | [www.mbcalliance.org](http://www.mbcalliance.org)

A national, independent, nonprofit advocacy group that is dedicated to the concerns of women and men living with metastatic breast cancer.

### **SHARE** | [www.sharecancersupport.org](http://www.sharecancersupport.org)

A network of breast and other cancer survivors who want to share their experience with others.

### **Susan G. Komen** | [www.komen.org](http://www.komen.org)

Information for people living with cancer, families, friends, and survivors.

### **Young Survival Coalition** | [www.youngsurvival.org](http://www.youngsurvival.org)

An organization dedicated to critical issues in young women with breast cancer.

This is a partial list of some cancer support organizations. They are not controlled by, endorsed by, or affiliated with Genentech, Inc. The list is meant for informational purposes only and is not intended to replace your healthcare professional's medical advice. Ask your doctor or your healthcare team any questions you have about your cancer or treatment plan.



## Glossary

**Co-pay assistance:** Programs available to help eligible patients pay for their medicines

**Endocrine therapy:** Treatment given to people with hormone receptor-positive breast cancer—it works by lowering the amount of hormones in the body or by stopping them from getting to the tumor cells. Also called hormonal therapy

**Genentech:** The maker of Itovebi. Genentech is committed to helping patients get the Itovebi their doctor prescribed

**Genentech Patient Foundation:** A program that gives free Genentech medicine to people who don't have health insurance coverage or who have financial concerns and meet certain eligibility criteria

**Hormone receptor:** Protein found on the surface of cells that bind hormones circulating in the blood. When hormones attach to hormone receptors, the cancer cells with these receptors grow

**Hormone receptor-positive breast cancer:** A type of cancer where the cells have a high number of hormone receptors on their surface

**Metastatic breast cancer:** Cancer that started in the breast and spread to another part of the body

**Mutation:** A change in the genetic material of a cell. This may occur randomly, be inherited, or be caused by environmental changes. Most mutations are not harmful, but some can result in a genetic disorder or cancer

**PI3K:** A type of protein that transmits signals in cells and is involved in cell growth

**PIK3CA:** A gene that helps make the PI3K protein. Mutations in the *PIK3CA* gene may cause PI3K to become overactive, which may make cancer cells grow

**PIK3CA-mutated breast cancer:** A type of breast cancer with one or more mutations in a specific gene called *PIK3CA*

**Placebo:** Inactive pill that may be used in studies to compare the effects of a given treatment with no treatment

**Protein:** Large, complex molecule that plays many important roles in cells

**Specialty pharmacy (SP):** An SP supplies certain medicines for patients. Some plans require you to use a certain SP to receive your medicine. SPs send your medicine to your doctor's office or your home. They may also offer other services, such as referrals to financial assistance

**Thrombocytopenia:** A condition in which there is a lower-than-normal number of platelets in the blood. It may result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes and other tissues

## What is Itovebi?

Itovebi (inavolisib) is a prescription medicine used in combination with the medicines palbociclib and fulvestrant to treat adults who have hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has an abnormal phosphatidylinositol-3-kinase catalytic subunit alpha (*PIK3CA*) gene, and has spread to nearby tissue or lymph nodes (locally advanced), or to other parts of the body (metastatic), and has come back after hormone (endocrine) therapy.

Your healthcare provider will test your cancer for abnormal *PIK3CA* genes to make sure that Itovebi is right for you.

It is not known if Itovebi is safe and effective in children.

## Important Safety Information

### What are the possible side effects of Itovebi?

#### Itovebi may cause serious side effects, including:

- **High blood sugar levels (hyperglycemia).** High blood sugar is common with Itovebi and may be severe. Your healthcare provider will monitor your blood sugar levels before you start and during treatment with Itovebi. Your blood sugar levels may be monitored more often if you have a history of Type 2 diabetes. Your healthcare provider may also ask you to self-monitor and report your blood sugar levels at home. This will be required more frequently in the first 4 weeks of treatment. If you are not sure how to test your blood sugar levels, talk to your healthcare provider. You should stay well-hydrated during treatment with Itovebi.

Tell your healthcare provider right away if you develop symptoms of high blood sugar, including:

- difficulty breathing
  - nausea and vomiting (lasting more than 2 hours)
  - stomach pain
  - excessive thirst
  - dry mouth
  - more frequent urination than usual or a higher amount of urine than normal
  - blurred vision
  - unusually increased appetite
  - weight loss
  - fruity-smelling breath
  - flushed face and dry skin
  - feeling unusually sleepy or tired
  - confusion
- **Mouth sores (stomatitis).** Mouth sores are common with Itovebi and may be severe. Tell your healthcare provider if you develop any of the following in your mouth:
    - pain
    - redness
    - swelling
    - ulcers



## Important Safety Information

### What are the possible side effects of Itovebi? (cont'd)

#### Itovebi may cause serious side effects, including:

- **Diarrhea.** Diarrhea is common with Itovebi and may be severe. Severe diarrhea can lead to the loss of too much body water (dehydration) and kidney injury. Tell your healthcare provider right away if you develop diarrhea, stomach-area (abdominal) pain, or see mucus or blood in your stool during treatment with Itovebi. Your healthcare provider may tell you to drink more fluids or take medicines to treat your diarrhea.

Your healthcare provider may tell you to decrease your dose, temporarily stop your treatment, or completely stop your treatment with Itovebi if you develop certain serious side effects.

#### The most common side effects and abnormal blood test results of Itovebi when used in combination with palbociclib and fulvestrant include:

- decreased white blood cell counts, red blood cell counts, and platelet counts
- decreased blood levels of calcium, potassium, sodium, and magnesium
- increased creatinine blood levels
- tiredness
- increased blood levels of the liver enzyme alanine transaminase (ALT)
- nausea
- rash
- loss of appetite
- COVID-19 infection
- headache

Itovebi may affect fertility in males and in females who are able to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of Itovebi. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). You may also report side effects to Genentech at (877) 436-3683.

#### Before you take Itovebi, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of diabetes or high blood sugar
- have kidney problems
- are pregnant or plan to become pregnant. Itovebi can harm your unborn baby.

#### Females who are able to become pregnant:

- Your healthcare provider will check to see if you are pregnant before you start treatment with Itovebi.
- You should use effective non-hormonal birth control (contraception) during treatment with Itovebi and for 1 week after your last dose. Talk to your healthcare provider about what birth control method is right for you during this time.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with Itovebi.

#### Males with female partners who are able to become pregnant:

- You should use effective birth control (contraception) during treatment with Itovebi and for 1 week after your last dose.
- are breastfeeding or plan to breastfeed. It is not known if Itovebi passes into your breastmilk. Do not breastfeed during treatment with Itovebi and for 1 week after your last dose. Talk to your healthcare provider about the best way to feed your baby during treatment with Itovebi.

**Tell your healthcare provider about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements.



Learn more  
at [Itovebi.com](https://www.itovebi.com)

**Genentech**  
*A Member of the Roche Group*

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use ITOVEBI safely and effectively. See full prescribing information for ITOVEBI.**

**ITOVEBI (inavolisib) tablets, for oral use**  
**Initial U.S. Approval: 2024**

-----**INDICATIONS AND USAGE**-----

ITOVEBI is a kinase inhibitor indicated in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. (1, 14.1)

-----**DOSAGE AND ADMINISTRATION**-----

- Select patients for the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer with ITOVEBI based on the presence of one or more *PIK3CA* mutations in plasma specimen. (2.1)
- Recommended dosage: 9 mg orally once daily with or without food. (2.3)
- See Full Prescribing Information for dosage modifications of ITOVEBI due to adverse reactions. (2.4)
- Reduce the starting dose in patients with moderate renal impairment. (2.5)

-----**DOSAGE FORMS AND STRENGTHS**-----

Tablets: 3 mg and 9 mg (3)

-----**CONTRAINDICATIONS**-----

None. (4)

-----**WARNINGS AND PRECAUTIONS**-----

- **Hyperglycemia:** ITOVEBI can cause hyperglycemia. Initiate or optimize anti-hyperglycemic medications as clinically indicated. Interrupt, reduce dose, or discontinue ITOVEBI if severe hyperglycemia occurs. (2.4, 5.1)
- **Stomatitis:** ITOVEBI can cause severe stomatitis. Consider treating with a corticosteroid-containing mouthwash if stomatitis occurs. Monitor

patients for signs and symptoms of stomatitis. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity. (2.4, 5.2)

- **Diarrhea:** ITOVEBI can cause diarrhea, which may be severe, and result in dehydration and acute kidney injury. Advise patients to start anti-diarrheal treatment, increase oral fluids, and notify their healthcare provider if severe diarrhea occurs. Interrupt, reduce dose, or discontinue ITOVEBI if severe diarrhea occurs. (2.4, 5.3)
- **Embryo-Fetal Toxicity:** ITOVEBI can cause fetal harm. Advise patients of potential risk to a fetus and to use effective non-hormonal contraception. (5.4, 8.1, 8.3)  
Refer to the Full Prescribing Information of palbociclib and fulvestrant for pregnancy and contraception information.

-----**ADVERSE REACTIONS**-----

The most common (≥ 20%) adverse reactions, including laboratory abnormalities, were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

-----**USE IN SPECIFIC POPULATIONS**-----

Lactation: Advise not to breastfeed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 10/2024**

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**FULL PRESCRIBING INFORMATION: CONTENTS\***

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Patient Selection
- 2.2 Recommended Evaluation Before Initiating ITOVEBI
- 2.3 Recommended Dosage
- 2.4 Dosage Modifications for Adverse Reactions
- 2.5 Dosage Modification for Moderate Renal Impairment

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Hyperglycemia
- 5.2 Stomatitis
- 5.3 Diarrhea
- 5.4 Embryo-Fetal Toxicity

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trial Experience

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

**14 CLINICAL STUDIES**

14.1 Locally Advanced or Metastatic Breast Cancer

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

ITOVEBI, in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy [see *Clinical Studies (14.1)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection

Select patients for the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer with ITOVEBI based on the presence of one or more *PIK3CA* mutations in plasma specimens [see *Clinical Studies (14.1)*].

Information on FDA-approved tests for the detection of *PIK3CA* mutations in breast cancer is available at: <http://www.fda.gov/companiondiagnostics>.

#### 2.2 Recommended Evaluation Before Initiating ITOVEBI

Evaluate fasting plasma glucose (FPG)/blood glucose (FBG) and hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>) and optimize blood glucose prior to starting ITOVEBI and at regular intervals during treatment [see *Warnings and Precautions (5.1)*].

#### 2.3 Recommended Dosage

The recommended dosage of ITOVEBI is 9 mg taken orally once daily, with or without food, until disease progression or unacceptable toxicity.

Advise patients to take ITOVEBI at approximately the same time each day.

Swallow ITOVEBI tablet(s) whole. Do not chew, crush, or split prior to swallowing.

If a patient misses a dose, instruct the patient to take the missed dose as soon as possible within 9 hours. After more than 9 hours, instruct the patient to skip the dose and take the next dose at the scheduled time.

If a patient vomits a dose, instruct patients not to take an additional dose on that day and resume the usual dosing schedule the next day.

Administer ITOVEBI in combination with palbociclib and fulvestrant. The recommended dosage of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days. Refer to the Full Prescribing Information for palbociclib and fulvestrant for dosing information.

For premenopausal and perimenopausal women, administer a luteinizing hormone-releasing hormone (LHRH) agonist in accordance with local clinical practice.

For men, consider administering an LHRH agonist in accordance with local clinical practice.

#### 2.4 Dosage Modifications for Adverse Reactions

The recommended dose reduction levels of ITOVEBI for adverse reactions are listed in Table 1. Permanently discontinue ITOVEBI if patients are unable to tolerate the second dose reduction.

**Table 1: Dose Reduction for Adverse Reactions**

Dose Level	Dose and Schedule
Recommended starting dose	9 mg daily
First dose reduction	6 mg daily

Dose Level	Dose and Schedule
Second dose reduction	3 mg daily

The recommended dosage modifications of ITOVEBI for adverse reactions are summarized in Table 2.

**Table 2: Recommended Dosage Modifications for Adverse Reactions**

Adverse Reaction	Severity	Dosage Modification
<b>Hyperglycemia<sup>a</sup></b> <i>[see Warnings and Precautions (5.1)]</i>	Fasting glucose levels (FPG or FBG) > ULN to 160 mg/dL (> ULN – 8.9 mmol/L)	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> <li>Consider dietary modifications and ensure adequate hydration.</li> <li>Initiate or intensify oral anti-hyperglycemic medications for patients with risk factors for hyperglycemia.</li> </ul>
	Fasting glucose levels > 160 to 250 mg/dL (> 8.9 – 13.9 mmol/L)	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until FPG or FBG <math>\leq</math> 160 mg/dL (<math>\leq</math> 8.9 mmol/L).</li> <li>Initiate or intensify anti-hyperglycemic medications.</li> <li>Resume ITOVEBI at the same dose level.</li> <li>If FPG or FBG persists &gt; 200 – 250 mg/dL (&gt; 11.1 – 13.9 mmol/L) for 7 days under appropriate anti-hyperglycemic treatment, consider consultation with a healthcare professional experienced in the treatment of hyperglycemia.</li> </ul>
	Fasting glucose levels > 250 to 500 mg/dL (> 13.9 – 27.8 mmol/L)	<ul style="list-style-type: none"> <li>Withhold ITOVEBI.</li> <li>Initiate or intensify anti-hyperglycemic medications.</li> <li>Administer appropriate hydration if required.</li> <li>If FPG or FBG decreases to <math>\leq</math> 160 mg/dL (<math>\leq</math> 8.9 mmol/L) within 7 days, resume ITOVEBI at the same dose level.</li> <li>If FPG or FBG decreases to <math>\leq</math> 160 mg/dL (<math>\leq</math> 8.9 mmol/L) in <math>\geq</math> 8 days, resume ITOVEBI at one lower dose level.</li> <li>If FPG or FBG &gt; 250 to 500 mg/dL (&gt; 13.9 – 27.8 mmol/L) recurs within 30 days, withhold ITOVEBI until FPG or FBG decreases to <math>\leq</math> 160 mg/dL (<math>\leq</math> 8.9 mmol/L). Resume ITOVEBI at one lower dose level.</li> </ul>
	Fasting glucose levels > 500 mg/dL (> 27.8 mmol/L)	<ul style="list-style-type: none"> <li>Withhold ITOVEBI.</li> <li>Initiate or intensify anti-hyperglycemic medications.</li> <li>Assess for volume depletion and ketosis and administer appropriate hydration.</li> <li>If FPG or FBG decreases to <math>\leq</math> 160 mg/dL (<math>\leq</math> 8.9 mmol/L), resume ITOVEBI at one lower dose level.</li> <li>If FPG or FBG &gt; 500 mg/dL (&gt; 27.8 mmol/L) recurs within 30 days, permanently discontinue ITOVEBI.</li> </ul>
<b>Stomatitis</b> <i>[see Warnings and Precautions (5.2)]</i>	Grade 1 <sup>b</sup>	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> <li>Initiate or intensify appropriate medical therapy (e.g., corticosteroid-containing mouthwash) as clinically indicated.</li> </ul>
	Grade 2 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq</math> 1.</li> <li>Initiate or intensify appropriate medical therapy. Resume ITOVEBI at the same dose level.</li> <li>For recurrent Grade 2 stomatitis, withhold ITOVEBI until recovery to Grade <math>\leq</math> 1, then resume ITOVEBI at one lower dose level.</li> </ul>
	Grade 3 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq</math> 1.</li> <li>Initiate or intensify appropriate medical therapy. Resume ITOVEBI at one lower dose level.</li> </ul>

Adverse Reaction	Severity	Dosage Modification
	Grade 4 <sup>b</sup>	<ul style="list-style-type: none"> <li>Permanently discontinue ITOVEBI.</li> </ul>
<b>Diarrhea</b> <i>[see Warnings and Precautions (5.3)]</i>	Grade 1 <sup>b</sup>	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> <li>Initiate appropriate medical therapy and monitor as clinically indicated.</li> </ul>
	Grade 2 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 1</math>, then resume ITOVEBI at the same dose level.</li> <li>Initiate or intensify appropriate medical therapy and monitor as clinically indicated.</li> <li>For recurrent Grade 2 diarrhea, withhold ITOVEBI until recovery to Grade <math>\leq 1</math>, then resume ITOVEBI at one lower dose level.</li> </ul>
	Grade 3 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 1</math>, then resume ITOVEBI at one lower dose level.</li> <li>Initiate or intensify appropriate medical therapy and monitor as clinically indicated.</li> </ul>
	Grade 4 <sup>b</sup>	<ul style="list-style-type: none"> <li>Permanently discontinue ITOVEBI.</li> </ul>
<b>Hematologic Toxicities</b> <i>[see Adverse Reactions (6.1)]</i>	Grade 1, 2, or 3 <sup>b</sup>	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> <li>Monitor complete blood count and for signs or symptoms of hematologic toxicities as clinically indicated.</li> </ul>
	Grade 4 <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 2</math>.</li> <li>Resume ITOVEBI at the same dose level or reduce to one lower dose level as clinically indicated.</li> </ul>
<b>Other Adverse Reactions</b> <i>[see Adverse Reactions (6.1)]</i>	Grade 1 <sup>b</sup>	<ul style="list-style-type: none"> <li>No adjustment of ITOVEBI required.</li> </ul>
	Grade 2 <sup>b</sup>	<ul style="list-style-type: none"> <li>Consider withholding ITOVEBI, if clinically indicated, until recovery to Grade <math>\leq 1</math>.</li> <li>Resume ITOVEBI at the same dose level.</li> </ul>
	Grade 3 (first event) <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 1</math>.</li> <li>Resume ITOVEBI at the same dose level or one lower dose level based on clinical evaluation.</li> </ul>
	Grade 3 (recurrent) <sup>b</sup>	<ul style="list-style-type: none"> <li>Withhold ITOVEBI until recovery to Grade <math>\leq 1</math>.</li> <li>Resume ITOVEBI at one lower dose level.</li> </ul>
	Grade 4 <sup>b</sup>	<ul style="list-style-type: none"> <li>Permanently discontinue ITOVEBI.</li> </ul>
<sup>a</sup> Before initiating treatment with ITOVEBI, test FPG or FBG, and HbA <sub>1C</sub> levels, and optimize plasma/blood glucose levels in all patients. After initiating treatment with ITOVEBI, monitor FPG or FBG levels based on the recommended schedule, and as clinically indicated <i>[see Warnings and Precautions (5.1)]</i> .		
<sup>b</sup> Based on CTCAE version 5.0.		

## 2.5 Dosage Modification for Moderate Renal Impairment

The recommended starting dosage of ITOVEBI for patients with moderate renal impairment (eGFR 30 to < 60 mL/min based on CKD-EPI) is 6 mg orally once daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 3 mg: red and round convex-shaped with an “INA 3” debossing on one side.
- 9 mg: pink and oval-shaped with an “INA 9” debossing on one side.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hyperglycemia

Severe hyperglycemia can occur in patients treated with ITOVEBI.

Increased fasting glucose occurred in 85% of patients treated with ITOVEBI, including 22% of patients with Grade 2 (FPG > 160 to 250 mg/dL), 12% with Grade 3 (FPG > 250 to 500 mg/dL), and 0.6% with Grade 4 (FPG > 500 mg/dL) events.

In INAVO120, 46% (74/162) of patients who received ITOVEBI were treated with oral anti-hyperglycemic medications and 7% (11/162) were treated with insulin to manage increased fasting glucose. In patients who experienced increased fasting glucose of > 160 mg/dL, 96% (52/54) had an improvement in fasting glucose of at least one grade level with a median time to improvement from the first event of 8 days (range: 2 to 43 days).

Among patients with hyperglycemia, the median time to first onset was 7 days (range: 2 to 955 days).

Hyperglycemia led to dose interruption in 28%, to dose reduction in 2.5%, and to discontinuation of ITOVEBI in 1.2% of patients.

The safety of ITOVEBI in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment have not been studied.

Before initiating treatment with ITOVEBI, test fasting glucose levels (FPG or FBG), HbA<sub>1C</sub> levels, and optimize fasting glucose.

After initiating treatment with ITOVEBI, or in patients who experience hyperglycemia after initiating treatment with ITOVEBI, monitor or self-monitor fasting glucose levels once every 3 days for the first week (Day 1 to 7), then once every week for the next 3 weeks (Day 8 to 28), then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated. Monitor HbA<sub>1C</sub> every 3 months and as clinically indicated.

Manage hyperglycemia with anti-hyperglycemic medications as clinically indicated. During treatment with anti-hyperglycemic medication, continue monitoring fasting glucose levels. Patients with a history of well-controlled Type 2 diabetes mellitus may require intensified anti-hyperglycemic treatment and close monitoring of fasting glucose levels.

Consider consultation with a healthcare professional experienced in the treatment of hyperglycemia, and initiation of fasting glucose monitoring at home for patients who have risk factors for hyperglycemia or who experience hyperglycemia. Advise patients of the signs and symptoms of hyperglycemia and counsel patients on lifestyle changes.

Based on the severity of the hyperglycemia, ITOVEBI may require dose interruption, reduction, or discontinuation [*see Dosage and Administration (2.4)*].

### 5.2 Stomatitis

Severe stomatitis can occur in patients treated with ITOVEBI.

Stomatitis occurred in 51% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant, including Grade 3 events in 6% of patients. The median time to first onset was 13 days (range: 1 to 610 days).

Stomatitis led to interruption of ITOVEBI in 10%, to dose reduction in 3.7%, and to discontinuation of ITOVEBI in 0.6% of patients.

In patients who received ITOVEBI in combination with palbociclib and fulvestrant, 38% used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis.

Monitor patients for signs and symptoms of stomatitis. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity [see *Dosage and Administration (2.4)*].

### **5.3 Diarrhea**

Severe diarrhea, including dehydration and acute kidney injury, can occur in patients treated with ITOVEBI.

Diarrhea occurred in 48% of patients treated with ITOVEBI in combination with palbociclib and fulvestrant, including Grade 3 events in 3.7% of patients. The median time to first onset was 15 days (range: 2 to 602 days). Anti-diarrheal medicines were used in 28% (46/162) of patients who received ITOVEBI in combination with palbociclib and fulvestrant to manage symptoms. Dose interruptions were required in 7% of patients, and dose reductions occurred in 1.2% of patients.

Monitor patients for signs and symptoms of diarrhea. Advise patients to increase oral fluids and start anti-diarrheal treatment at the first sign of diarrhea while taking ITOVEBI. Withhold, reduce dose, or permanently discontinue ITOVEBI based on severity [see *Dosage and Administration (2.4)*].

### **5.4 Embryo-Fetal Toxicity**

Based on findings in animals and its mechanism of action, ITOVEBI can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. In an animal reproduction study, oral administration of inavolisib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, structural abnormalities, and alterations to growth at maternal exposures approximately equivalent to the human exposure at the recommended dose of 9 mg/day based on area under the curve (AUC).

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ITOVEBI and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ITOVEBI and for 1 week after the last dose [see *Use in Specific Populations (8.1 and 8.3)*].

ITOVEBI is used in combination with palbociclib and fulvestrant. Refer to the Full Prescribing Information of palbociclib and fulvestrant for pregnancy and contraception information.

## **6 ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hyperglycemia [see *Warnings and Precautions (5.1)*]
- Stomatitis [see *Warnings and Precautions (5.2)*]
- Diarrhea [see *Warnings and Precautions (5.3)*]

### **6.1 Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### Locally Advanced or Metastatic Breast Cancer

##### *INAVO120*

The safety of ITOVEBI was evaluated in a randomized, double-blind, placebo-controlled study (INAVO120) in 324 patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer [see *Clinical Studies (14.1)*].

Patients received either ITOVEBI 9 mg (n=162) or placebo (n=162) with palbociclib and fulvestrant. The median duration of treatment with ITOVEBI was 9 months (range: 0 to 39 months) in the ITOVEBI with palbociclib and fulvestrant arm.



Serious adverse reactions occurred in 24% of patients who received ITOVEBI with palbociclib and fulvestrant. Serious adverse reactions in  $\geq 1\%$  of patients included anemia (1.9%), diarrhea (1.2%), and urinary tract infection (1.2%).

Fatal adverse reactions occurred in 3.7% of patients who received ITOVEBI with palbociclib and fulvestrant, including (0.6% each) acute coronary syndrome, cerebral hemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal hemorrhage.

Permanent discontinuation of ITOVEBI due to an adverse reaction occurred in 6% of patients. Adverse reactions which resulted in permanent discontinuation of ITOVEBI included hyperglycemia (1.2%), and (0.6% each) stomatitis, gastric ulcer, intestinal perforation, anal abscess, increased ALT, decreased weight, bone pain, musculoskeletal pain, transitional cell carcinoma, and acute kidney injury.

Dosage interruptions of ITOVEBI due to an adverse reaction occurred in 69% of patients. Adverse reactions which required dosage interruption in  $\geq 2\%$  of patients included hyperglycemia (28%), neutropenia (23%), COVID-19 infection (16%), stomatitis (10%), diarrhea (7%), thrombocytopenia (4.9%), anemia (4.3%), upper respiratory tract infection (4.3%), decreased white blood cell count (3.7%), pyrexia (3.1%), nausea (2.5%), and fatigue (2.5%).

Dose reductions of ITOVEBI due to adverse reactions occurred in 14% of patients. Adverse reactions which required dose reduction of ITOVEBI in  $\geq 2\%$  of patients were stomatitis (3.7%) and hyperglycemia (2.5%).

The most common ( $\geq 20\%$ ) adverse reactions, including laboratory abnormalities, were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache.

Adverse reactions and laboratory abnormalities in INAVO120 are summarized in Table 3 and Table 4, respectively. Patient-reported symptoms are summarized in Table 5.

**Table 3: Adverse Reactions ( $\geq 10\%$  with  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grade 3-4] Higher Incidence in the ITOVEBI Arm) in INAVO120**

Adverse Reaction	ITOVEBI + Palbociclib + Fulvestrant N=162		Placebo + Palbociclib + Fulvestrant N=162	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
<b>Gastrointestinal Disorders</b>				
Stomatitis <sup>a</sup>	51	6*	27	0
Diarrhea	48	3.7*	16	0
Nausea	28	0.6*	17	0
Vomiting	15	0.6*	5	1.2*
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	38	1.9*	25	1.2*
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash <sup>b</sup>	26	0	19	0
Alopecia	19	0	6	0
Dry skin <sup>c</sup>	13	0	4.3	0
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	24	0	9	0
<b>Infections and Infestations</b>				

Adverse Reaction	ITOVEBI + Palbociclib + Fulvestrant N=162		Placebo + Palbociclib + Fulvestrant N=162	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
COVID-19 infection	23	1.9	10	0.6
Urinary tract infection <sup>b</sup>	15	1.2*	9	0
<b>Nervous System Disorders</b>				
Headache <sup>b</sup>	22	0	14	0
<b>Investigations</b>				
Decreased weight	17	3.7*	0.6	0

\* No Grade 4 adverse reactions were observed.

<sup>a</sup> Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.

<sup>b</sup> Includes other related terms.

<sup>c</sup> Includes dry skin, skin fissures, xerosis, and xeroderma.

Clinically relevant adverse reactions occurring in < 10% of patients who received ITOVEBI in combination with palbociclib and fulvestrant included abdominal pain, dry eye, dysgeusia, and dyspepsia.

**Table 4: Select Laboratory Abnormalities (≥ 10% with a ≥ 2% [All Grades or Grade 3-4] Higher Incidence in the ITOVEBI Arm) in INAVO120**

Laboratory Abnormality	ITOVEBI + Palbociclib + Fulvestrant <sup>a</sup>		Placebo + Palbociclib + Fulvestrant <sup>b</sup>	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
<b>Hematology</b>				
Neutrophils (total, absolute) decreased	95	82	97	79
Hemoglobin decreased	88	8*	85	2.5*
Platelets decreased	84	16	71	3.7
Lymphocytes (absolute) decreased	72	9	68	14
<b>Chemistry</b>				
Glucose (fasting) increased <sup>c</sup>	85	12	43	0
Calcium decreased	42	3.1	32	3.7
Potassium decreased	38	6	21	0.6*
Creatinine increased	38	1.9*	30	1.2*
ALT increased	34	3.1*	29	1.2*
Sodium decreased	28	2.5*	19	2.5
Magnesium decreased	27	0.6	21	0
Lipase (fasting) increased	16	1.4*	7	0

ALT = alanine aminotransferase

\* No Grade 4 laboratory abnormalities were observed.

<sup>a</sup> The denominator used to calculate the rate varied from 122 to 160 based on the number of patients with a baseline value and at least one post-treatment value.

<sup>b</sup> The denominator used to calculate the rate varied from 131 to 161 based on the number of patients with a baseline value and at least one post-treatment value.

Laboratory Abnormality	ITOVEBI + Palbociclib + Fulvestrant <sup>a</sup>		Placebo + Palbociclib + Fulvestrant <sup>b</sup>	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)

<sup>c</sup> Grading according to CTCAE version 4.03.

In INAVO120, patient-reported symptomatic toxicities (i.e., diarrhea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash) were assessed via the Patient-Reported Outcomes – Common Terminology Criteria for Adverse Events (PRO-CTCAE) at baseline, every two weeks through Cycle 3 Day 15, and then Day 1 of every other 28-day cycle until treatment discontinuation.

Completion rates in both arms were > 90% at baseline and > 80% at subsequent time points where > 50% of randomized patients were on treatment.

**Table 5: Patient-Reported Symptoms Assessed by PRO-CTCAE in INAVO120**

Symptom (Attribute) <sup>a</sup>	Any Symptom Before Treatment (%) <sup>b</sup>		Any Worsening on Treatment (%) <sup>c</sup>		Worsening to Score 3 or 4 (%) <sup>d</sup>	
	ITOVEBI + P + F (N=148) <sup>e</sup>	Placebo + P + F (N=152) <sup>e</sup>	ITOVEBI + P + F (N=148) <sup>e</sup>	Placebo + P + F (N=152) <sup>e</sup>	ITOVEBI + P + F (N=148) <sup>e</sup>	Placebo + P + F (N=152) <sup>e</sup>
Diarrhea (frequency), %	23	15	78	49	32	8
Nausea (frequency), %	21	21	59	50	20	11
Vomiting (frequency), %	9	6	35	26	6	3.3
Fatigue (severity), %	72	69	72	58	32	22
Mouth sores (severity), %	11	14	74	52	30	9
Decreased appetite (severity), %	38	28	78	55	26	12

Symptom (Attribute)	Baseline Presence		Post-baseline Presence	
	ITOVEBI + P + F (N=148)	Placebo + P + F (N=152)	ITOVEBI + P + F (N=148)	Placebo + P + F (N=152)
Rash (yes), %	5	5	50	38

ITOVEBI+P+F = ITOVEBI with palbociclib and fulvestrant arm; Placebo+P+F = placebo with palbociclib and fulvestrant arm.

<sup>a</sup> The symptom attribute scoring is defined by amount/frequency/severity with a score of 0 = ‘not at all’/‘never’/‘none’; 1 = ‘a little bit’/‘rarely’/‘mild’; 2 = ‘somewhat’/‘occasionally’/‘moderate’; 3 = ‘quite a bit’/‘frequently’/‘severe’; 4 = ‘very much’/‘almost constantly’/‘very severe’.

<sup>b</sup> The percentage of patients whose symptom score before treatment was 1-4.

<sup>c</sup> The percentage of patients whose symptom score increased during treatment, with respect to their score before treatment.

<sup>d</sup> The percentage of patients whose symptom score increased to 3 or 4 during treatment, with respect to their score before treatment.

<sup>e</sup> The number of patients who provided a score before treatment and at least one on-treatment score.

Patient-reported overall side-effect impact was assessed using the Modified Bother Item (MBI). Patients provided a response to “I am bothered by side effects of treatment,” and at baseline the proportion of patients

with MBI responses of “not at all” were 70% in the ITOVEBI with palbociclib and fulvestrant arm and 76% in the placebo with palbociclib and fulvestrant arm. At Cycle 2 Day 15, the proportion of patients with MBI responses of “not at all” were 25% in the ITOVEBI with palbociclib and fulvestrant arm and 53% in the placebo with palbociclib and fulvestrant arm. Through 31 cycles of treatment, patients in the ITOVEBI with palbociclib and fulvestrant arm reported more side effect bother compared to the placebo with palbociclib and fulvestrant arm.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

ITOVEBI is used in combination with palbociclib and fulvestrant. Refer to the Full Prescribing Information of palbociclib and fulvestrant for pregnancy information.

Based on animal data and its mechanism of action, ITOVEBI can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data on the use of ITOVEBI in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of inavolisib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, structural abnormalities, and alterations to growth at maternal exposures approximately equivalent to the human exposure at the recommended dose of 9 mg/day based on AUC (see *Data*). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies in the U.S. general population.

#### Data

##### *Animal Data*

In an embryo-fetal development study, pregnant rats received oral doses of inavolisib up to 6 mg/kg/day during the period of organogenesis. Administration of doses  $\geq 2$  mg/kg/day resulted in decreases in fetal body weight and placental weight, post-implantation loss, lower fetal viability, fetal malformations (including kyphosis of vertebral column, fused thoracic arch, microphthalmia) and variations (including dilated renal pelvis, short supernumerary rib, wavy rib). At a dose of 2 mg/kg/day, maternal exposures were 0.9 times the human exposure at the recommended dose of 9 mg/day based on AUC.

### **8.2 Lactation**

#### Risk Summary

ITOVEBI is used in combination with palbociclib and fulvestrant. Refer to the Full Prescribing Information of palbociclib and fulvestrant for lactation information.

There are no data on the presence of inavolisib or its metabolites in human milk, its effects on milk production or a breastfed child. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women to not breastfeed during treatment with ITOVEBI and for 1 week after the last dose.

### **8.3 Females and Males of Reproductive Potential**

ITOVEBI is used in combination with palbociclib and fulvestrant. Refer to the Full Prescribing Information of palbociclib and fulvestrant for contraception and infertility information.

ITOVEBI can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with ITOVEBI.

#### Contraception

## Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ITOVEBI and for 1 week after the last dose.

## Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ITOVEBI and for 1 week after the last dose.

## Infertility

Based on animal studies, ITOVEBI may impair fertility in females and males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

## 8.4 Pediatric Use

The safety and efficacy of ITOVEBI in pediatric patients have not been established.

## 8.5 Geriatric Use

Of the 162 patients who received ITOVEBI in INAVO120, 15% were  $\geq 65$  years of age, and 3% were  $\geq 75$  years of age.

Dosage modifications or interruptions of ITOVEBI due to adverse reactions occurred at a higher incidence for patients  $\geq 65$  years of age compared to younger patients (79% versus 68%, respectively).

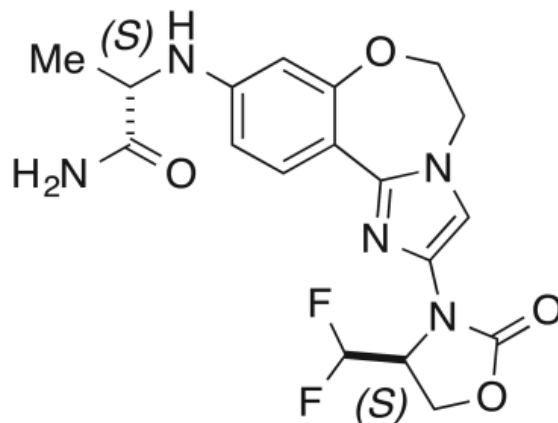
Clinical studies of ITOVEBI did not include sufficient numbers of patients  $\geq 65$  years of age to determine whether they respond differently from younger patients.

## 8.6 Renal Impairment

Reduce the dosage in patients with moderate renal impairment (eGFR 30 to  $< 60$  mL/min based on CKD-EPI) [see *Dosage and Administration (2.5)*]. No dosage modification is recommended in patients with mild renal impairment (eGFR 60 to  $< 90$  mL/min). ITOVEBI has not been evaluated in patients with severe renal impairment (eGFR  $< 30$  mL/min).

## 11 DESCRIPTION

ITOVEBI contains inavolisib, a kinase inhibitor. The chemical name of inavolisib is (2S)-2-[[[2-[(4S)-4-(difluoromethyl)-2-oxo-oxazolidin-3-yl]-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]amino]propanamide. Inavolisib is a white to off-white, greyish pink, greyish orange, or greyish yellow powder or powder with lumps. Inavolisib demonstrates pH-dependent aqueous solubility; the greatest solubility is at low pH, and solubility decreases with increasing pH. The molecular formula for inavolisib is  $C_{18}H_{19}F_2N_5O_4$  and the molecular weight is 407.37 g/mol. The chemical structure of inavolisib is shown below:



ITOVEBI film-coated tablets are supplied for oral administration with two strengths that contain 3 mg and 9 mg of inavolisib. The tablets also contain lactose, magnesium stearate, microcrystalline cellulose, and sodium

starch glycolate. The film-coating contains the following inactive ingredients: polyvinyl alcohol (partially hydrolyzed), titanium dioxide, macrogol/polyethylene glycol, talc, iron oxide red, and iron oxide yellow (in the 9 mg tablet only).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Inavolisib is an inhibitor of phosphatidylinositol 3-kinase (PI3K) with inhibitory activity predominantly against PI3K $\alpha$ . In vitro, inavolisib induced the degradation of mutated PI3K catalytic alpha subunit p110 $\alpha$  (encoded by the *PIK3CA* gene), inhibited phosphorylation of the downstream target AKT, reduced cellular proliferation, and induced apoptosis in *PIK3CA*-mutated breast cancer cell lines. In vivo, inavolisib reduced tumor growth in *PIK3CA*-mutated, estrogen receptor-positive, breast cancer xenograft models. The combination of inavolisib with palbociclib and fulvestrant increased tumor growth inhibition compared to each treatment alone or the doublet combinations.

### 12.2 Pharmacodynamics

#### Exposure-Response Relationships

The exposure-response relationship for the efficacy of inavolisib has not been fully characterized. Inavolisib time course of pharmacodynamic response is unknown. Higher systemic exposure of inavolisib was associated with higher incidence of Grade  $\geq 2$  anemia, Grade  $\geq 2$  hyperglycemia, and inavolisib dosage modifications due to adverse reactions.

#### Cardiac Electrophysiology

At the recommended approved dosage, a mean increase in the QTc interval of  $> 20$  ms is unlikely.

### 12.3 Pharmacokinetics

Inavolisib pharmacokinetics are presented as geometric mean (geometric coefficient of variation [geo CV]%) following administration of the approved recommended dosage unless otherwise specified. The inavolisib steady-state AUC is 1,010 h\*ng/mL (25%) and C<sub>max</sub> is 69 ng/mL (27%). Steady-state concentrations are predicted to be attained by day 5.

Inavolisib accumulation is approximately 2-fold.

Inavolisib steady-state AUC is proportional with dose from 6 to 12 mg (0.7 to 1.3 times the approved recommended dosage).

#### Absorption

Inavolisib absolute oral bioavailability is 76%. Inavolisib steady-state median (min, max) time to maximum plasma concentration (T<sub>max</sub>) is 3 hours (0.5, 4 hours).

#### *Effect of Food*

No clinically significant differences in inavolisib pharmacokinetics were observed following administration of inavolisib with a high-fat meal (approximately 1,000 calories, 50% fat).

#### Distribution

Inavolisib apparent (oral) volume of distribution is 155 L (26%). Inavolisib plasma protein binding is 37% and is not concentration-dependent in vitro. Inavolisib blood-to-plasma ratio is 0.8.

#### Elimination

Inavolisib elimination half-life is 15 hours (24%) with a total clearance of 8.8 L/hr (29%).

#### *Metabolism*

Inavolisib is primarily metabolized by hydrolysis. In vitro, inavolisib was minimally metabolized by CYP3A.

## *Excretion*

Following oral administration of a single radiolabeled dose, 49% of the administered dose was recovered in urine (40% unchanged) and 48% in feces (11% unchanged).

## Specific Populations

No clinically significant differences in the pharmacokinetics of inavolisib were observed based on age (27 to 85 years), sex, race (Asian or White), body weight (39 to 159 kg), or mild hepatic impairment (total bilirubin > ULN to  $\leq 1.5 \times$  ULN or AST > ULN and total bilirubin  $\leq$  ULN). The effect of moderate to severe hepatic impairment on inavolisib pharmacokinetics is unknown.

### *Patients with Renal Impairment*

Inavolisib AUC was 73% higher in patients with moderate renal impairment compared to patients with normal renal function (eGFR  $\geq 90$  mL/min).

No clinically significant differences in the pharmacokinetics of inavolisib were observed in patients with mild renal impairment compared to patients with normal renal function. The effect of severe renal impairment (eGFR < 30 mL/min) on the pharmacokinetics of inavolisib is unknown.

## Drug Interaction Studies

### *Clinical Studies and Model-Informed Approaches*

*Proton Pump Inhibitors:* No clinically significant difference in steady-state inavolisib pharmacokinetics were observed based upon concomitant use of a proton pump inhibitor (lansoprazole, omeprazole, esomeprazole, pantoprazole, or rabeprazole).

### *In Vitro Studies*

*CYP450 Enzymes:* Inavolisib induces CYP3A and CYP2B6. Inavolisib is a time-dependent inhibitor of CYP3A. Inavolisib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

*Transporter Systems:* Inavolisib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2K, OAT1, OAT2. Inavolisib does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, or MATE2K.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenicity studies with inavolisib have not been conducted.

Inavolisib was not mutagenic in the bacterial reverse mutation (Ames) assay. Inavolisib was clastogenic in an in vitro human lymphocyte micronucleus assay. Inavolisib was not genotoxic in an in vivo rat bone marrow micronucleus test and did not induce DNA break in a liver comet assay.

Fertility studies with inavolisib have not been conducted. In repeat-dose toxicity studies, inavolisib was administered orally once daily for up to 3 months duration in rats and dogs.

In male rats, dose-dependent atrophy of the prostate and seminal vesicle and decreased organ weights of the prostate, seminal vesicle, epididymis and testis were observed at doses  $\geq 1.5$  mg/kg/day ( $\geq 0.4$  times the human exposure at the recommended dose of 9 mg/day based on AUC). In male dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed following 4 weeks of dosing at  $\geq 1.5$  mg/kg/day ( $\geq 2$  times the human exposure at the recommended dose of 9 mg/day based on AUC) and decreased sperm count was observed following 3 months of dosing at  $\geq 1$  mg/kg/day ( $\geq 1.2$  times the human exposure at the recommended dose of 9 mg/day based on AUC). Findings in dogs were not observed following a recovery period.

In female rats, atrophy in the uterus and vagina, decreased ovarian follicles, and findings suggestive of an interruption/alteration of the estrous cycle were observed following up to 3 months of dosing at doses  $\geq 3$  mg/kg/day ( $\geq 1.2$  times the human exposure at the recommended dose of 9 mg/day based on AUC). Findings in the uterus, vagina, and estrous cycle observed in the 4-week toxicity study were not observed following recovery. Recovery was not assessed in the 3-month study in rats.

### **13.2 Animal Toxicology and/or Pharmacology**

Lens degeneration, characterized by lens fiber swelling, separation of lens fibers, and/or accumulation of subcapsular proteinaceous material, was observed in rats at an oral inavolisib dose of 10 mg/kg/day (6.3 times the human exposure at the recommended dose of 9 mg/day based on AUC). In dogs, lens fiber swelling and lens cortex vacuolation were observed at oral inavolisib doses  $\geq 0.3$  mg/kg/day ( $\geq 0.5$  times the human exposure at the recommended dose based on AUC) and  $\geq 1$  mg/kg/day ( $\geq 1.2$  times the human exposure at the recommended dose based on AUC), respectively. Lens degeneration was present in rats following a 4-week recovery period but was not present in dogs following a 12-week recovery period.

## **14 CLINICAL STUDIES**

### **14.1 Locally Advanced or Metastatic Breast Cancer**

#### INAVO120

INAVO120 (NCT04191499) was a randomized (1:1), double-blind, placebo-controlled trial evaluating the efficacy of ITOVEBI in combination with palbociclib and fulvestrant in adult patients with endocrine-resistant *PIK3CA*-mutated, HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-), locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease.

Randomization was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

Patients were required to have HbA<sub>1c</sub> < 6% and fasting blood glucose < 126 mg/dL. The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment at the start of study treatment.

*PIK3CA* mutation status was prospectively determined in a central laboratory using the FoundationOne<sup>®</sup> Liquid CDx assay on plasma-derived circulating tumor DNA (ctDNA) or in local laboratories using various validated polymerase chain reaction (PCR) or next-generation sequencing (NGS) assays on tumor tissue or plasma. All patients were required to provide both a freshly collected pre-treatment blood sample and a tumor tissue sample for central evaluation and determination of *PIK3CA* mutation(s) status.

Patients received either ITOVEBI 9 mg (n=161) or placebo (n=164) orally once daily, in combination with palbociclib 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days, and fulvestrant 500 mg administered intramuscularly on Cycle 1, Days 1 and 15, and then on Day 1 of every 28-day cycle. Patients received treatment until disease progression or unacceptable toxicity. In addition, all pre/perimenopausal women and men received an LHRH agonist throughout therapy.

The baseline demographic and disease characteristics were: median age 54 years (range: 27 to 79 years); 98% female, of which 39% were pre/perimenopausal; 59% White, 38% Asian, 2.5% unknown, 0.6% Black or African American; 6% Hispanic or Latino; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 (63%) or 1 (36%). Tamoxifen (57%) and aromatase inhibitors (50%) were the most commonly used adjuvant endocrine therapies. Sixty-four percent of patients were considered to have secondary endocrine resistance. Eighty-three percent of patients had received prior chemotherapy (in the neo/adjuvant setting) and 1.2% of patients had been treated with a CDK4/6 inhibitor.



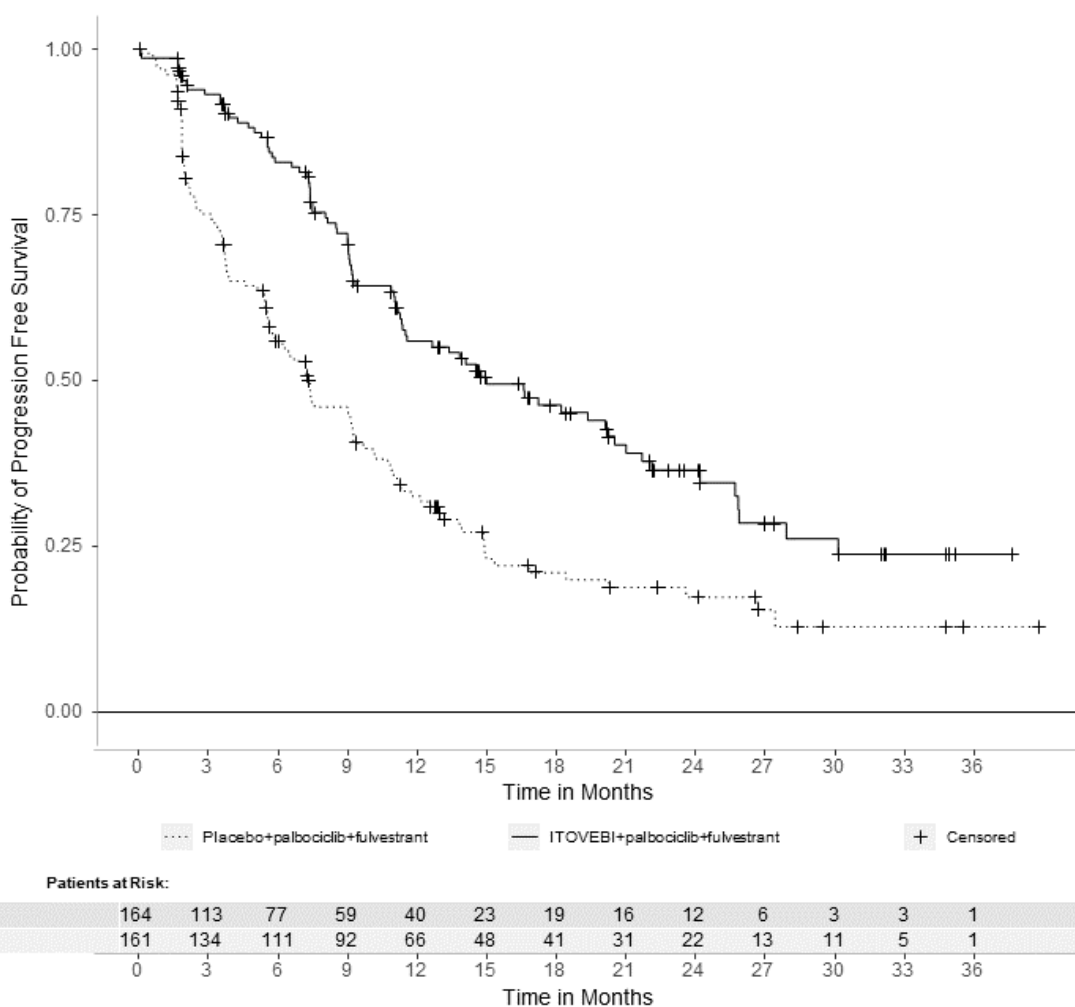
The major efficacy outcome measure was investigator (INV)-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional efficacy outcome measures included overall survival (OS), INV-assessed objective response rate (ORR), and INV-assessed duration of response (DOR).

Efficacy results are summarized in Table 6 and Figure 1. INV-assessed PFS results were supported by consistent results from a blinded independent central review (BICR) assessment. At the time of the PFS analysis, OS data were not mature with 30% deaths in the overall population.

**Table 6: Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120**

<b>Efficacy Endpoint</b>	<b>ITOVEBI + Palbociclib + Fulvestrant N=161</b>	<b>Placebo + Palbociclib + Fulvestrant N=164</b>
<b>Progression-Free Survival<sup>a,b</sup></b>		
Patients with event, n (%)	82 (51)	113 (69)
Median, months (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Hazard ratio (95% CI)	0.43 (0.32, 0.59)	
p-value	< 0.0001	
<b>Objective Response Rate<sup>a,b,c</sup></b>		
Patients with CR or PR, n (%)	94 (58)	41 (25)
95% CI	(50, 66)	(19, 32)
<b>Duration of Response<sup>b</sup></b>		
Median DOR, months (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)
CI = confidence interval; CR = complete response; DOR = duration of response; PR = partial response		
<sup>a</sup> Per RECIST version 1.1.		
<sup>b</sup> Based on investigator assessment.		
<sup>c</sup> Based on confirmed ORR.		

**Figure 1: Kaplan-Meier Curve for Investigator-Assessed Progression-Free Survival in INAVO120**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

ITOVEBI is supplied in the following strengths and package configurations:

Package Configuration	Tablet Strength	NDC	Tablet Description
Bottle of 28 tablets	3 mg	50242-084-08	Red and round convex-shaped with an “INA 3” debossing on one side
Bottle of 28 tablets	9 mg	50242-079-08	Pink and oval-shaped with an “INA 9” debossing on one side

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Hyperglycemia

Advise patients that ITOVEBI may cause hyperglycemia and the need to monitor fasting glucose levels periodically during therapy. Advise patients to contact their healthcare provider immediately for signs and symptoms of hyperglycemia (e.g., excessive thirst, urinating more often, blurred vision, mental confusion, difficulty breathing, or increased appetite with weight loss) [see Warnings and Precautions (5.1)].

## Stomatitis

Advise patients that ITOVEBI may cause stomatitis, which may be severe, and to notify their healthcare provider if they develop symptoms of stomatitis (e.g., painful redness, swelling, or sores in the mouth) [*see Warnings and Precautions (5.2)*].

## Diarrhea

Advise patients that ITOVEBI may cause diarrhea, which may be severe, and to start antidiarrheal treatment, increase oral fluids, and notify their healthcare provider if diarrhea occurs while taking ITOVEBI [*see Warnings and Precautions (5.3)*].

## Embryo-Fetal Toxicity

- Inform pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ITOVEBI and for 1 week after the last dose [*see Use in Specific Populations (8.3)*].
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ITOVEBI and for 1 week after the last dose [*see Use in Specific Populations (8.3)*].
- Refer to the Full Prescribing Information of palbociclib and fulvestrant for pregnancy and contraception information.

## Lactation

Advise women not to breastfeed during treatment with ITOVEBI and for 1 week after the last dose [*see Use in Specific Populations (8.2)*]. Refer to the Full Prescribing Information of palbociclib and fulvestrant for lactation information.

## Infertility

Advise females and males of reproductive potential that ITOVEBI may impair fertility [*see Use in Specific Populations (8.3)*]. Refer to the Full Prescribing Information of palbociclib and fulvestrant for infertility information.

## Dosing

- Instruct patients to take ITOVEBI at approximately the same time each day [*see Dosage and Administration (2.3)*].
- Instruct patients that if a dose of ITOVEBI is missed, to take the missed dose as soon as possible within 9 hours. After more than 9 hours, skip the dose and take the next dose at the scheduled time [*see Dosage and Administration (2.3)*].
- Instruct patients that if vomiting occurs after taking the ITOVEBI dose, do not take an additional dose on that day. Resume the usual dosing schedule the next day [*see Dosage and Administration (2.3)*].

Distributed by:

**Genentech USA, Inc.**

A Member of the Roche Group

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South San Francisco, CA 94080-4990

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**PATIENT INFORMATION**  
ITOVEBI™ (eye-TOVE-bee)  
(inavolisib)  
tablets, for oral use

**Important: ITOVEBI is used with palbociclib and fulvestrant. You should also read the Patient Information that comes with palbociclib and fulvestrant.**

**What is ITOVEBI?**

ITOVEBI is a prescription medicine used in combination with the medicines palbociclib and fulvestrant to treat adults who have hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has an abnormal phosphatidylinositol-3-kinase catalytic subunit alpha (*PIK3CA*) gene, and has spread to nearby tissue or lymph nodes (locally advanced), or to other parts of the body (metastatic), and has come back after hormone (endocrine) therapy.

Your healthcare provider will test your cancer for abnormal *PIK3CA* genes to make sure that ITOVEBI is right for you. It is not known if ITOVEBI is safe and effective in children.

**Before you take ITOVEBI, tell your healthcare provider about all of your medical conditions, including if you:**

- have a history of diabetes or high blood sugar.
- have kidney problems.
- are pregnant or plan to become pregnant. ITOVEBI can harm your unborn baby.

**Females who are able to become pregnant:**

- Your healthcare provider will check to see if you are pregnant before you start treatment with ITOVEBI.
- You should use effective non-hormonal birth control (contraception) during treatment with ITOVEBI and for 1 week after your last dose. Talk to your healthcare provider about what birth control method is right for you during this time.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with ITOVEBI.

**Males with female partners who are able to become pregnant:**

- You should use effective birth control (contraception) during treatment with ITOVEBI and for 1 week after your last dose.
- are breastfeeding or plan to breastfeed. It is not known if ITOVEBI passes into your breastmilk. Do not breastfeed during treatment with ITOVEBI and for 1 week after your last dose. Talk to your healthcare provider about the best way to feed your baby during treatment with ITOVEBI.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

**How should I take ITOVEBI?**

- Take ITOVEBI exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking ITOVEBI unless your healthcare provider tells you.
- Take ITOVEBI 1 time each day, at about the same time each day.
- Take ITOVEBI with or without food.
- Swallow ITOVEBI tablet(s) whole. Do not chew, crush, or split the tablet(s).
- If you miss a dose of ITOVEBI, you may still take your missed dose within 9 hours from the time you usually take it. If it has been more than 9 hours after you usually take your dose, skip the dose for that day. The next day, take the dose at your usual time.
- If you vomit after taking a dose of ITOVEBI, do not take an extra dose on that day. Take your regular dose of ITOVEBI at your usual time the next day.
- For women who have not reached menopause or are just starting menopause, your healthcare provider will prescribe a medicine called luteinizing hormone-releasing hormone (LHRH) agonist. For men, your healthcare provider may prescribe a LHRH agonist.

**What are the possible side effects of ITOVEBI?**

**ITOVEBI may cause serious side effects, including:**

- **High blood sugar levels (hyperglycemia).** High blood sugar is common with ITOVEBI and may be severe. Your healthcare provider will monitor your blood sugar levels before you start and during treatment with ITOVEBI. Your blood sugar levels may be monitored more often if you have a history of Type 2 diabetes. Your healthcare provider may also ask you to self-monitor and report your blood sugar levels at home. This will be required more frequently in the first 4 weeks of treatment. If you are not sure how to test your blood sugar levels, talk to your healthcare provider. You should stay well-hydrated during treatment with ITOVEBI.

Tell your healthcare provider right away if you develop symptoms of high blood sugar, including:

- difficulty breathing
- nausea and vomiting (lasting more than 2 hours)
- stomach pain
- excessive thirst
- dry mouth
- more frequent urination than usual or a higher amount of urine than normal
- blurred vision
- unusually increased appetite
- weight loss
- fruity-smelling breath
- flushed face and dry skin
- feeling unusually sleepy or tired
- confusion

- **Mouth sores (stomatitis).** Mouth sores are common with ITOVEBI and may be severe. Tell your healthcare provider if you develop any of the following in your mouth:
  - pain
  - redness
  - swelling
  - ulcers
- **Diarrhea.** Diarrhea is common with ITOVEBI and may be severe. Severe diarrhea can lead to the loss of too much body water (dehydration) and kidney injury. Tell your healthcare provider right away if you develop diarrhea, stomach-area (abdominal) pain, or see mucus or blood in your stool during treatment with ITOVEBI. Your healthcare provider may tell you to drink more fluids or take medicines to treat your diarrhea.

Your healthcare provider may tell you to decrease your dose, temporarily stop your treatment, or completely stop your treatment with ITOVEBI if you develop certain serious side effects.

**The most common side effects and abnormal blood test results of ITOVEBI when used in combination with palbociclib and fulvestrant include:**

- decreased white blood cell counts, red blood cell counts, and platelet counts
- decreased blood levels of calcium, potassium, sodium, and magnesium
- increased creatine blood levels
- tiredness
- increased blood levels of the liver enzyme alanine transaminase (ALT)
- nausea
- rash
- loss of appetite
- COVID-19 infection
- headache

ITOVEBI may affect fertility in males and in females who are able to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of ITOVEBI.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store ITOVEBI?**

- Store ITOVEBI at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep ITOVEBI and all medicines out of the reach of children.**

**General information about the safe and effective use of ITOVEBI.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ITOVEBI for a condition for which it was not prescribed. Do not give ITOVEBI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ITOVEBI that is written for health professionals.

**What are the ingredients in ITOVEBI?**

**Active ingredient:** inavolisib

**Inactive ingredients:** lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablet film-coating contains iron oxide red, and iron oxide yellow (in the 9 mg tablet only), macrogol/polyethylene glycol, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

Distributed by: **Genentech USA, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

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For more information, go to [www.ITOVEBI.com](http://www.ITOVEBI.com) or call 1-877-436-3683.