TRACKING YOUR JOURNEY
Welcome to an easy way to stay on track with your treatment

This journal is designed to help you and your doctor keep track of your treatment with Esbriet® (pirfenidone). There are also places to write down activities and other events in your life.

For each week, there are 3 sections of this book for you to write in:

1. **Weekly Tracker** helps you stay on schedule taking your medicine with meals

2. **What Inspires You** is a journal for jotting down your thoughts and feelings that inspire you

3. **Your Medical Notes** is space for writing down how you feel, as well as any questions or comments you want to talk to your doctor about
**Why write this down?**
As you start Esbriet® (pirfenidone), you may find you need to slightly change your routines. Use this journal to:

- Get into the habit of taking your medicine with or at the end of a meal each time
- Jot down questions to help you remember at your next doctor’s appointment
- Write thoughts and feelings to help you stay motivated

**12-week journal**
This book is designed to be used for 12 weeks. Use it to write about your treatment with Esbriet. Call the 24-Hour Nurse Support Line, 1-844-My-Esbriet (844-693-7274), if you would like another journal.* We’ll mail it to your address.

*The nurse support line does not offer medical advice. If you have questions about your health or treatment, you are encouraged to contact your healthcare provider.

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**TAKING YOUR DOSE CORRECTLY, FROM THE START AND THROUGHOUT TREATMENT**

When starting a new medicine, it can take time for your body to adjust. Your doctor will slowly increase your dose over 2 weeks.

- **Always take Esbriet with food** to reduce side effects like nausea and dizziness
- If you miss a dose of Esbriet, take it with food as soon as you remember
- **Do not take 2 doses at the same time** to make up for a missed dose
- **Do not take more than 3 doses a day**
- If you take too much Esbriet, call your doctor or go to the nearest hospital emergency room right away

Store Esbriet at room temperature, 77°F (25°C). Keep in a tightly closed container. Safely throw away any Esbriet that is out of date or no longer needed. Keep Esbriet and all medicines out of reach of children.

**Remember:** Follow the dosing schedule your doctor gave you. It is always important to follow your doctor’s instructions. If you miss 14 days or more, call your doctor right away.
1. **Weekly Tracker**

**Check the boxes** each time you take Esbriet. Make one check for each tablet. Making checks in these boxes can help you develop a routine.

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You may also find it helpful to record things you did each day that you enjoyed. Was it chatting with an old friend? Was it a visit from your child?

What was one thing you did today that you enjoyed?

Day 1: **Read the newspaper**
2. **What Inspires You?**
   Jot down your thoughts and hopes that inspire you. Was it reading a great book? Was it a TV series or a movie? Did you take a short trip to meet friends or family? Was it a story you read about in the newspaper?
   They can help you focus on things that are meaningful to you.

3. **Your Medical Notes**
   Use this section to write down anything you may want to discuss with your doctor at your next appointment.
   To make the most of your time with your doctor, consider these topics:
   **How you feel**
   - Is your energy level the same?
   - Are you able to continue doing what you do?
   - Are you feeling less tired or more tired?
   - Any new health issues you have experienced?
   **How you sleep**
   - Are you sleeping more, less or the same?
   - Are you doing anything to help you sleep better?
   **What you eat**
   - What do you eat at breakfast?
   - What do you eat at lunch?
   - What do you eat at dinner?
   **Other questions you have**
   - Having any side effects?
   - Have you started taking any new medicines for other health conditions?
     - Any over-the-counter medicines?
     - Any nutritional supplements?
   - Questions about lung function tests and what test results mean
It is important to follow the Esbriet® (pirfenidone) dosing schedule your doctor prescribed for you. Your doctor may modify your dose. When starting Esbriet, your dosing schedule could look a lot like this one:

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Once you are doing well on 3 yellow tablets 3 times a day, **ask your doctor if transitioning to fewer pills per day is an option for you.**

**TIP OF THE WEEK:**
Be sure to take Esbriet with or at the end of a meal.

**INSPIRATIONAL QUOTE OF THE WEEK:**
“Our greatest glory is not in never falling, but in rising every time we fall.”
—Confucius
**WEEK 1**: Take 1 yellow tablet (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

Check the box each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

**DATE**

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During your first week of treatment, your doctor may ask you to take 1 yellow tablet per meal. **Be sure to take Esbriet with or at the end of a meal.**

What was one thing you did today that you enjoyed?

Day 1: ______________________________________

Day 2: ______________________________________

Day 3: ______________________________________

Day 4: ______________________________________

Day 5: ______________________________________

Day 6: ______________________________________

Day 7: ______________________________________
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

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Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

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What you eat
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Other questions you have
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WEEK 2

TIP OF THE WEEK:
Your doctor may recommend you take 2 yellow tablets (267 mg each) with meals in your second week of treatment. Follow your doctor’s instructions.

INSPIRATIONAL QUOTE OF THE WEEK:
“What lies behind us and what lies before us are tiny matters compared to what lies within us.”
—Ralph Waldo Emerson
**WEEK 2:** Take 2 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

**Check the box** each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

During your second week of treatment, your doctor may ask you to take 2 yellow tablets per meal. **Be sure to take Esbriet with or at the end of a meal.**

What was one thing you did today that you enjoyed?
Day 1: ____________________________
Day 2: ____________________________
Day 3: ____________________________

Day 4: ____________________________
Day 5: ____________________________
Day 6: ____________________________
Day 7: ____________________________
**What Inspires You?**

What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

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**Your Medical Notes**

Use this page to write down anything you may want to discuss with your doctor at your next appointment.

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TIP OF THE WEEK:
Your doctor may tell you to take 3 yellow tablets (267 mg each) with each meal in your third week of treatment. Continue taking the pills as your doctor directed.

INSPIRATIONAL QUOTE OF THE WEEK:
“We know what we are, but know not what we may be.”
—William Shakespeare
**What was one thing you did today that you enjoyed?**

Day 1: ____________________________________________

Day 2: ____________________________________________

Day 3: ____________________________________________

**During your third week of treatment, your doctor may ask you to take 3 tablets per meal. Be sure to take Esbriet with or at the end of a meal.**

During your third week of treatment, your doctor may ask you to take 3 tablets per meal. Be sure to take Esbriet with or at the end of a meal.
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

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Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

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TIP OF THE WEEK:
After you are doing well with the 9 pills (267 mg each) of Esbriet® (pirfenidone) a day, you and your doctor may want to talk about moving to a 3 tablet (801 mg each) per day option.

INSPIRATIONAL QUOTE OF THE WEEK:
“Every morning we are born again. What we do today is what matters most.”
—Gautama Buddha
**WEEK 4:** Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

**Check the box** each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

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What was one thing you did today that you enjoyed?
Day 1: 
Day 2: 
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Day 4: 
Day 5: 
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Be sure to take Esbriet with or at the end of a meal.
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

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Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

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Week 5

TIP OF THE WEEK:
Always take Esbriet® (pirfenidone) with a meal. It may help reduce possible side effects such as nausea and dizziness. Follow the dosing schedule prescribed by your doctor. If your doctor tells you to change your dosage, follow his or her instructions.

INSPIRATIONAL QUOTE OF THE WEEK:
“Don’t judge each day by the harvest you reap but by the seeds you plant.”
—Robert Louis Stevenson

Please see Select Important Safety Information and accompanying full Prescribing Information, including Patient Information.
**WEEK 5:** Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

**Check the box** each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

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What was one thing you did today that you enjoyed?

Day 1: ______________________________
Day 2: ______________________________
Day 3: ______________________________

Day 4: ______________________________
Day 5: ______________________________
Day 6: ______________________________
Day 7: ______________________________

Be sure to take Esbriet with or at the end of a meal.
What Inspires You?

What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

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Your Medical Notes

Use this page to write down anything you may want to discuss with your doctor at your next appointment.

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**TIP OF THE WEEK:**

Going outside? Esbriet® (pirfenidone) can make your skin more sensitive to sunlight.

To help protect yourself against sun sensitivity, always use a broad-spectrum (UVA/UVB) sunscreen with SPF 50 or higher. Reapply it often through the day.

Avoid taking other medicines that can make your skin sensitive to light, the light from sunlamps and tanning beds.

Wear a hat and clothing that protect your skin, including your face, arms and legs.

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**INSPIRATIONAL QUOTE OF THE WEEK:**

“Yesterday’s the past, tomorrow’s the future, but today is a GIFT. That’s why it’s called the present.”

—Bil Keane
**WEEK 6**: Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

**Check the box** each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

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What was one thing you did today that you enjoyed?

Day 1: __________________________________________

Day 2: __________________________________________

Day 3: __________________________________________

Day 4: __________________________________________

Day 5: __________________________________________

Day 6: __________________________________________

Day 7: __________________________________________
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

How you feel

How you sleep

What you eat

Other questions you have
WEEK 7

TIP OF THE WEEK:
The next time you see your doctor, be sure to take a few minutes to schedule your next appointment.

INSPIRATIONAL QUOTE OF THE WEEK:
“Fear less, hope more; talk less, say more; love more, and all good things will be yours.”
—Swedish Proverb
WEEK 7: Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

☑ Check the box each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

What was one thing you did today that you enjoyed?
Day 1: ___________________________________
Day 2: ___________________________________
Day 3: ___________________________________

Be sure to take Esbriet with or at the end of a meal.

Day 4: ___________________________________
Day 5: ___________________________________
Day 6: ___________________________________
Day 7: ___________________________________
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

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Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

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TIP OF THE WEEK:
Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

INSPIRATIONAL QUOTE OF THE WEEK:
“We are shaped by our thoughts; we become what we think.”
—Gautama Buddha
**WEEK 8:** Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

**Check the box** each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

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What was one thing you did today that you enjoyed?

**Day 1:** ________________________________

**Day 2:** ________________________________

**Day 3:** ________________________________

**Day 4:** ________________________________

**Day 5:** ________________________________

**Day 6:** ________________________________

**Day 7:** ________________________________

Be sure to take Esbriet with or at the end of a meal.
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

How you feel

How you sleep

What you eat

Other questions you have
TIP OF THE WEEK:
Always let your doctor know if you have side effects. If they’re really troublesome, he or she may decide to adjust or discontinue your dose. Remember, do not adjust your dose without your doctor’s advice.

INSPIRATIONAL QUOTE OF THE WEEK:
“Happiness resides not in possessions and not in gold; happiness dwells in the soul.”
—Democritus
**WEEK 9:** Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

✅ **Check the box** each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

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What was one thing you did today that you enjoyed?

Day 1: ___________________________
Day 2: ___________________________
Day 3: ___________________________

Day 4: ___________________________
Day 5: ___________________________
Day 6: ___________________________
Day 7: ___________________________

Be sure to take Esbriet with or at the end of a meal.
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

How you feel

How you sleep

What you eat

Other questions you have
TIP OF THE WEEK:
If you miss 14 days or more of Esbriet® (pirfenidone), call your doctor right away for further instructions about how to take your medicine. Do not take 2 doses at the same time to make up for your missed dose. Do not take more than 3 doses each day.

INSPIRATIONAL QUOTE OF THE WEEK:
“Be not afraid of life. Believe that life is worth living and your belief will help create the fact.”
—William James
**WEEK 10:** Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

- **Check the box** each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

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What was one thing you did today that you enjoyed?
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Day 2: __________________________________________
Day 3: __________________________________________
Day 4: __________________________________________
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Be sure to take Esbriet with or at the end of a meal.
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

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Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

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WEEK 11

TIP OF THE WEEK:
If you have any questions about tests that your doctor ordered for you, make sure you ask.

INSPIRATIONAL QUOTE OF THE WEEK:
“You have power over your mind—not outside events. Realize this, and you will find strength.”
—Marcus Aurelius
WEEK 1: Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

Check the box each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

Be sure to take Esbriet with or at the end of a meal.

What was one thing you did today that you enjoyed?
Day 1: ______________________________________
Day 2: ______________________________________
Day 3: ______________________________________
Day 4: ______________________________________
Day 5: ______________________________________
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Day 7: ______________________________________
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

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Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

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________________________________________________________________________

What you eat
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Other questions you have
________________________________________________________________________
________________________________________________________________________
TIP OF THE WEEK:
Store Esbriet® (pirfenidone) tablets at room temperature, 77°F (25°C). Keep in a tightly closed container. Safely throw away any Esbriet that is out of date or no longer needed. Keep Esbriet and all medicines out of reach of children.

INSPIRATIONAL QUOTE OF THE WEEK:
“Being deeply loved by someone gives you strength, while loving someone deeply gives you courage.”
—Lao Tzu
**WEEK 12:** Take 3 yellow tablets (267 mg each) 3 times a day with a meal. If your doctor gave you different instructions, follow those instead.

Check the box each time you take your Esbriet® (pirfenidone) tablets (267 mg each).

<table>
<thead>
<tr>
<th>DATE</th>
<th>Medication (Breakfast)</th>
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<tr>
<th>DATE</th>
<th>Medication (Lunch)</th>
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<table>
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<tr>
<th>DATE</th>
<th>Medication (Dinner)</th>
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</table>

What was one thing you did today that you enjoyed?
Day 1: ____________________________
Day 2: ____________________________
Day 3: ____________________________

Day 4: ____________________________
Day 5: ____________________________
Day 6: ____________________________
Day 7: ____________________________

Be sure to take Esbriet with or at the end of a meal.
What Inspires You?
What are the things that made you smile and feel good? Jot down your thoughts and hopes that inspire you.

________________________________________________________________________
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Your Medical Notes
Use this page to write down anything you may want to discuss with your doctor at your next appointment.

How you feel
________________________________________________________________________
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________________________________________________________________________
How you sleep
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________________________________________________________________________
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What you eat
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________________________________________________________________________
Other questions you have
________________________________________________________________________
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________________________________________________________________________
INDICATION AND SELECT IMPORTANT SAFETY INFORMATION

About Esbriet® (pirfenidone)
Esbriet is a prescription medicine used to treat people with a lung disease called idiopathic pulmonary fibrosis (IPF). It is not known if Esbriet is safe and effective in children.

SELECT IMPORTANT SAFETY INFORMATION
Before you take Esbriet, tell your doctor if you:

- have other medical conditions (particularly liver or kidney problems).
- are a smoker.
- are or plan to become pregnant or breastfeed (Esbriet has not been studied in these patients).
- are taking any prescription or over-the-counter medicines, vitamins, or herbal supplements.
Important Safety Information

What are the possible side effects of Esbriet® (pirfenidone)?

Esbriet may cause serious side effects, including:

- **Liver problems.** Call your doctor if you have symptoms such as yellowing of your skin or eyes, dark or brown urine, pain on the upper right side of your stomach area, bleeding or bruising more easily than normal, or increased fatigue. Your doctor will also do regular blood tests to check your liver.

- **Sun sensitivity and rash.** When you are outside, use sunscreen (SPF 50) and wear a hat and clothes that cover your skin to avoid getting a sunburn.

- **Stomach problems.** Esbriet may cause stomach problems such as nausea, vomiting, diarrhea, indigestion, heartburn, and stomach pain. Your doctor may change your dose or discontinue Esbriet if side effects do not go away.

The most common side effects of Esbriet include upper respiratory tract infections, feeling tired, headache, dizziness, loss of appetite, sinusitis, insomnia, or weight loss. These are not all the possible side effects of Esbriet.

What should you avoid while taking Esbriet?

- Direct exposure to sunlight, or light from sunlamps and tanning beds.
- Other medicines that can make your skin sensitive to sunlight.
- Smoking, which may affect how well Esbriet works.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or to Genentech at 1-888-835-2555.

Remember: The information in this booklet does not replace discussions with your doctor. Please contact your doctor with any questions about your condition and treatment options, including Esbriet, as well as any side effects you may experience while taking Esbriet.
All the important numbers all in
one place to fill out and keep

My pulmonologist: ____________________________

My primary care doctor: ______________________

My specialty pharmacy: ________________________

We are here when you need us.

To reach an Esbriet Nurse, 24 hours a day,
7 days a week, call 1-844-693-7274 and press 1.*

Genentech Access Solutions:
Call 1-844-ESBRIET (844-372-7438)
8 AM to 5 PM PT, Monday through Friday for questions
about understanding your insurance, ways to pay for
your Esbriet and what to expect during your treatment.

*The nurse support line does not offer medical advice. If you have questions about
your health or treatment, you are encouraged to contact your healthcare provider.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ESBRIET safely and effectively. See full prescribing information for ESBRIET.

ESBRIET® (pirfenidone) capsules and film-coated tablets, for oral use
Initial U.S. Approval: 2014

------------------------------ RECENT MAJOR CHANGES ------------------------------
Warnings and Precautions (5.1)  7/2019

------------------------------ INDICATIONS AND USAGE -----------------------------
ESBRIET is a pyridone indicated for the treatment of idiopathic pulmonary fibrosis (IPF). (1)

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

• Take with food.
• Recommended dosage: 801 mg three times daily (2403 mg/day). (2)
• Upon initiation of treatment, titrate to the full dosage of 2403 mg/day over a 14-day period as follows:

<table>
<thead>
<tr>
<th>Treatment days</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 through 7</td>
<td>267 mg three times daily (801 mg/day)</td>
</tr>
<tr>
<td>Days 8 through 14</td>
<td>334 mg three times daily (1602 mg/day)</td>
</tr>
<tr>
<td>Days 15 onward</td>
<td>801 mg three times daily (2403 mg/day)</td>
</tr>
</tbody>
</table>

• Consider temporary dosage reduction, treatment interruption, or discontinuation for management of adverse reactions. (2.3, 5.1, 5.2, 5.3)
• Prior to treatment, conduct liver function tests. (2.1)

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

• Capsules: 267 mg (3)
• Tablets: 267 mg, 801 mg (3)

------------------------------ CONTRAINDICATIONS -----------------------------
None

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

• Elevated liver enzymes and drug-induced liver injury: ALT, AST, and bilirubin elevations have occurred with ESBRIET including cases of drug-induced liver injury. In the postmarketing setting, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcomes, have been reported. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuations may be required. (2.1, 5.1)
• Photosensitivity and rash: Photosensitivity and rash have been noted with ESBRIET. Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily. Temporary dosage reductions or discontinuations may be required. (5.2)
• Gastrointestinal disorders: Nausea, vomiting, diarrhea, dyspepsia, gastro-esophageal reflux disease, and abdominal pain have occurred with ESBRIET. Temporary dosage reductions or discontinuations may be required. (5.3)

------------------------------ ADVERSE REACTIONS -------------------------------
The most common adverse reactions (≥10%) are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia. (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.

------------------------------ DRUG INTERACTIONS ------------------------------
Moderate (e.g., ciprofloxacin) and strong inhibitors of CYP1A2 (e.g., fluvoxamine) increase systemic exposure of ESBRIET and may alter the adverse reaction profile of ESBRIET. Discontinue fluvoxamine prior to administration of ESBRIET or reduce to 267 mg three times a day. Consider dosage reduction with use of ciprofloxacin. (7.1)

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

• Hepatic Impairment: Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed. ESBRIET is not recommended for use in patients with severe hepatic impairment. (8.6, 12.3)
• Renal Impairment: Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed. ESBRIET is not recommended for use in patients with end stage renal disease on dialysis. (8.7, 12.3)
• Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of ESBRIET. (8.8)

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

Revised: 7/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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  2.1 Testing Prior to ESBRIET Administration
  2.2 Recommended Dosage
  2.3 Dosage Modifications due to Adverse Reactions
  2.4 Dosage Modifications due to Drug Interactions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
  5.1 Elevated Liver Enzymes and Drug-Induced Liver Injury
  5.2 Photosensitivity Reaction or Rash
  5.3 Gastrointestinal Disorders

6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Postmarketing Experience

7 DRUG INTERACTIONS
  7.1 CYP1A2 Inhibitors
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8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy

8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
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8.7 Renal Impairment
8.8 Smokers

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11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
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13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed
FULL PRESCRIBING INFORMATION

1  INDICATIONS AND USAGE
ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

2  DOSAGE AND ADMINISTRATION

2.1  Testing Prior to ESBRIET Administration
Conduct liver function tests prior to initiating treatment with ESBRIET [see Warnings and Precautions (5.1)].

2.2  Recommended Dosage
The recommended daily maintenance dosage of ESBRIET is 801 mg three times daily for a total of 2403 mg/day. Doses should be taken with food at the same time each day.

Upon initiation of treatment, titrate to the full dosage of 2403 mg/day over a 14-day period as follows:

Table 1.  Dosage Titration for ESBRIET in Patients with IPF

<table>
<thead>
<tr>
<th>Treatment days</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 through 7</td>
<td>267 mg three times daily (801 mg/day)</td>
</tr>
<tr>
<td>Days 8 through 14</td>
<td>534 mg three times daily (1602 mg/day)</td>
</tr>
<tr>
<td>Days 15 onward</td>
<td>801 mg three times daily (2403 mg/day)</td>
</tr>
</tbody>
</table>

Dosages above 2403 mg/day are not recommended for any patient. Patients should not take 2 doses at the same time to make up for a missed dose. Patients should not take more than 3 doses per day.

2.3  Dosage Modifications due to Adverse Reactions
Patients who miss 14 or more days of ESBRIET should re-initiate treatment by undergoing the initial 2-week titration regimen up to the full maintenance dosage [see Dosage and Administration (2.2)]. For treatment interruption of less than 14 days, the dosage prior to the interruption can be resumed.

If patients experience significant adverse reactions (i.e., gastrointestinal, photosensitivity reaction or rash), consider temporary dosage reductions or interruptions of ESBRIET to allow for resolution of symptoms [see Warnings and Precautions (5.1, 5.2, 5.3)].

Dosage Modification due to Elevated Liver Enzymes
Dosage modifications or interruptions may also be necessary when liver enzyme and bilirubin elevations are exhibited. For liver enzyme elevations, modify the dosage as follows:
If a patient exhibits $>3$ but $\leq 5 \times$ the upper limit of normal (ULN) ALT and/or AST without symptoms or hyperbilirubinemia after starting ESBRIET therapy:

- Discontinue confounding medications, exclude other causes, and monitor the patient closely.
- Repeat liver chemistry tests as clinically indicated.
- The full daily dosage may be maintained, if clinically appropriate, or reduced or interrupted (e.g., until liver chemistry tests are within normal limits) with subsequent retitration to the full dosage as tolerated.

If a patient exhibits $>3$ but $\leq 5 \times$ ULN ALT and/or AST accompanied by symptoms or hyperbilirubinemia:

- Permanently discontinue ESBRIET.
- Do not rechallenge patient with ESBRIET.

If a patient exhibits $>5 \times$ ULN ALT and/or AST:

- Permanently discontinue ESBRIET.
- Do not rechallenge patient with ESBRIET.

### 2.4 Dosage Modification due to Drug Interactions

**Strong CYP1A2 Inhibitors (e.g., fluvoxamine, enoxacin)**
Reduce ESBRIET to 267 mg three times a day (801 mg/day).

**Moderate CYP1A2 Inhibitors (e.g., ciprofloxacin)**
With use of ciprofloxacin at a dosage of 750 mg twice daily, reduce ESBRIET to 534 mg three times a day (1602 mg/day).

### 3 DOSAGE FORMS AND STRENGTHS

Capsules: 267 mg, white to off-white, hard gelatin capsules printed with “PFD 267 mg” on the cap of the capsule in brown ink.

Film-coated tablets: oval, biconvex, debossed with “PFD”, containing 267 mg (yellow) and 801 mg (brown) pirfenidone

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Elevated Liver Enzymes and Drug-Induced Liver Injury

Cases of drug-induced liver injury (DILI) have been observed with ESBRIET. In the postmarketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. Patients treated with Esbriet 2403 mg/day in three Phase 3 trials had a higher incidence of elevations in ALT or AST $\geq 3 \times$ ULN than placebo.
patients (3.7% vs 0.8%, respectively). Elevations \(\geq 10\times ULN\) in ALT or AST occurred in 0.3% of patients in the Esbriet 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST \(\geq 3\times ULN\) were reversible with dose modification or treatment discontinuation.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations [see Dosage and Administration (2.1, 2.3)].

5.2 Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash [see Dosage and Administration (2.3)].

5.3 Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions [see Dosage and Administration (2.3)].

6 ADVERSE REACTIONS

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

- Liver Enzyme Elevations and Drug-Induced Liver Injury [see Warnings and Precautions (5.1)]
- Photosensitivity Reaction or Rash [see Warnings and Precautions (5.2)]
- Gastrointestinal Disorders [see Warnings and Precautions (5.3)]
6.1 Clinical Trials 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.

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.
Table 2.  Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>% of Patients (0 to 118 Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESBRIET 2403 mg/day (N = 623)</td>
</tr>
<tr>
<td>Nausea</td>
<td>36%</td>
</tr>
<tr>
<td>Rash</td>
<td>30%</td>
</tr>
<tr>
<td>Abdominal Pain(^1)</td>
<td>24%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>27%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26%</td>
</tr>
<tr>
<td>Headache</td>
<td>22%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13%</td>
</tr>
<tr>
<td>Gastro-esophageal Reflux Disease</td>
<td>11%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10%</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>10%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10%</td>
</tr>
</tbody>
</table>

\(^1\) Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

6.2  Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post-approval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

**Blood and Lymphatic System Disorders**
Agranulocytosis

**Immune System Disorders**
Angioedema

**Hepatobiliary Disorders**
Drug-induced liver injury [see Warnings and Precautions (5.1)]

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A2 Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET [see Clinical Pharmacology (12.3)]. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed [see Dosage and Administration (2.4)].

Moderate CYP1A2 Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET [see Clinical Pharmacology (12.3)]. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended [see Dosage and Administration (2.4)]. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

7.2 CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risks for major birth defects and miscarriage. In animal reproduction studies, pirfenidone was not teratogenic in rats and rabbits at oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults [see Data].
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

Animal reproductive studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. In these studies, pirfenidone at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m² basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m² basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, female rats received pirfenidone at oral doses of 0, 100, 300, and 1000 mg/kg/day from GD 7 to lactation day 20. Prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m² basis at a maternal oral dose of 1000 mg/kg/day).

8.2 Lactation

Risk Summary

No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ESBRIET and the potential adverse effects on the breastfed child from ESBRIET or from the underlying maternal condition.

Data

Animal Data: A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk, the effects of pirfenidone on the breastfed child, or its effects on milk production.

8.4 Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

8.6 Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see Dosage and Administration (2.3)].

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment [see Clinical Pharmacology (12.3)].

8.7 Renal Impairment

ESBRIET should be used with caution in patients with mild (CL\text{cr} 50–80 mL/min), moderate (CL\text{cr} 30–50 mL/min), or severe (CL\text{cr} less than 30 mL/min) renal impairment [see Clinical Pharmacology (12.3)]. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see Dosage and Administration (2.3)]. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

8.8 Smokers

Smoking causes decreased exposure to ESBRIET [see Clinical Pharmacology (12.3)], which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

10 OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

11 DESCRIPTION

ESBRIET belongs to the chemical class of pyridone. ESBRIET is available as a white to off-white hard gelatin capsule containing 267 mg of pirfenidone for oral administration, or, as film-coated tablets containing 267 mg (yellow) and 801 mg (brown) pirfenidone.
Pirfenidone has a molecular formula of C$_{12}$H$_{11}$NO and a molecular weight of 185.23. Pirfenidone has the following structural formula, which has been referred to as 5-methyl-1-phenyl-2-(1H)-pyridone or 5-methyl-1-phenyl-2-(1H)-pyridone.

Pirfenidone is a white to pale yellow, non-hygroscopic powder. It is more soluble in methanol, ethyl alcohol, acetone and chloroform than in water and 1.0 N HCl. The melting point is approximately 109°C.

ESBRIET capsule contains pirfenidone and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate.

In addition, the capsule shell contains gelatin and titanium dioxide. The capsule brown printing ink includes shellac, iron oxide black, iron oxide red, iron oxide yellow, propylene glycol, ammonium hydroxide.

ESBRIET tablets contain pirfenidone and the following inactive ingredients: Microcrystalline cellulose, colloidal anhydrous silica, povidone, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol (polyethylene glycol), talc, and iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of pirfenidone in the treatment of IPF has not been established.

12.2 Pharmacodynamics

Cardiac Electrophysiology:

The effect of ESBRIET on QT interval was evaluated in a randomized, placebo, and positive controlled parallel study in 160 healthy adult volunteers. Volunteers received ESBRIET 2403 mg/day (recommended dose) and 4005 mg/day (1.6 times recommended dose) or placebo for 10 days or a single dose of 400 mg moxifloxacin (active control).

Relative to placebo, the maximum mean change from baseline in study-specific QT interval was 3.2 milliseconds (ms) and 2.2 ms for ESBRIET 2403 mg/day and 4005 mg/day, respectively. No volunteer had a QTc interval greater than 480 ms or change from baseline greater than 60 ms. Although there was no evidence that ESBRIET prolonged the QTc interval in this study, a definitive conclusion may not be drawn as the positive control (moxifloxacin) did not perform as expected in this study, and ESBRIET at 4005 mg/day
(1.7 times the maximum recommended dose) did not cover the maximum pirfenidone exposure increase with co-administration of fluvoxamine, a strong CYP1A2 inhibitor.

12.3 Pharmacokinetics

Absorption:
After single oral-dose administration of 801 mg ESBRIET (three 267 mg capsules), the maximum observed plasma concentration ($C_{\text{max}}$) was achieved between 30 minutes and 4 hours (median time of 0.5 hours). Food decreased the rate and extent of absorption. Median $T_{\text{max}}$ increased from 0.5 hours to 3 hours with food. Maximum plasma concentrations ($C_{\text{max}}$) and $\text{AUC}_{0-\text{inf}}$ decreased by approximately 49% and 16% with food, respectively.

Bioequivalence was demonstrated in the fasted state when comparing the 801 mg tablet to three 267 mg capsules. The effect of food on pirfenidone exposure was consistent between the tablet and capsule formulations.

A reduced incidence of adverse reactions was observed in the fed group when compared to the fasted group. In controlled studies with IPF patients, ESBRIET was taken with food [see Dosage and Administration (2) and Clinical Studies (14)].

The absolute bioavailability of pirfenidone has not been determined in humans.

Distribution:
ESBRIET binds to human plasma proteins, primarily to serum albumin, in a concentration-independent manner over the range of concentrations observed in clinical trials. The overall mean binding was 58% at concentrations observed in clinical studies (1 to 10 µg/mL). Mean apparent oral volume of distribution is approximately 59 to 71 liters.

Metabolism:
In vitro profiling studies in hepatocytes and liver microsomes have shown that ESBRIET is primarily metabolized in the liver by CYP1A2 and multiple other CYPs (CYP2C9, 2C19, 2D6, and 2E1). Oral administration of ESBRIET results in the formation of four metabolites. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities. The mean metabolite-to-parent ratio ranged from approximately 0.6 to 0.7.

No formal radiolabeled studies have assessed the metabolism of pirfenidone in humans. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination:
The mean terminal half-life is approximately 3 hours in healthy subjects. Pirfenidone is excreted predominantly as metabolite 5-carboxy-pirfenidone, mainly in the urine (approximately 80% of the dose). The majority of ESBRIET was excreted as the 5-carboxy metabolite (approximately 99.6% of that recovered).
Specific Populations:

Hepatic Impairment
The pharmacokinetics of ESBRIET and the 5-carboxy-pirfenidone metabolite were studied in 12 subjects with moderate hepatic impairment (Child Pugh Class B) and in 12 subjects with normal hepatic function. Results showed that the mean exposure, $\text{AUC}_{0-\text{inf}}$ and $C_{\text{max}}$ of pirfenidone increased approximately 1.6- and approximately 1.4-fold in subjects with moderate hepatic impairment, respectively. The exposure of 5-carboxy-pirfenidone did not change significantly in subjects with moderate hepatic impairment.

Renal Impairment
The pharmacokinetics of pirfenidone and the 5-carboxy-pirfenidone metabolite were studied in 18 subjects with mild ($\text{CL}_{\text{cr}}$ 50 to 80 mL/min), moderate ($\text{CL}_{\text{cr}}$ 30 to 50 mL/min), and severe ($\text{CL}_{\text{cr}}$ less than 30 mL/min) renal impairment (n=6/group) and in 6 subjects with normal $\text{CL}_{\text{cr}}$ (greater than or equal to 80 mL/min) renal function. Results showed that systemic exposure ($\text{AUC}_{0-\text{inf}}$) to pirfenidone increased approximately 1.4, 1.5, and 1.2-fold in subjects with mild, moderate and severe renal impairment, respectively. The corresponding $\text{AUC}_{0-\text{inf}}$ of 5-carboxy-pirfenidone increased 1.7, 3.4, and 5.6-fold, although the change in the patients with mild renal impairment was not statistically significant. The renal clearance of 5-carboxy-pirfenidone decreased significantly in patients with moderate to severe renal impairment.

The pharmacokinetics and safety of ESBRIET has not been studied in subjects with end-stage renal disease requiring dialysis.

Geriatric
Results of population pharmacokinetic analysis suggest that no dosage adjustment is needed in geriatric patients.

Gender
Results of population pharmacokinetic analysis of ESBRIET showed no significant differences in pharmacokinetics between males and females.

Obesity
Results of population pharmacokinetic analysis showed that obesity (Body Mass Index [BMI] greater than or equal to 30 kg/m²) has no significant effect on the pharmacokinetics of ESBRIET.

Race
Population pharmacokinetic analysis showed that race has no significant effect on the pharmacokinetics of pirfenidone.

Drug Interaction Studies:
Cytochrome P450 1A2 Inhibitors
Pirfenidone is a substrate of cytochrome P450 1A2. In a single-dose drug interaction study in 25 healthy nonsmokers and 25 smokers, ESBRIET was coadministered with fluvoxamine.
(50 mg at bedtime for 3 days; 50 mg twice a day for 3 days, and 50 mg in the morning and 100 mg at bedtime for 4 days). An approximately 4-fold increase in exposure to pirfenidone in nonsmokers and approximately 7-fold increase in exposure in smokers was observed.

In a single-dose drug interaction study in 27 healthy subjects, coadministration of 801 mg of ESBRIET and 750 mg of ciprofloxacin (a moderate inhibitor of CYP1A2) on Day 6 (ciprofloxacin was dosed at 750 mg twice daily from Day 2 to Day 7) increased the exposure to pirfenidone by 81%.

**Cytochrome P450 1A2 Inducers**

Following a single oral dose of 801 mg ESBRIET in 25 smokers and 25 healthy nonsmokers, the systemic exposure in smokers was significantly lower compared to nonsmokers. AUC$_{0-\inf}$ and C$_{\text{max}}$ of pirfenidone in smokers were 46% and 68% of those in nonsmokers, respectively.

**Inhibitory Effect of Pirfenidone on P-glycoprotein (Pgp)**

The potential for pirfenidone to inhibit Pgp mediated transport of digoxin (5.0 µM) was evaluated in the absence and presence of pirfenidone at concentrations ranging from 1 to 1000 µM in *in vitro* system. Pirfenidone showed weak inhibition (10 to 30%) of Pgp facilitated digoxin B-A efflux at concentrations of 100 µM and above. Effect of pirfenidone upon Pgp substrate pharmacokinetics and safety has not been evaluated in humans.

**Inhibitory Effect of Pirfenidone on CYP2C9, 2C19 or 1A2, 2D6, 3A4**

The potential for pirfenidone to inhibit CYP2C9, 2C19 or 1A2 was evaluated *in vitro* at concentrations up to 1000 µM (approximately 10-fold the mean human C$_{\text{max}}$). Pirfenidone showed a concentration-dependent inhibition on CYP2C9, 2C19 or 1A2, 2D6, and 3A4. At 1000 µM, pirfenidone inhibits the activity of these enzymes by 30.4%, 27.5%, 34.1%, 21%, and 9.6%, respectively. Effect of pirfenidone upon pharmacokinetics and safety of CYP2C9, 2C19, 1A2, 2D6, and 3A4 substrates has not been evaluated in humans.

13 **NONCLINICAL TOXICOLOGY**

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

**Carcinogenesis**

Long-term studies were conducted in mice and rats with admixture of pirfenidone to the diet to evaluate its carcinogenic potential.

In a 24-month carcinogenicity study in B6C3F1 mice, pirfenidone caused statistically significant dose-related increases of the combination of hepatocellular adenoma and carcinoma and hepatoblastoma in male mice at doses of 800 mg/kg and above (AUC exposure approximately 0.4 times adult exposure at the MRDD). There were statistically significant dose-related increases of the combination of hepatocellular adenoma and carcinoma in female mice at doses of 2000 mg/kg and above (AUC exposure approximately 0.7 times adult exposure at the MRDD).
In a 24-month carcinogenicity study in Fischer rats, pirfenidone caused statistically significant dose-related increases of the combination of hepatocellular adenoma and carcinoma in male rats at doses of 750 mg/kg and above (AUC exposure approximately 1.9 times adult exposure at the MRDD). There were statistically significant increases of the combination of hepatocellular adenoma and carcinoma and the combination of uterine adenocarcinoma and adenoma at a dose of 1500 mg/kg/day (AUC exposure approximately 3.0 times adult exposure at the MRDD).

The relevance of these tumor findings in rodents to humans is unknown.

Mutagenesis
Pirfenidone was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacteria, a chromosomal aberration test in Chinese hamster lung cells, and a micronucleus test in mice.

Impairment of Fertility
Pirfenidone had no effects on fertility and reproductive performance in rats at dosages up to 1000 mg/kg/day (approximately 3 times the MRDD in adults on a mg/m² basis).

14 CLINICAL STUDIES
The efficacy of ESBRIET was evaluated in patients with IPF in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials (Studies 1, 2, and 3).

Study 1 was a 52-week trial comparing ESBRIET 2403 mg/day (n=278) versus placebo (n=277) in patients with IPF. Study 2 and Study 3 were nearly identical to each other in design, with few exceptions, including an intermediate dose treatment arm in Study 2. Study 2 compared treatment with either ESBRIET 2403 mg/day (n=174) or ESBRIET 1197 mg/day (n=87) to placebo (n=174), while Study 3 compared ESBRIET 2403 mg/day (n=171) to placebo (n=173). Study drug was administered three times daily with food for a minimum of 72 weeks. Patients continued on treatment until the last patient completed 72 weeks of treatment, which included observations to approximately 120 weeks of study treatment. The primary endpoint was the change in percent predicted forced vital capacity (%FVC) from baseline to study end, measured at 52 weeks in Study 1, and at 72 weeks in Studies 2 and 3.

Studies 1, 2 and 3 enrolled adult patients who had a clinical and radiographic diagnosis of IPF (with or without accompanying surgical lung biopsy), without evidence or suspicion of an alternative diagnosis for interstitial lung disease. Eligible patients were to have %FVC greater than or equal to 50% at baseline and a percent predicted diffusing capacity of the lungs for carbon monoxide (%DLCO) greater than or equal to 30% (Study 1) or 35% (Studies 2 and 3) at baseline. In all three trials, over 80% of patients completed study treatment.

A total of 1247 patients with IPF were randomized to receive ESBRIET 2403 mg/day (n=623) or placebo (n=624) in these three trials. Baseline characteristics were generally
balanced across treatment groups. The study population ranged from 40 to 80 years of age (mean age 67 years). Most patients were male (74%), white (95%), and current or former smokers (65%). Approximately 93% of patients met criteria for definite IPF on high resolution computed tomography (HRCT). Baseline mean %FVC and %DLCO were 72% and 46%, respectively. Approximately 15% subjects discontinued from each treatment group.

Change from Baseline in Percent Predicted Forced Vital Capacity
In Study 1, the primary efficacy analysis for the change in %FVC from baseline to Week 52 demonstrated a statistically significant treatment effect of ESBRIET 2403 mg/day (n=278) compared with placebo (n=277) using a rank ANCOVA with the lowest rank imputation for missing data due to death. In Study 2, there was a statistically significant difference at Week 72 for the change in %FVC from baseline. In Study 3, there was no statistically significant difference at Week 72 for the change in %FVC from baseline.

Figure 1 presents the cumulative distribution for all cut-offs for the change from baseline in %FVC at Week 52 for Study 1. For all categorical declines in lung function, the proportion of patients declining was lower on ESBRIET than on placebo. Study 2 showed similar results.

**Figure 1.** Cumulative Distribution of Patients by Change in Percent Predicted FVC from Baseline to Week 52 (Study 1). The Dashed Lines Indicate ≥10% Decline or ≥0% Decline.
Mean Change from Baseline in FVC (mL)
In Study 1, a reduction in the mean decline in FVC (in mL) was observed in patients receiving ESBRIET 2403 mg/day (-235 mL) compared to placebo (-428 mL) (mean treatment difference 193 mL) at Week 52 (see Figure 2). In Study 2, a reduction in the decline in FVC volume was also observed in patients receiving ESBRIET 2403 mg/day compared with placebo (mean treatment difference 157 mL) at Week 72. There was no statistically significant difference in decline in FVC volume seen in Study 3.

Figure 2. Mean Change from Baseline in Forced Vital Capacity (Study 1)

![Graph showing mean change from baseline in FVC (mL) over weeks for ESBRIET and placebo]

Survival
Survival was evaluated for ESBRIET compared to placebo in Studies 1, 2, and 3 as an exploratory analysis to support the primary endpoint (FVC). All-cause mortality was assessed over the study duration and available follow-up period, irrespective of cause of death and whether patients continued treatment. All-cause mortality did not show a statistically significant difference (see Figure 3).
Figure 3. Kaplan-Meier Estimates of All-Cause Mortality at Vital Status – End of Study: Studies 1, 2, and 3

16 HOW SUPPLIED/STORAGE AND HANDLING

ESBRIET white to off-white hard gelatin capsules contain 267 mg of pirfenidone. The cap of the capsule is printed with “PFD 267 mg” in brown ink. The capsule is supplied either in a bottle, a 14-day titration blister pack or a 4-week maintenance blister pack.

ESBRIET film-coated tablets are oval, biconvex, debossed with “PFD”, containing 267 mg (yellow) and 801 mg (brown) pirfenidone. The film-coated tablets are supplied in bottles.

ESBRIET capsules:
• NDC 50242-121-01, bottle for a 30-day supply containing 270 capsules and closed with a child-resistant closure
• NDC 50242-121-02, 14-day titration blister pack, carton containing a total of 63 capsules in two blister cards – a Week 1 blister card containing 21 capsules (1 capsule per blister well) and a Week 2 blister card containing 42 capsules (2 capsules per blister well)
• NDC 50242-121-03, 4-week maintenance blister pack, carton containing a total of 252 capsules in four blister cards each with 63 capsules (3 capsules per blister well)

ESBRIET film-coated tablets:
• NDC 50242-122-05, carton containing 3 bottles, each containing ninety 267 mg tablets (270 tablets total) with a child-resistant closure
• NDC 50242-122-06, carton containing 1 bottle containing 270 tablets, 267 mg each, with a child-resistant closure

• NDC 50242-123-01, carton containing 1 bottle containing ninety 801 mg tablets, with a child-resistant closure

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) (see USP Controlled Room Temperature).

Keep the bottle tightly closed. Do not use if the seal over the bottle opening is broken or missing. Safely throw away any ESBRIET that is out of date or no longer needed.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Liver Enzyme Elevations
Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) [see Warnings and Precautions (5.1)].

Photosensitivity Reaction or Rash
Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required [see Warnings and Precautions (5.2)].

Gastrointestinal Events
Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required [see Warnings and Precautions (5.3)].

Smokers
Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET [see Clinical Pharmacology (12.3)].

Take with Food
Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Distributed by:
Genentech USA, Inc.
What is ESBRIET?
• ESBRIET is a prescription medicine used to treat people with a lung disease called idiopathic pulmonary fibrosis (IPF).
• It is not known if ESBRIET is safe and effective in children.

Before you take ESBRIET, tell your doctor about all of your medical conditions, including if you:
• have liver problems
• have kidney problems
• are a smoker
• are pregnant or plan to become pregnant. It is not known if ESBRIET will harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if ESBRIET passes into your breast milk. You and your doctor should decide if you will take ESBRIET.

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

How should I take ESBRIET?
• Take ESBRIET exactly as your doctor tells you to take it.
• Your doctor may change your dose of ESBRIET as needed.
• Take ESBRIET with food at the same time each day. This may help to decrease your nausea and dizziness.
• ESBRIET 267 mg is supplied as either a white to off-white capsule or a yellow tablet. If you have been prescribed ESBRIET 267 mg, take it as follows:
  o Take 1 ESBRIET 267 mg capsule or tablet 3 times each day for days 1 through 7.
  o Take 2 ESBRIET 267 mg capsule or tablet 3 times each day for days 8 through 14.
  o Take 3 ESBRIET 267 mg capsule or tablet 3 times each day on day 15 and each day after.

<table>
<thead>
<tr>
<th>Week</th>
<th>Morning (Breakfast)</th>
<th>Afternoon (Lunch)</th>
<th>Evening (Dinner)</th>
<th>Total Pills Each Day</th>
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<tr>
<td>Days 1-7</td>
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<td>1</td>
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<td>3</td>
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<tr>
<td>Days 8-14</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Days 15 onward</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

• If you have been prescribed the brown 801 mg ESBRIET film-coated tablets, take it as follows:
  o Take 1 brown 801 mg ESBRIET tablet 3 times each day.

<table>
<thead>
<tr>
<th>Week</th>
<th>Morning (Breakfast)</th>
<th>Afternoon (Lunch)</th>
<th>Evening (Dinner)</th>
<th>Total Pills Each Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 15 onward</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
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</table>

• If you miss 14 days or more of ESBRIET call your doctor right away for further instructions about how to take your medicine.
• Do not take 2 doses at the same time to make up for your missed dose.
• Do not take more than 3 doses each day.
• If you take too much ESBRIET, call your doctor or go to the nearest hospital emergency room right away.
• Your doctor should do certain blood tests before you start taking ESBRIET.
What should I avoid while taking ESBRIET?

- Avoid sunlight. ESBRIET can make your skin sensitive to the sun and the light from sunlamps and tanning beds. You could get a severe sunburn. Use sunscreen (SPF 50) and wear a hat and clothes that cover your skin if you have to be in sunlight. Talk to your doctor if you get sunburn or a rash.
- Avoid taking ESBRIET with other medicines that can make your skin sensitive to the sun, the light from sunlamps and tanning beds.
- Avoid smoking. Smoking may affect how well ESBRIET works.

What are the possible side effects of ESBRIET?

ESBRIET may cause serious side effects, including:

- **Liver problems.** Call your doctor right away if you have unexplained symptoms such as yellowing of your skin or the white part of your eyes (jaundice), dark or brown (tea colored) urine, pain on the upper right side of your stomach area (abdomen), bleeding or bruising more easily than normal, feeling tired.
  
  Your doctor will do blood tests to check how your liver is working during your treatment with ESBRIET.

- **Sensitivity to sunlight (photosensitivity) and rash.** See “What should I avoid while taking ESBRIET?”

- **Stomach problems.** ESBRIET may cause stomach problems such as nausea, vomiting, diarrhea, indigestion, heartburn, and stomach pain. Tell your doctor right away if your stomach problems get worse or do not go away.
  
  Your doctor may need to change your dose of ESBRIET.

The most common side effects of ESBRIET include feeling tired, insomnia, upper respiratory tract infections, sinusitis, headache, dizziness, decreased weight and decreased or loss of appetite.

These are not all the possible side effects of ESBRIET. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ESBRIET?

- Store ESBRIET capsules and tablets at room temperature, 77°F (25°C).
- Keep in a tightly closed container.

Safely throw away any ESBRIET that is out of date or no longer needed. Keep ESBRIET and all medicines out of reach of children.

General information about the safe and effective use of ESBRIET.

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

What are the ingredients in ESBRIET capsules?

**Active ingredient:** pirfenidone

**Inactive ingredients:** microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate

**Capsule Shell:** gelatin and titanium dioxide

**Capsule Brown Printing Ink:** shellac, iron oxide black, iron oxide red, iron oxide yellow, propylene glycol, ammonium hydroxide

What are the ingredients in ESBRIET film-coated tablets?

**Active ingredient:** pirfenidone

**Inactive ingredients:** microcrystalline cellulose, colloidal anhydrous silica, povidone, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol (polyethylene glycol), talc, and iron oxide

For more information, go to www.ESBRIET.com or call 1-888-835-2555.

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