



**Otezla**<sup>®</sup>  
(apremilast) 30mg  
tablets

show *more* of you

for plaque psoriasis or psoriatic arthritis

*little knot*  
**big hero**

**\$0 co-pay\***  
program  
[otezla.com/copay](http://otezla.com/copay)

When you're living with moderate to severe  
**plaque psoriasis or psoriatic arthritis**, little moments can mean a lot.

Otezla is a prescription medicine approved for the treatment of patients with moderate to severe plaque psoriasis for whom phototherapy or systemic therapy is appropriate.

It is also approved for the treatment of adult patients with active psoriatic arthritis.

**Please see Important Safety Information on page 14.**

\*Certain restrictions apply.



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Is your current treatment  
working for you?

If not, think about Otezla—  
it's a pill that works **differently**.



Not an injection,  
cream, or biologic—  
*Otezla is a pill*



#### For moderate to severe plaque psoriasis

**75% clearer skin** is achievable in some people after just 4 months of treatment, **with reduced redness, thickness, and scaliness** of plaques



#### For psoriatic arthritis

Otezla can help reduce the **joint swelling, tenderness, and pain** in some people **with psoriatic arthritis** after just 4 months of treatment



#### No blood testing required

The Otezla Prescribing Information has **no requirement** for initial or routine **blood testing**

Otezla is the #1 prescribed  
branded *pill* for *plaque psoriasis*<sup>†</sup>  
or *psoriatic arthritis*<sup>‡</sup>

### Side effects of Otezla

The most common side effects of Otezla in plaque psoriasis were diarrhea, nausea, upper respiratory tract infection, tension headache, and headache.

The most common side effects of Otezla in psoriatic arthritis were diarrhea, nausea, and headache.

\*Certain restrictions apply; eligibility not based on income.

<sup>†</sup>Source: Symphony Health Solutions PrescriberSource PatientFocus data, Amgen proprietary methodology. Jan2016–Jan2020. Data include only oral formulations for scripts tagged with a plaque psoriasis indication.

<sup>‡</sup>Source: Symphony Health Solutions PrescriberSource PatientFocus data, Amgen proprietary methodology. Jan2016–Jan2020. Data include only oral formulations for scripts tagged with a psoriatic arthritis indication.

Please see Important Safety Information on page 14.



## How do plaque psoriasis and psoriatic arthritis start?

Plaque psoriasis and psoriatic arthritis are **chronic conditions**, which means they're always there—even when you aren't experiencing symptoms.

Both plaque psoriasis and psoriatic arthritis are associated with overactive inflammation inside the body. Lab research has shown that an enzyme known as phosphodiesterase 4 (PDE4), located inside cells, contributes to inflammation.

It's thought that **overactive inflammation is responsible for the symptoms** of plaque psoriasis and psoriatic arthritis.

### The role of overactive inflammation



#### In plaque psoriasis:

Thought to speed up the growth cycle of skin cells



Eventually, skin cells build up and result in red, itchy, raised plaques on the skin



#### In psoriatic arthritis:

Thought to cause tissue around the joints to thicken



Over time, thickened tissue results in swollen, painful joints

### Did *you* know



Otezla is a pill that works inside the body to help reduce inflammation



"Living with psoriatic arthritis is challenging and unpredictable. You don't know if you're going to wake up one day and have difficulty walking."

—Cindy C., Jamaica, NY  
Actual Otezla patient

*little visitors*  
**big day**



The only *pill* approved for plaque psoriasis or psoriatic arthritis that doesn't require routine lab monitoring according to the Otezla Prescribing Information

*little sunshine*  
**big day**

## What sets Otezla apart from other *treatments*



It's a *pill* that works differently



Part of what makes Otezla different is how it works.

While the exact way Otezla works isn't completely understood, here's what we do know:

- Otezla works inside inflammatory cells to reduce **PDE4** activity
- A reduction in PDE4 activity is thought to reduce **overactive inflammation**
- Less inflammation can lead to a reduction in symptoms (in plaque psoriasis or psoriatic arthritis)

“Otezla works from the inside to reduce inflammation.”

—**DR. ERIN BOH**, board certified dermatologist



Watch a panel of professionals including Dr. Boh talk about Otezla at [otezla.com/learn](https://otezla.com/learn)

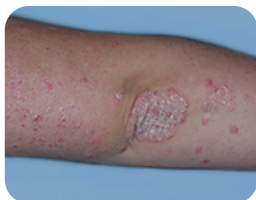




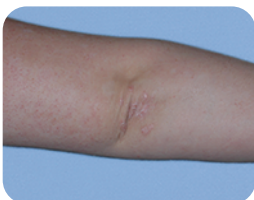
## Proven *results* in plaque psoriasis

Otezla is a pill that can help you achieve clearer skin

BEFORE OTEZLA



WITH OTEZLA AT 16 WEEKS



BEFORE OTEZLA



WITH OTEZLA AT 16 WEEKS



BEFORE OTEZLA



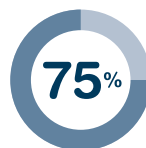
WITH OTEZLA AT 16 WEEKS



Actual Otezla patients. Not everyone responds to Otezla, and those who do respond may respond differently.

See more before and after photos at [otezla.com](https://www.otezla.com)

Studies showed clearer skin on Otezla



Studies showed that after just 4 months on Otezla, a 75% reduction in moderate to severe plaque psoriasis is achievable in some people.

### Did *you* know

Psoriasis severity isn't just measured by physical skin symptoms. It's also important to think about the emotional impact it has on your life—especially when considering your treatment options.

### Common side effects of Otezla

The most common side effects of Otezla were diarrhea, nausea, upper respiratory tract infection, tension headache, and headache.

### Selected Safety Information

**You must not take Otezla if you are allergic to apremilast or to any of the ingredients in Otezla.**

**Otezla can cause severe diarrhea, nausea, and vomiting, especially within the first few weeks of treatment.** Use in elderly patients and the use of certain medications with Otezla appears to increase the risk of having diarrhea, nausea, or vomiting. Tell your doctor if any of these conditions occur.

## Understanding side effects

### Otezla *in* clinical studies

Otezla clinical studies involved 1,426 adults with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy.

In each study, some people took 30 mg of Otezla twice daily, and others took a placebo (sugar pill).

### Side effects

The table below shows the most common side effects reported by people taking Otezla compared to those reported by people taking a placebo (sugar pill).

Most common side effects (up to week 16)*	Otezla (920 people)	Placebo (506 people)
Diarrhea	17% of patients	6% of patients
Nausea	17%	7%
Upper respiratory tract infection	9%	6%
Tension headache	8%	4%
Headache	6%	4%

\*Data from day 6 through day 112 (the titration period was days 1-5, during which the dose was gradually increased until the recommended dose of 30 mg twice daily was reached).

These are not all the possible side effects of Otezla. Tell your doctor about any side effect that bothers you or does not go away. If you're experiencing side effects, please consult your doctor. For a full list of possible side effects, see the Prescribing Information in the back pocket of this brochure.

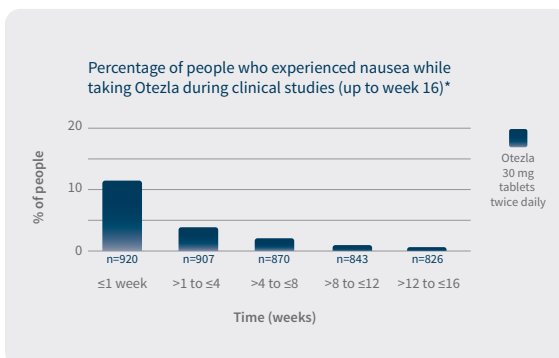
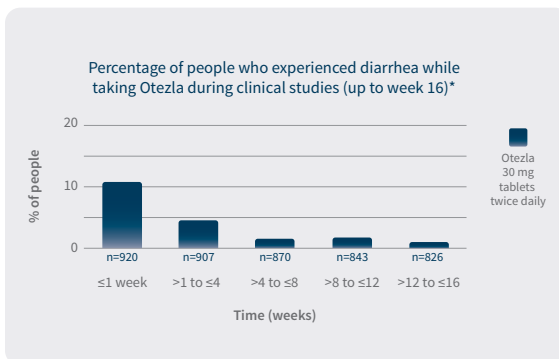


**"I tried creams, lotions, and washes. I tried everything. Some would work for a while, but they never really got to the root of the problem."**

**–Janice B., Gilbert, AZ**  
Actual Otezla patient

## Most common gastrointestinal side effects over time

In most people, the side effects of diarrhea and nausea occurred within the first 2 weeks of treatment and tended to go away over time without stopping Otezla. In some cases, patients with severe diarrhea or nausea were hospitalized. Tell your doctor if any side effects occur.



\*These studies involved 920 adults with moderate to severe plaque psoriasis who initially received Otezla 30 mg twice daily.

"n" represents the number of people participating in the studies during the given week(s).





## Errin's Otezla story: *Now she's feeling like herself again*

Errin is a published historian and doctoral candidate in European history. She's also a dancer, softball player, wife, and dog owner. In other words, Errin leads a busy life—which is why she didn't want plaque psoriasis to get in her way.

Errin started with topical treatments, but they weren't right for her—between the time commitment and the results she experienced, they just weren't worth it. Phototherapy and laser therapy worked for a while, but her plaques would always come back.

### Why she chose Otezla

After seeing a commercial for Otezla, Errin was intrigued; she liked that Otezla is a pill that works differently. "I knew there were potential side effects, but I still wanted to talk to my doctor about Otezla. I immediately called my dermatologist's office to schedule an appointment. I met with my dermatologist, and together, we decided that Otezla would be a good fit for me."

Finally, Errin feels like she's gained some of her confidence back. After taking Otezla for over a year now, she is satisfied with the results. As she puts it, "Everyone will have different results, but for me personally, Otezla is working in a way that no other treatment did."



Hear from more people taking Otezla at  
**OtezlaStories.com**



**Otezla**<sup>®</sup>  
(apremilast) 30mg  
tablets

[otezla.com](http://otezla.com)



"My skin hasn't been this clear in a long time."

—ERRIN S., NORTHVILLE, MI  
*Historian and doctoral candidate*

Please see Important Safety Information on page 14.



## Proven *results* in psoriatic arthritis

Otezla is the only pill approved for psoriatic arthritis or moderate to severe plaque psoriasis that doesn't require routine lab monitoring.

**In some people, after just 4 months, Otezla is proven to:**



**Reduce joint swelling, tenderness, and pain**



**Improve the ability to perform physical activities of daily living**

### Common side effects of Otezla

The most common side effects of Otezla were diarrhea, nausea, and headache.

### Selected Safety Information

**Otezla is associated with an increase in depression.**

In clinical studies, some patients reported depression, or suicidal behavior while taking Otezla. Some patients stopped taking Otezla due to depression. Before starting Otezla, tell your doctor if you have had feelings of depression, or suicidal thoughts or behavior. Be sure to tell your doctor if any of these symptoms or other mood changes develop or worsen during treatment with Otezla.

**Some patients taking Otezla lost body weight.**

Your doctor should monitor your weight regularly. If unexplained or significant weight loss occurs, your doctor will decide if you should continue taking Otezla.



Are you treating with methotrexate or NSAIDs\* (*a common type of pain reliever*)?

*Otezla is a different kind of pill*

Did *you* know



Up to **30% of people** with psoriasis **develop psoriatic arthritis**, which causes **pain, stiffness**, and **swelling** in and around the joints.

**Talk to your doctor if you have any of these symptoms**

*little help*  
**big impression**



\*Nonsteroidal anti-inflammatory drugs.

**Please see Important Safety Information on page 14.**





## Understanding side effects

Otezla was tested in clinical studies in 1,493 adults with active psoriatic arthritis. All patients in these studies had been diagnosed with psoriatic arthritis for at least 6 months. They ranged in age from 18 to 83 years.

In each study, some people took 30 mg of Otezla twice daily, and others took a placebo (sugar pill).

### Common side effects of Otezla

The table below shows the most common side effects reported by people taking Otezla compared to those reported by people taking a placebo (sugar pill).

Most common side effects (up to week 16)*	Otezla (493 people)	Placebo (490 people)
Nausea	9% of patients	3% of patients
Diarrhea	8%	2%
Headache	6%	2%

\*Data from day 6 through day 112 (the titration period was days 1-5, during which the dose was gradually increased until the recommended dose of 30 mg twice daily was reached).

**These are not all the possible side effects of Otezla. Tell your doctor about any side effect that bothers you or does not go away. If you're experiencing side effects, please consult your doctor.**



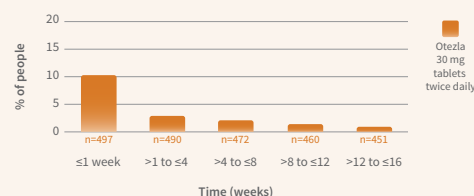
**"When I wasn't seeing any improvements on the drugs I was taking, I started searching for something that worked differently."**

**—Cindy C., Jamaica, NY**  
Actual Otezla patient

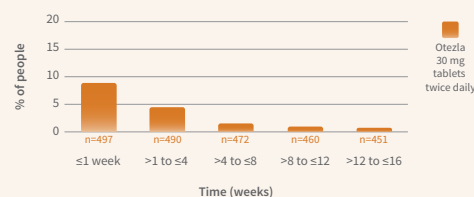
## The most common side effects over time

In most people, these common side effects of headache, diarrhea, and nausea occurred within the first 2 weeks of treatment and tended to go away over time without stopping Otezla. In some cases, patients with severe diarrhea or nausea were hospitalized. Tell your doctor if any of these occur.

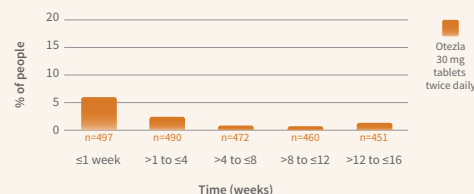
Percentage of people who experienced diarrhea while taking Otezla during clinical studies (up to week 16)\*



Percentage of people who experienced nausea while taking Otezla during clinical studies (up to week 16)\*



Percentage of people who experienced headache while taking Otezla during clinical studies (up to week 16)\*



\*These studies involved 497 adults with active psoriatic arthritis who initially received Otezla 30 mg twice daily.

"n" represents the number of people participating in the studies during the given week(s).

## Anne's Otezla story: *Crafting a path forward*

Anne is a passionate hobbyist—you name it and she does it. She sews, bakes, gardens, refinishes and reupholsters antique furniture, and even creates topiaries. She ignored her psoriatic arthritis symptoms for years, until they got so bad that she had trouble dressing herself. Finally, she went to the doctor, who was able to confirm that Anne had psoriatic arthritis.

### Something different than methotrexate

Anne tried several different treatments over the years, including methotrexate. But none gave her the results she wanted, and if she did experience some results, they didn't last. Then, Anne's doctor brought up Otezla as a different option. After they discussed the potential risks and benefits, Anne decided to give it a try.

While not everyone will have the same results, for Anne, after 4 months of treatment with Otezla, the pain and swelling in her wrists started to go down.

**Note:** In clinical studies, some people with active psoriatic arthritis had less joint pain and swelling after taking Otezla for 4 months.



Hear more from Anne:

Watch her video at [OtezlaPsAStories.com](https://www.OtezlaPsAStories.com)



**Otezla**<sup>®</sup>  
(apremilast) 30mg  
tablets

[otezla.com](https://www.otezla.com)



"I wish I would have  
started treating with  
Otezla sooner."

—ANNE C., DREXEL HILL, PA  
*Insurance agent*

Please see Important Safety Information on page 14.



## Learn about the Otezla SupportPlus program

Otezla SupportPlus™ is a **suite of services** available to you from the day you start treatment, and even before.



### Highlights of joining the SupportPlus program

**Help with insurance questions** Any insurance coverage help or assistance in working with a specialty pharmacy to get your Otezla.

**\$0 co-pay\* program** The majority of people pay nothing out of pocket for Otezla with the \$0 co-pay program.

**The Otezla Bridge Program** If you have private insurance and are experiencing delays or your private insurance doesn't cover Otezla, you may be eligible for **free medication** through the Otezla Bridge Program.†

**Assisting the uninsured or underinsured** If you have government-issued insurance (Medicare or Medicaid) or are uninsured/underinsured, you may be eligible for the **Patient Assistance Program**.

**24/7 nurse access** Otezla nurses are on staff 24/7, so you'll always have someone to talk to whenever you need them.

**Resources and ongoing support** Access to helpful tools, resources and all the information you'll need about Otezla—including the GOtezla® app to help you achieve your treatment goals.

\*Certain restrictions apply; eligibility not based on income, must be 18 years or older. This offer is not valid for persons eligible for reimbursement of this product, in whole or in part under Medicaid, Medicare, or similar state or federal programs. Offer not valid for cash-paying patients. People who are not eligible can call 1-844-4OTEZLA to discuss other financial assistance opportunities.

†To receive a free bridge supply of Otezla, you must have an on-label diagnosis and be denied or experiencing a delay in obtaining coverage. Federal, State, or similar plans are not eligible for Bridge. Once Otezla is approved by your commercial insurance plan, you will no longer be eligible for the Bridge Program.

## 3 easy ways to *sign up*

Enrolling in SupportPlus is easy, and the services are free for everyone who signs up. Here's how to join:

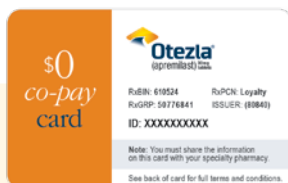
1. Go to [otezla.com/supportplus](https://otezla.com/supportplus)
2. Call **1-844-4OTEZLA** (1-844-468-3952)
3. Ask your doctor to sign you up when he or she prescribes Otezla



Please see Important Safety Information on page 14.

## Savings and cost support for Otezla

Most people with private insurance pay nothing out of pocket for their prescription. After you're prescribed, you have the same opportunity to save.



How to get the \$0 co-pay offer:

1. Go to [otezla.com/copay](https://otezla.com/copay)
2. Call 1-844-4OTEZLA (1-844-468-3952)
3. Ask your doctor about the \$0 co-pay card

## More ways to save

If you have private insurance and are experiencing delays or your private insurance doesn't cover Otezla, you may be eligible for **free medication** through the **Otezla Bridge Program**.

If you have government-issued insurance (Medicare or Medicaid) or are uninsured/underinsured, you may be eligible for the **Patient Assistance Program**.



For all Otezla savings questions:  
call 1-844-4OTEZLA (1-844-468-3952)



**Otezla**  
(apremilast) 30mg tablets

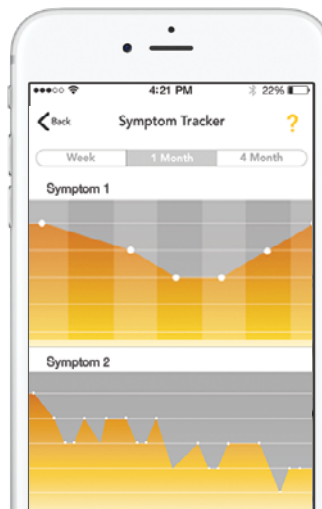
[otezla.com](https://otezla.com)

little trip  
big excitement



## Download GOtezla®

The GOtezla app has tools to track your progress, tips on what to expect during treatment, and medication reminders—and you can download it for free.



Download  
the app here

GET IT ON  
Google Play

Download on the  
App Store



## Working with your healthcare team

Plaque psoriasis and psoriatic arthritis are chronic conditions that are always there, even when you aren't experiencing symptoms. That's why open and honest communication with your healthcare team is extremely important.



Make sure you're getting the right treatment for you:

### Check in with yourself

Am I satisfied with my current treatment?

How much time do I spend daily on my current treatment regimen?

Am I having to step back from the things I love?

Am I ready for something different?

### Check in with your doctor

What makes Otezla different?

How long does it take Otezla to work?

Which symptoms will Otezla treat?

How can I save on Otezla?

What are the most common side effects of Otezla?

Does Otezla require any blood tests?



"I come to my doctor's appointments with questions, so I always get the information I need to feel comfortable."

**—Errin S., Northville, MI**  
Actual Otezla patient



Watch a patient, a dermatologist, and an Otezla SupportPlus specialist discuss what makes Otezla different at [otezla.com/learn](https://www.otezla.com/learn)



## IMPORTANT SAFETY INFORMATION

**You must not take Otezla if you are allergic to apremilast or to any of the ingredients in Otezla.**

**Otezla can cause severe diarrhea, nausea, and vomiting, especially within the first few weeks of treatment.** Use in elderly patients and the use of certain medications with Otezla appears to increase the risk of having diarrhea, nausea, or vomiting. Tell your doctor if any of these conditions occur.

**Otezla is associated with an increase in depression.**

In clinical studies, some patients reported depression, or suicidal behavior while taking Otezla. Some patients stopped taking Otezla due to depression. Before starting Otezla, tell your doctor if you have had feelings of depression, or suicidal thoughts or behavior. Be sure to tell your doctor if any of these symptoms or other mood changes develop or worsen during treatment with Otezla.

**Some patients taking Otezla lost body weight.** Your doctor should monitor your weight regularly. If unexplained or significant weight loss occurs, your doctor will decide if you should continue taking Otezla.

**Some medicines may make Otezla less effective, and should not be taken with Otezla.** Tell your doctor about all the medicines you take, including prescription and nonprescription medicines.

**Side effects of Otezla** include diarrhea, nausea, vomiting, upper respiratory tract infection, runny nose, sneezing, or congestion, abdominal pain, tension headache, and headache. These are not all the possible side effects with Otezla. Ask your doctor about other potential side effects. Tell your doctor about any side effect that bothers you or does not go away.

**Tell your doctor if you are pregnant, planning to become pregnant or planning to breastfeed.** Otezla has not been studied in pregnant women or in women who are breastfeeding.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-332-1088.

**Please see Full Prescribing Information starting on page 15.**



Need some help?  
Give us a *call*.

Our team is available 8 AM – 8 PM ET,  
Monday – Friday, at  
**1-844-4OTEZLA** (1-844-468-3952).

Ask your doctor about *Otezla*.  
With the *2-week starter pack* you  
can get started right away!

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OTEZLA® (apremilast) tablets, for oral use  
Initial U.S. approval: 2014

### RECENT MAJOR CHANGES

Indications and Usage (1.3)	07/2019
Dosage and Administration (2.1)	07/2019
Warnings and Precautions (5.2, 5.3)	07/2019

### INDICATIONS AND USAGE

OTEZLA, an inhibitor of phosphodiesterase 4 (PDE4), is indicated for the treatment of:

- Adult patients with active psoriatic arthritis (1.1)
- Patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy (1.2)
- Adult patients with oral ulcers associated with Behçet's Disease (1.3)

### DOSAGE AND ADMINISTRATION

- To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg twice daily according to the following schedule (2.1)
  - Day 1: 10 mg in morning
  - Day 2: 10 mg in morning and 10 mg in evening
  - Day 3: 10 mg in morning and 20 mg in evening
  - Day 4: 20 mg in morning and 20 mg in evening
  - Day 5: 20 mg in morning and 30 mg in evening
  - Day 6 and thereafter: 30 mg twice daily
- Dosage in Severe Renal Impairment:
  - Recommended dose is 30 mg once daily (2.2)
  - For initial dosage titration, titrate using only morning schedule listed in Table 1 and skip afternoon doses (2.2)

### DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, 20 mg, 30 mg (3)

### CONTRAINDICATIONS

Known hypersensitivity to apremilast or any excipients in formulation (4)

### WARNINGS AND PRECAUTIONS

- **Diarrhea, Nausea, and Vomiting:** Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting (5.1)
- **Depression:** Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes and if such changes occur to contact their healthcare provider. Carefully weigh risks and benefits of treatment with OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior (5.2)
- **Weight Decrease:** Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of OTEZLA (5.3)
- **Drug Interactions:** Use with strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended because loss of efficacy may occur (5.4, 7.1)

### ADVERSE REACTIONS

- **Psoriatic Arthritis:** The most common adverse reactions (≥5%) are diarrhea, nausea, and headache (6.1)
- **Psoriasis:** The most common adverse reactions (≥5%) are diarrhea, nausea, upper respiratory tract infection, and headache, including tension headache (6.1)
- **Behçet's Disease:** The most common adverse reactions (≥10%) are diarrhea, nausea, headache, and upper respiratory tract infection (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### USE IN SPECIFIC POPULATIONS

**Severe Renal Impairment:** Increased systemic exposure of OTEZLA has been observed, reduction in dose to 30 mg once daily is recommended (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2019

## FULL PRESCRIBING INFORMATION: CONTENTS\*

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



FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Psoriatic Arthritis

OTEZLA is indicated for the treatment of adult patients with active psoriatic arthritis.

1.2 Psoriasis

OTEZLA is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.3 Oral Ulcers Associated with Behçet’s Disease

OTEZLA is indicated for the treatment of adult patients with oral ulcers associated with Behçet’s Disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Psoriatic Arthritis, Psoriasis, and Behçet’s Disease

The recommended initial dosage titration of OTEZLA from Day 1 to Day 5 is shown in Table 1. Following the 5-day titration, the recommended maintenance dosage is 30 mg twice daily taken orally starting on Day 6. This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy.

OTEZLA can be administered without regard to meals. Do not crush, split, or chew the tablets.

Table 1: Dosage Titration Schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

2.2 Dosage Adjustment in Patients with Severe Renal Impairment

OTEZLA dosage should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance (CLcr) of less than 30 mL per minute estimated by the Cockcroft–Gault equation) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]. For initial dosage titration in this group, it is recommended that OTEZLA be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped.

3 DOSAGE FORMS AND STRENGTHS

OTEZLA is available as diamond shaped, film coated tablets in the following dosage strengths:

- 10-mg pink tablet engraved with “APR” on one side and “10” on the other side
- 20-mg brown tablet engraved with “APR” on one side and “20” on the other side
- 30-mg beige tablet engraved with “APR” on one side and “30” on the other side.

4 CONTRAINDICATIONS

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see Adverse Reactions (6.1)].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Diarrhea, Nausea, and Vomiting

There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases, patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

### 5.2 Depression

Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

Psoriatic arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of subjects treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo-treated subjects (0/495). Depression was reported as serious in 0.2% (3/1441) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of subjects while receiving OTEZLA, compared to none in placebo-treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA-treated subjects.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of subjects treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/1308) of subjects treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated subjects (0/506). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated subjects. In the clinical trials, one subject treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Behçet's disease: During the placebo-controlled period of the phase 3 study, 1% (1/104) of patients treated with OTEZLA reported depression/depressed mood compared to 1% (1/103) treated with placebo. None of these reports of depression was serious or led to study discontinuation. No instances of suicidal ideation or behavior were reported during the placebo-controlled period of the phase 3 study in patients treated with OTEZLA (0/104) or treated with placebo (0/103).

### 5.3 Weight Decrease

During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (49/497) of subjects treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo.

During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of subjects treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of  $\geq 10\%$  of body weight occurred in 2% (16/784) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3/382) subjects treated with placebo.

During the controlled period of the phase 3 study in Behçet's disease, weight decrease  $>5\%$  of body weight was reported in 4.9% (5/103) of subjects treated with OTEZLA 30 mg twice daily compared to 3.9% (4/102) patients treated with placebo.

Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered [see *Adverse Reactions* (6.1)].

### 5.4 Drug Interactions

Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.3)].

## 6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Diarrhea, Nausea, and Vomiting [see *Warnings and Precautions* (5.1)]
- Depression [see *Warnings and Precautions* (5.2)]
- Weight Decrease [see *Warnings and Precautions* (5.3)]
- Drug Interactions [see *Warnings and Precautions* (5.4)]

### 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 clinical practice.

#### Psoriatic Arthritis Clinical Trials

OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials [Studies PsA-1, PsA-2, and PsA-3] of similar design in adult patients with active psoriatic arthritis [see *Clinical Studies* (14.1)]. Across the 3 studies, there were 1493 patients randomized equally to placebo, OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titration was used over the first 5 days [see *Dosage and Administration* (2.1)]. Placebo patients whose tender and swollen joint counts had not improved by at least 20% were re-randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or 30 mg twice daily at week 16 while OTEZLA patients remained on their initial treatment. Patients ranged in age from 18 to 83 years, with an overall median age of 51 years.

The majority of the most common adverse reactions presented in Table 2 occurred within the first 2 weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of patients with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

**Table 2: Adverse Reactions Reported in ≥2% of Patients on OTEZLA 30 mg Twice Daily and ≥1% Than That Observed in Patients on Placebo for up to Day 112 (Week 16)**

Preferred Term	Placebo		OTEZLA 30 mg BID	
	Day 1 to 5 (N=495) n (%) <sup>c</sup>	Day 6 to Day 112 (N=490) n (%)	Day 1 to 5 (N=497) n (%)	Day 6 to Day 112 (N=493) n (%)
Diarrhea <sup>a</sup>	6 (1.2)	8 (1.6)	46 (9.3)	38 (7.7)
Nausea <sup>a</sup>	7 (1.4)	15 (3.1)	37 (7.4)	44 (8.9)
Headache <sup>a</sup>	9 (1.8)	11 (2.2)	24 (4.8)	29 (5.9)
Upper respiratory tract infection <sup>b</sup>	3 (0.6)	9 (1.8)	3 (0.6)	19 (3.9)
Vomiting <sup>a</sup>	2 (0.4)	2 (0.4)	4 (0.8)	16 (3.2)
Nasopharyngitis <sup>b</sup>	1 (0.2)	8 (1.6)	1 (0.2)	13 (2.6)
Abdominal pain upper <sup>b</sup>	0 (0.0)	1 (0.2)	3 (0.6)	10 (2.0)

<sup>a</sup> Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in OTEZLA 30 mg twice daily; 1 subject treated with OTEZLA 20 mg twice daily experienced a serious adverse reaction of diarrhea; 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction of headache.

<sup>b</sup> Of the reported adverse drug reactions none were serious.

<sup>c</sup> n (%) indicates number of patients and percent.

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies:

**Immune system disorders:** Hypersensitivity

**Investigations:** Weight decrease

**Gastrointestinal Disorders:** Frequent bowel movement, gastroesophageal reflux disease, dyspepsia

**Metabolism and Nutrition Disorders:** Decreased appetite\*



**Nervous System Disorders:** Migraine

**Respiratory, Thoracic, and Mediastinal Disorders:** Cough

**Skin and Subcutaneous Tissue Disorders:** Rash

\*1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

#### Psoriasis Clinical Trials

The safety of OTEZLA was assessed in 1426 subjects in 3 randomized, double-blind, placebo-controlled trials in adult subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Subjects were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days [see *Dosage and Administration (2.1)*]. Subjects ranged in age from 18 to 83 years, with an overall median age of 46 years.

Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking OTEZLA were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for subjects treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated subjects.

**Table 3: Adverse Reactions Reported in ≥1% of Subjects on OTEZLA and With Greater Frequency Than in Subjects on Placebo; up to Day 112 (Week 16)**

<b>Preferred Term</b>	<b>Placebo (N=506) n (%)</b>	<b>OTEZLA 30 mg BID (N=920) n (%)</b>
Diarrhea	32 (6)	160 (17)
Nausea	35 (7)	155 (17)
Upper respiratory tract infection	31 (6)	84 (9)
Tension headache	21 (4)	75 (8)
Headache	19 (4)	55 (6)
Abdominal pain*	11 (2)	39 (4)
Vomiting	8 (2)	35 (4)
Fatigue	9 (2)	29 (3)
Dyspepsia	6 (1)	29 (3)
Decreased appetite	5 (1)	26 (3)
Insomnia	4 (1)	21 (2)
Back pain	4 (1)	20 (2)
Migraine	5 (1)	19 (2)
Frequent bowel movements	1 (0)	17 (2)
Depression	2 (0)	12 (1)
Bronchitis	2 (0)	12 (1)
Tooth abscess	0 (0)	10 (1)
Folliculitis	0 (0)	9 (1)
Sinus headache	0 (0)	9 (1)

\*Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.

Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) subjects following discontinuation of treatment with OTEZLA.

#### Behçet's Disease Clinical Trials

OTEZLA was evaluated in a Phase 3, multicenter, randomized, placebo-controlled study (BCT-002) in adult patients with Behçet's Disease (BD) with active oral ulcers. A total of 207 patients were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days [see *Dosage and Administration (2.1)*]. After Week 12, all patients received treatment with OTEZLA 30 mg twice daily. Patients ranged in age from 19 to 72, with a mean age of 40 years.

Diarrhea, nausea, headache, and upper respiratory tract infection were the most commonly reported adverse reactions. The proportion of patients with BD who discontinued treatment due to any adverse reaction during the placebo-controlled period of the study, was 2.9% for patients treated with OTEZLA 30 mg twice daily and 4.9% for placebo-treated patients.

**Table 4: Adverse Reactions Reported in ≥5% of Patients on OTEZLA and with at least 1% Greater Frequency than Patients on Placebo; up to Week 12**

Preferred Term	Placebo (N=103) n (%)	OTEZLA 30 mg twice daily (N=104) n (%)
Diarrhea <sup>a</sup>	21 (20.4)	43 (41.3)
Nausea <sup>a</sup>	11 (10.7)	20 (19.2)
Headache	11 (10.7)	15 (14.4)
Upper respiratory tract infection	5 (4.9)	12 (11.5)
Abdominal pain upper	2 (1.9)	9 (8.7)
Vomiting <sup>a</sup>	2 (1.9)	9 (8.7)
Back pain	6 (5.8)	8 (7.7)
Viral upper respiratory tract infection	5 (4.9)	7 (6.7)
Arthralgia	3 (2.9)	6 (5.8)

<sup>a</sup> There were no serious adverse reactions of diarrhea, nausea or vomiting.

## 7 DRUG INTERACTIONS

### 7.1 Strong CYP450 Inducers

Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting <https://mothertobaby.org/ongoing-study/otezla/>.

#### Risk Summary

Available pharmacovigilance data with OTEZLA use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but these data are extremely limited. Based on findings from animal reproduction studies, OTEZLA may increase the risk for fetal loss. In animal embryo-fetal development studies, the administration of apremilast to pregnant cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. When administered to pregnant mice, during organogenesis there were no apremilast-induced malformations up to exposures 4.0-times the MRHD (see Data). Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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*

In an embryo-fetal developmental study, pregnant cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation Days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during Weeks 3 to 4 of dosing in the first trimester, at doses approximately 2.1-times the MRHD and greater (on an area under the curve [AUC] basis at doses ≥50 mg/kg/day). No abortifacient effects were observed at a dose approximately 1.4-times the MRHD (on an AUC basis at a dose of 20 mg/kg/day). Although, there was no evidence for a teratogenic effect at doses of 20 mg/kg/day and greater when examined at day 100, aborted fetuses were not examined.

In an embryo-fetal development study in mice, apremilast was administered at doses of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation Day 6 through 15). In a combined fertility and embryo-fetal development study in mice, apremilast was administered at doses of 10, 20, 40, or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation Day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of 2.3-times the MRHD and greater (≥20 mg/kg/day). At doses of ≥20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose

approximately 1.3-times the MRHD (10 mg/kg/day).

Apremilast distributed across the placenta into the fetal compartment in mice and monkeys.

In a pre- and postnatal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from Day 6 of gestation through Day 20 of lactation, with weaning on Day 21. Dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to  $\geq 4.0$ -times the MRHD (on an AUC basis at doses  $\geq 80$  mg/kg/day). No adverse effects occurred at a dose 1.3-times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to 7.5-times the MRHD (on an AUC basis at a dose of 300 mg/kg/day).

## 8.2 Lactation

### Risk Summary

There are no data on the presence of apremilast in human milk, the effects on the breastfed infant, or the effects on milk production. However, apremilast was detected in the milk of lactating mice. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OTEZLA and any potential adverse effects on the breastfed infant from OTEZLA or from the underlying maternal condition.

### Data

In mice, following a single oral administration of 10 mg/kg to dams on postpartum day 13, apremilast concentrations in milk were approximately 1.5-times that of simultaneously collected blood samples.

## 8.4 Pediatric Use

The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established.

## 8.5 Geriatric Use

Of the 1493 subjects who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis subjects were 65 years of age and older, including 19 subjects 75 years and older. No overall differences were observed in the safety profile of elderly subjects  $\geq 65$  years of age and younger adult subjects  $< 65$  years of age in the clinical studies.

Of the 1257 subjects who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis subjects were 65 years of age and older, including 9 subjects who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly subjects  $\geq 65$  years of age and younger adult subjects  $< 65$  years of age in the clinical trials.

## 8.6 Renal Impairment

Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft–Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)].

## 8.7 Hepatic Impairment

Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

# 10 OVERDOSAGE

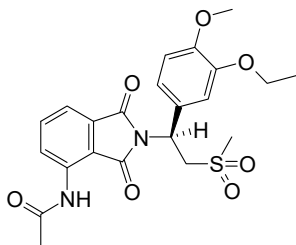
In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

# 11 DESCRIPTION

The active ingredient in OTEZLA tablets is apremilast. Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. Apremilast is known chemically as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1H-indol-4-yl]acetamide. Its empirical formula is  $C_{22}H_{24}N_2O_7S$  and the molecular weight is 460.5.



The chemical structure is:



OTEZLA tablets are supplied in 10-, 20-, and 30-mg strengths for oral administration. Each tablet contains apremilast as the active ingredient and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, iron oxide yellow (20 and 30 mg only) and iron oxide black (30 mg only).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels. The specific mechanism(s) by which apremilast exerts its therapeutic action is not well defined.

### 12.3 Pharmacokinetics

#### Absorption

Apremilast when taken orally is absorbed with an absolute bioavailability of ~73%, with peak plasma concentrations ( $C_{\max}$ ) occurring at a median time ( $t_{\max}$ ) of ~2.5 hours. Co-administration with food does not alter the extent of absorption of apremilast.

#### Distribution

Human plasma protein binding of apremilast is approximately 68%. Mean apparent volume of distribution ( $V_d$ ) is 87 L.

#### Metabolism

Following oral administration in humans, apremilast is a major circulating component (45%) followed by inactive metabolite M12 (39%), a glucuronide conjugate of O-demethylated apremilast. It is extensively metabolized in humans with up to 23 metabolites identified in plasma, urine and feces. Apremilast is metabolized by both cytochrome (CYP) oxidative metabolism with subsequent glucuronidation and non-CYP mediated hydrolysis. In vitro, CYP metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6.

#### Elimination

The plasma clearance of apremilast is about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 6-9 hours. Following oral administration of radio-labeled apremilast, about 58% and 39% of the radioactivity is recovered in urine and feces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and feces, respectively.

#### Specific Populations

**Hepatic Impairment:** The pharmacokinetics of apremilast is not affected by moderate or severe hepatic impairment.

**Renal Impairment:** The pharmacokinetics of apremilast is not affected by mild or moderate renal impairment. In 8 subjects with severe renal impairment administered a single dose of 30 mg apremilast, the AUC and  $C_{\max}$  of apremilast increased by approximately 88% and 42%, respectively [see *Dosage and Administration* (2.2) and *Use in Specific Populations* (8.6)].

**Age:** A single oral dose of 30-mg apremilast was studied in young adults and elderly healthy subjects. The apremilast exposure in elderly subjects (65 to 85 years of age) was about 13% higher in AUC and about 6% higher in  $C_{\max}$  than in young subjects (18 to 55 years of age) [see *Use in Specific Populations* (8.5)].

**Gender:** In pharmacokinetic studies in healthy volunteers, the extent of exposure in females was about 31% higher and  $C_{max}$  was about 8% higher than that in male subjects.

**Race and Ethnicity:** The pharmacokinetics of apremilast in Chinese and Japanese healthy male subjects is comparable to that in Caucasian healthy male subjects. In addition, apremilast exposure is similar among Hispanic Caucasians, non-Hispanic Caucasians, and African Americans.

#### Drug Interactions

**In vitro data:** Apremilast is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 and not an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4. Apremilast is a substrate, but not an inhibitor of P-glycoprotein (P-gp) and is not a substrate or an inhibitor of organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP).

Drug interaction studies were performed with apremilast and CYP3A4 substrates (oral contraceptive containing ethinyl estradiol and norgestimate), CYP3A and P-gp inhibitor (ketoconazole), CYP450 inducer (rifampin) and frequently co-administered drug in this patient population (methotrexate).

No significant pharmacokinetic interactions were observed when 30-mg oral apremilast was administered with either oral contraceptive, ketoconazole, or methotrexate. Co-administration of the CYP450 inducer rifampin (600 mg once daily for 15 days) with a single oral dose of 30-mg apremilast resulted in reduction of apremilast AUC and  $C_{max}$  by 72% and 43%, respectively [see *Warnings and Precautions (5.3) and Drug Interactions (7.1)*].

### **13 NONCLINICAL TOXICOLOGY**

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

Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors was observed in mice at oral doses up to 8.8-times the Maximum Recommended Human Dose (MRHD) on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively).

Apremilast tested negative in the Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay.

In a fertility study of male mice, apremilast at oral doses up to approximately 3-times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral doses of 10, 20, 40, or 80 mg/kg/day. At doses  $\geq 1.8$ -times the MRHD ( $\geq 20$  mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early postimplantation losses. There was no effect of apremilast approximately 1.0-times the MRHD (10 mg/kg/day).

### **14 CLINICAL STUDIES**

#### **14.1 Psoriatic Arthritis**

The safety and efficacy of OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials (Studies PsA-1, PsA-2, and PsA-3) of similar design. A total of 1493 adult patients with active PsA ( $\geq 3$  swollen joints and  $\geq 3$  tender joints) despite prior or current treatment with disease-modifying antirheumatic drug (DMARD) therapy were randomized. Patients enrolled in these studies had a diagnosis of PsA for at least 6 months. One qualifying psoriatic skin lesion of at least 2 cm in diameter was required in Study PsA- 3. Previous treatment with a biologic, including TNF-blockers was allowed (up to 10% could be TNF-blocker therapeutic failures). Across the 3 studies, patients were randomly assigned to placebo (n=496), OTEZLA 20 mg (n=500), or OTEZLA 30 mg (n=497) given orally twice daily. Titration was used over the first 5 days [see *Dosage and Administration (2.1)*]. Patients were allowed to receive stable doses of concomitant methotrexate [MTX ( $\leq 25$  mg/week)], sulfasalazine [SSZ ( $\leq 2$  g/day)], leflunomide [LEF ( $\leq 20$  mg/day)], low dose oral corticosteroids (equivalent to  $\leq 10$  mg of prednisone a day), and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the trial. Treatment assignments were stratified based on small-molecule DMARD use at baseline in Studies PsA-1, PsA-2 and PsA-3. There was an additional stratification of BSA  $>3\%$  with psoriasis in study PsA-3. The patients who were therapeutic failures of  $>3$  agents for PsA (small molecules or biologics), or  $>1$  biologic TNF blocker were excluded.

The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16. Placebo-controlled efficacy data were collected and analyzed through Week 24. Patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo non-responders were re-randomized 1:1 in a blinded fashion



to either OTEZLA 20 mg twice daily or 30 mg twice daily following the titration schema [see Dosage and Administration (2.1)]. OTEZLA patients remained on their initial treatment. At Week 24, all remaining placebo patients were re-randomized to either 20 mg twice daily or 30 mg twice daily.

Patients with subtypes of PsA were enrolled across the 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (27.0%), distal interphalangeal (DIP) joint arthritis (6.0%), arthritis mutilans (3.0%), and predominant spondylitis (2.1%). The median duration of PsA disease was 5 years. Patients received concomitant therapy with at least one DMARD (65.0%), MTX (55.0%), SSZ (9.0%), LEF (7.0%), low dose oral corticosteroids (14.0%), and NSAIDs (71.0%). Prior treatment with small-molecule DMARDs only was reported in 76.0% of patients and prior treatment with biologic DMARDs was reported in 22.0% of patients, which includes 9.0% who had failed prior biologic DMARD treatment.

Clinical Response in Patients with Psoriatic Arthritis

The percent of patients achieving ACR 20, 50 and 70 responses in Studies PsA-1, PsA-2, and PsA-3 are presented in Table 5 below. OTEZLA ± DMARDs, compared with Placebo ± DMARDs resulted in a greater improvement in signs and symptoms of psoriatic arthritis as demonstrated by the proportion of patients with an ACR 20 response at Week 16.

Table 5: Proportion of Patients With ACR Responses in Studies PsA-1, PsA-2 and PsA-3

	PsA-1		PsA-2		PsA-3	
	Placebo ± DMARDs	OTEZLA 30 mg twice daily ± DMARDs	Placebo ± DMARDs	OTEZLA 30 mg twice daily ± DMARDs	Placebo ± DMARDs	OTEZLA 30 mg twice daily ± DMARDs
N <sup>a</sup>	N=168	N=168	N=159	N=162	N=169	N=167
<u>ACR 20</u> Week 16	19%	38% <sup>b</sup>	19%	32% <sup>b</sup>	18%	41% <sup>b</sup>
<u>ACR 50</u> Week 16	6%	16%	5%	11%	8%	15%
<u>ACR 70</u> Week 16	1%	4%	1%	1%	2%	4%

<sup>a</sup> N is number of randomized and treated patients.

<sup>b</sup> Statistically significantly different from placebo (p<0.05).

OTEZLA 30 mg twice daily resulted in improvement for each ACR component, compared to placebo at Week 16 in Study PsA-1 (Table 6). Consistent results were observed in Studies PsA-2 and PsA-3.

Table 6: ACR Components Mean Change from Baseline at Week 16 in Study PsA- 1

	Placebo (N*=168)	OTEZLA 30 mg twice daily (N*=168)
Number of tender joints <sup>a</sup>		
Sample Size	166	164
Baseline	23	23
Mean Change at Week 16	-2	-7
Number of swollen joints <sup>b</sup>		
Sample Size	166	164
Baseline	13	13
Mean Change at Week 16	-2	-5
Patient's assessment of pain <sup>c</sup>		
Sample Size	165	159
Baseline	61	58
Mean Change at Week 16	-6	-14

Patient's global assessment of disease activity <sup>c</sup>		
Sample Size	165	159
Baseline	59	56
Mean Change at Week 16	-3	-10
Physician's global assessment of disease activity <sup>c</sup>		
Sample Size	158	159
Baseline	55	56
Mean Change at Week 16	-8	-19
HAQ-DI <sup>d</sup> score		
Sample Size	165	159
Baseline	1.2	1.2
Mean Change at Week 16	-0.09	-0.2
CRP <sup>e</sup>		
Sample Size	166	167
Baseline	1.1	0.8
Mean Change at Week 16	0.1	-0.1

Mean changes from baseline are least square means from analyses of covariance.

<sup>a</sup> Scale 0-78.

<sup>b</sup> Scale 0-76.

<sup>c</sup> VAS=Visual Analog Scale; 0=best, 100=worst.

<sup>d</sup> HAQ-DI=Health Assessment Questionnaire-Disability Index; 0=best, 3=worst; measures the subject's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

<sup>e</sup> CRP=C-reactive protein; Reference range 0-0.5 mg/dL.

\* N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.

Treatment with OTEZLA resulted in improvement in dactylitis and enthesitis in patients with pre-existing dactylitis or enthesitis.

## Physical Function Response

OTEZLA 30 mg twice daily demonstrated a greater improvement compared to placebo in mean change from baseline for the Health Assessment Questionnaire Disability Index (HAQ-DI) score at Week 16 [-0.244 vs. -0.086, respectively; 95% CI for the difference was (-0.26, -0.06)] in Study PsA-1. The proportions of HAQ-DI responders ( $\geq 0.3$  improvement from baseline) at Week 16 for the OTEZLA 30 mg twice daily group were 38%, compared to 27%, for the placebo group in Study PsA-1. Consistent results were observed in Studies PsA-2 and PsA-3.

## 14.2 Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled trials (Studies PSOR-1 and PSOR-2) enrolled a total of 1257 subjects 18 years of age and older with moderate to severe plaque psoriasis [body surface area (BSA) involvement of  $\geq 10\%$ , static Physician Global Assessment (sPGA) of  $\geq 3$  (moderate or severe disease), Psoriasis Area and Severity Index (PASI) score  $\geq 12$ , candidates for phototherapy or systemic therapy]. Subjects were allowed to use low-potency topical corticosteroids on the face, axilla and groin. Subjects with scalp psoriasis were allowed to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions.

Study PSOR-1 enrolled 844 subjects and Study PSOR-2 enrolled 413 subjects. In both studies, subjects were randomized 2:1 to OTEZLA 30 mg BID or placebo for 16 weeks. Both studies assessed the proportion of subjects who achieved PASI-75 at Week 16 and the proportion of subjects who achieved a sPGA score of clear (0) or almost clear (1) at Week 16. Across both studies, subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. The mean baseline BSA involvement was 25.19% (median 21.0%), the mean baseline PASI score was 19.07 (median 16.80), and the proportion of subjects with sPGA score of 3 (moderate) and 4 (severe) at baseline were 70.0% and 29.8%, respectively. Approximately 30% of all subjects had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one-third of subjects had not received prior phototherapy, conventional systemic nor biologic therapy. A total of 18% of subjects had a history of psoriatic arthritis.

## Clinical Response in Subjects with Plaque Psoriasis

The proportion of subjects who achieved PASI -75 responses, and sPGA score of clear (0) or almost clear (1), are presented in [Table 7](#).

**Table 7: Clinical Response at Week 16 in Studies PSOR-1 and PSOR-2**

	Study PSOR-1		Study PSOR-2	
	Placebo	OTEZLA 30 mg BID	Placebo	OTEZLA 30 mg BID
<b>N<sup>a</sup></b>	<b>N=282</b>	<b>N=562</b>	<b>N=137</b>	<b>N=274</b>
<b>PASI<sup>b</sup> -75, n (%)</b>	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
<b>sPGA<sup>c</sup> of Clear or Almost Clear, n (%)</b>	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)

<sup>a</sup> N is number of randomized and treated patients.

<sup>b</sup> PASI=Psoriasis Area and Severity Index.

<sup>c</sup> sPGA=Static Physician Global Assessment.

The median time to loss of PASI-75 response among the subjects re-randomized to placebo at Week 32 during the Randomized Treatment Withdrawal Phase was 5.1 weeks.

### 14.3 Oral Ulcers Associated with Behçet's Disease

A multicenter, randomized, placebo-controlled trial (BCT-002) enrolled a total of 207 adult patients with BD with active oral ulcers. Patients were previously treated with at least one nonbiologic BD medication and were candidates for systemic therapy. Patients met the International Study Group (ISG) Criteria for BD. Patients had at least 2 oral ulcers at screening and at least 2 oral ulcers at randomization and without currently active major organ involvement. Concomitant treatment for BD was not allowed.

Patients were randomized 1:1 to receive either OTEZLA 30 mg twice daily (n=104) or placebo (n=103) for 12 weeks. After Week 12, all patients received OTEZLA 30 mg twice daily.

Efficacy was assessed based on the number and pain of oral ulcers.

Patients ranged in age from 19 to 72, with a mean age of 40 years. The mean duration of BD was 6.84 years. All subjects had a history of recurrent oral ulcers that were currently active. Subjects had a history of skin lesions (98.6%), genital ulcers (90.3%), musculoskeletal manifestations (72.5%), ocular manifestations (17.4%), central nervous system (9.7%), gastrointestinal (GI) manifestations (9.2%) and vascular involvement (1.4%). The mean baseline oral ulcer counts were 4.2 and 3.9 in the OTEZLA and placebo groups, respectively.

#### Measures of Oral Ulcers

Improvements in measures of oral ulcers at Week 12 are presented in [Table 8](#).

**Table 8: Clinical Response of Oral Ulcers at Week 12 in the BCT-002 Study (ITT<sup>a</sup> Population)**

<b>Endpoint</b>	<b>Placebo N=103</b>	<b>OTEZLA 30 mg twice daily N=104</b>	<b>Treatment Difference<sup>b</sup> (95% CI)<sup>c</sup></b>
Change <sup>d</sup> from baseline in the pain of oral ulcers as measured by VAS <sup>e</sup> at Week 12	-18.7	- 42.7	-24.1 (-32.4, -15.7)
Proportion <sup>f</sup> of subjects achieving oral ulcer complete response (oral ulcer-free) at Week 12	22.3%	52.9%	30.6% <sup>g</sup> (18.1%, 43.1%)
Proportion <sup>f</sup> of subjects achieving oral ulcer complete response (oral ulcer-free) by Week 6, and who remained oral ulcer-free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase	4.9%	29.8%	25.1% <sup>g</sup> (15.5%, 34.6%)

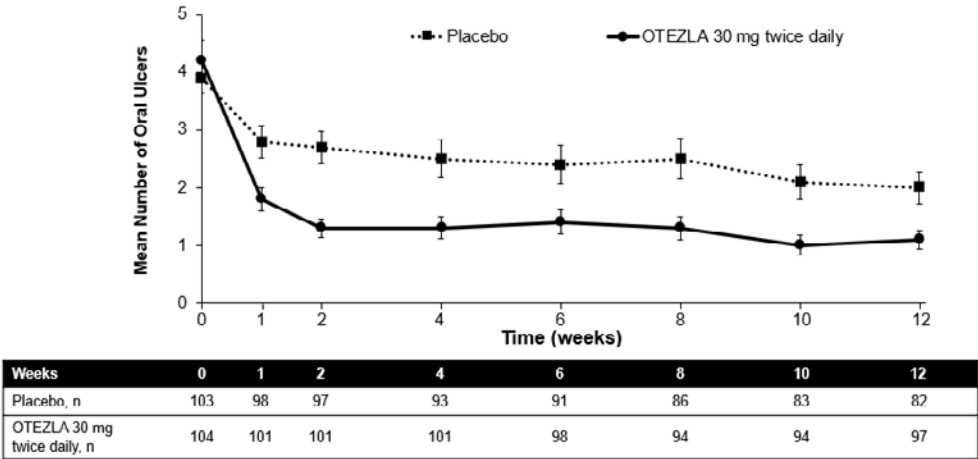


Daily average <sup>h,i</sup> number of oral ulcers during the 12-week Placebo-controlled Treatment Phase	2.6	1.5	-1.1 (-1.6, -0.7)
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<sup>a</sup> ITT=intent to treat.  
<sup>b</sup> OTEZLA – Placebo.  
<sup>c</sup> CI=confidence interval.  
<sup>d</sup> Mean changes from baseline are least square means from mixed-effects model for repeated measures, adjusting for sex, region, and baseline pain of oral ulcers as measured by the visual analog scale.  
<sup>e</sup> VAS=visual analog scale; 0=no pain, 100=worst possible pain.  
<sup>f</sup> Patients for whom data are not available to determine response status are considered non-responders.  
<sup>g</sup> Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the Cochran-Mantel-Haenszel weights.  
<sup>h</sup> Mean daily averages are least squares means from analysis of covariance, after adjusting for sex, region, and baseline number of oral ulcers.  
<sup>i</sup> Based on oral ulcer counts measured at baseline and at Weeks 1, 2, 4, 6, 8, 10, and 12.

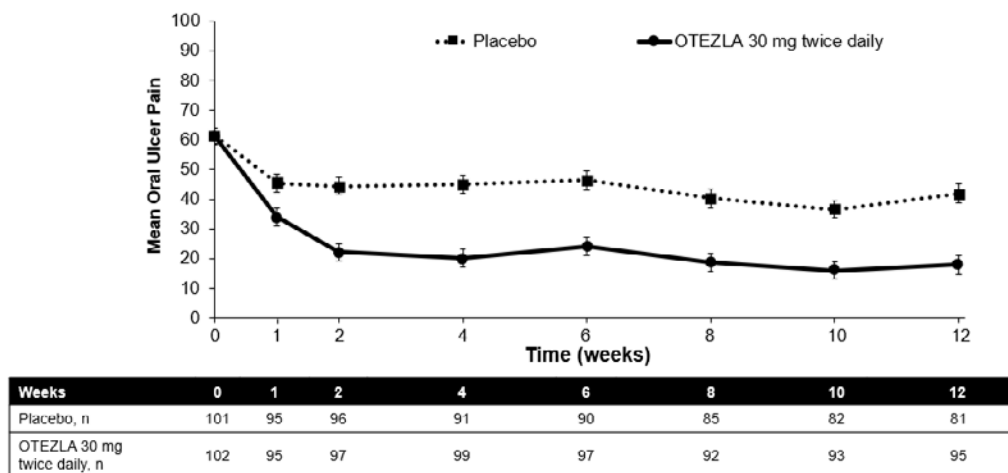
Figure 1 displays the mean number of oral ulcers for each treatment group at each visit, while Figure 2 displays the mean oral ulcer pain on a visual analog scale for each treatment group at each visit.

Figure 1: Mean (± SE) Number of Oral Ulcers by Time Point Through Week 12 (ITT Population)



ITT = intent-to-treat; SE = standard error.

**Figure 2: Mean ( $\pm$  SE) Oral Ulcer Pain on a Visual Analog Scale by Time Point Through Week 12 (ITT Population)**



ITT=intent-to-treat; SE=standard error.

Oral ulcer pain was assessed on a 100-mm Visual Analog Scale with 0 = no pain and 100 = worst possible pain. Mean baseline Visual Analog Scale pain scores were 61.2 and 60.8 in the OTEZLA 30 mg twice daily treatment group and placebo treatment group, respectively.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

OTEZLA is available as diamond-shaped, film-coated tablets in the following dosage strengths: 10-mg pink tablet engraved with “APR” on one side and “10” on the other side; 20-mg brown tablet engraved with “APR” on one side and “20” on the other side; 30-mg beige tablet engraved with “APR” on one side and “30” on the other side.

Tablets are supplied in the following strengths and package configurations:

Package configuration	Tablet strength	NDC number
Bottles of 60	30 mg	59572-631-06
Two-week starter pack	13-tablet blister titration pack containing: (4) 10-mg, (4) 20-mg, and (5) 30-mg tablets with an additional (14) 30-mg tablets	59572-630-27
28-count carton	Two 30-mg blister cards containing (14) 30-mg tablets	59572-631-28
28-day starter pack	13-tablet blister titration pack containing: (4) 10-mg, (4) 20-mg, and (5) 30-mg tablets with an additional (42) 30-mg tablets	59572-632-55

### Storage and Handling

Store tablets below 30°C (86°F).

## 17 PATIENT COUNSELING INFORMATION

### • Diarrhea, Nausea, and Vomiting

Instruct patients to contact their healthcare provider if they experience severe diarrhea, nausea, or vomiting. Prescribers should advise patients of the potential complications of severe diarrhea, nausea, or vomiting. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting [see *Warnings and Precautions* (5.1)].

- **Depression**

Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur [see *Warnings and Precautions* (5.2)].

- **Weight Decrease**

Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered [see *Warnings and Precautions* (5.3)].

- **Drug Interactions**

The use of strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended [see *Warnings and Precautions* (5.4), *Drug Interactions* (7.1), and *Clinical Pharmacology* (12.3)].

- Instruct patients to take OTEZLA only as prescribed.
- Advise patients OTEZLA can be taken with or without food.
- Advise patients that the tablets should not be crushed, split, or chewed.
- Advise patients about the side effects associated with OTEZLA [see *Adverse Reactions* (6.1)].

- **Pregnancy**

Inform patients that there is a pregnancy registry for pregnant women who have taken OTEZLA during pregnancy. Advise patients to contact the registry at 1-877-311-8972 to enroll or visit <https://mothertobaby.org/ongoing-study/otezla/> [see *Use in Specific Populations* (8.1)]. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy.

Manufactured for: Celgene Corporation  
Summit, NJ 07901

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Pat. <http://www.celgene.com/therapies>

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