Si vive con **psoriasis en placas** de moderada a grave o **artritis psoriásica**, los pequeños momentos pueden tener un gran significado.

Otezla es un medicamento de venta con receta, aprobado para el tratamiento de pacientes que padecen de psoriasis en placas de moderada a grave para quienes resulta adecuada la fototerapia o la terapia sistémica.

También está aprobado para el tratamiento de pacientes adultos con artritis psoriásica activa.

Consulte la Información Importante de Seguridad en la página 14.

*Se aplican ciertas restricciones.

Otezla® (apremilast) 30mg tablets

Contenido:

¿Le está resultando su tratamiento actual?

Si la respuesta es negativa, piense en Otezla; una tableta que actúa diferente.

*Se aplican ciertas restricciones; la elegibilidad no se basa en los ingresos.

†Fuente: Symphony Health Solutions PrescriberSource PatientFocus, metodología de propiedad de Amgen. Enero de 2016–Enero de 2020. Los datos incluyen solo las formulaciones para uso oral para las recetas etiquetadas con una indicación para la psoriasis en placas.

‡Fuente: Symphony Health Solutions PrescriberSource PatientFocus, metodología de propiedad de Amgen. Enero de 2016–Enero de 2020. Los datos incluyen solo las formulaciones para uso oral para las recetas etiquetadas con una indicación para la artritis psoriásica.

No es una inyección, una crema ni un producto biológico; *Otezla es una tableta*

En los casos de psoriasis en placas de moderada a grave

algunas personas logran una **piel un 75% más clara** después de tan solo 4 meses de tratamiento, con una **reducción del enrojecimiento, el espesor y la descamación** de las placas

En los casos de artritis psoriásica

Otezla puede ayudar a **reducir la inflamación**, la **sensibilidad** y el **dolor de las articulaciones de algunas personas con artritis psoriásica** después de tan solo 4 meses de tratamiento

No se necesitan análisis de sangre

La Información sobre la Prescripción de Otezla **no exige análisis de sangre** iniciales o de rutina

Otezla es la *tableta* de marca recetada #1 para la *psoriasis en placas*† o la *artritis psoriásica*‡

Efectos secundarios de Otezla

Los efectos secundarios más comunes de Otezla en las personas con psoriasis en placas fueron diarrea, náuseas, infección de las vías respiratorias superiores, dolor de cabeza por tensión y dolor de cabeza común.

Los efectos secundarios más comunes de Otezla en las personas con artritis psoriásica fueron diarrea, náuseas y dolor de cabeza común.

Consulte la Información Importante de Seguridad en la página 14.

¿Cómo empiezan la psoriasis en placas y la artritis psoriásica?

La psoriasis en placas y la artritis psoriásica son **enfermedades crónicas**, lo que significa que están siempre ahí (incluso cuando usted no tiene ningún síntoma).

Tanto la psoriasis en placas como la artritis psoriásica están asociadas con una inflamación hiperactiva dentro del cuerpo. Las investigaciones de laboratorio han demostrado que una enzima conocida como fosfodiesterasa 4 (PDE4), que se encuentra en las células, contribuye a la inflamación.

Se cree que la **inflamación hiperactiva es responsable de los síntomas** de la psoriasis en placas y la artritis psoriásica.

El papel de la inflamación hiperactiva

En la psoriasis en placas:

Se cree que acelera el ciclo de crecimiento de las células de la piel

↓

Con el tiempo, las células de la piel se acumulan y producen placas rojas y elevadas en la piel que dan comezón

En la artritis psoriásica:

Se cree que hace que el tejido que rodea las articulaciones se engrose

↓

Con el tiempo, el tejido engrosado provoca dolor e inflamación en las articulaciones

¿Lo sabía?

Otezla es una tableta que actúa dentro del cuerpo para ayudar a reducir la inflamación.

"Vivir con artritis psoriásica es desafiante e impredecible. Uno no sabe si al levantarse un día va a tener dificultad para caminar".

–Cindy C., Jamaica, NY
Paciente real de Otezla

pequeñas visitas
un gran día

Consulte la Información Importante de Seguridad en la página 14.

La única *tableta* aprobada para la psoriasis en placas o la artritis psoriásica que no requiere controles de laboratorio de rutina según la Información sobre la prescripción de Otezla

Qué distingue a Otezla de otros *tratamientos*

Es una *tableta* que actúa diferente

Parte de lo que hace que Otezla sea diferente es cómo actúa.

Si bien no se conoce completamente la manera en la que actúa Otezla, esto es lo que se sabe:

- Otezla actúa dentro de las células inflamatorias para reducir la actividad de la **PDE4**.
- Se cree que la reducción de la actividad de la PDE4 reduce la **inflamación hiperactiva**.
- Una menor inflamación puede hacer que los síntomas (de la psoriasis en placas y la artritis psoriásica) se reduzcan.

"Otezla actúa desde adentro del cuerpo para reducir la inflamación".
—DRA. ERIN BOH, *dermatóloga certificada*

Vea un panel de profesionales, entre los que se encuentra la Dra. Boh, hablando sobre Otezla en otezla.com/learn

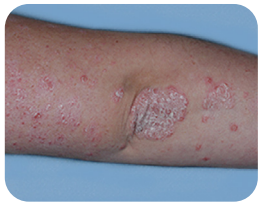
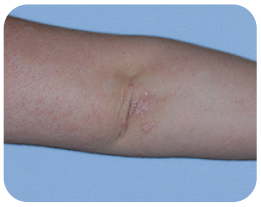
Otezla® (apremilast) 30mg tablets | otezla.com

Consulte la Información Importante de Seguridad en la página 14.

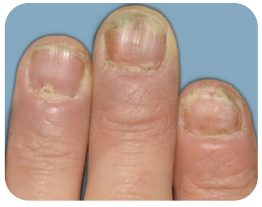
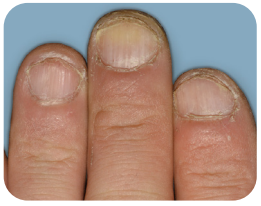
Resultados comprobados en la psoriasis en placas

Otezla es una tableta que puede ayudarlo a lograr una piel más clara.

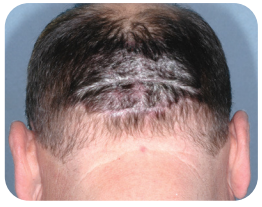
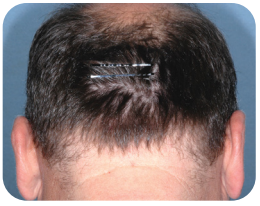
ANTES DE OTEZLA | **CON OTEZLA A LAS 16 SEMANAS**

ANTES DE OTEZLA | **CON OTEZLA A LAS 16 SEMANAS**

ANTES DE OTEZLA | **CON OTEZLA A LAS 16 SEMANAS**

Pacientes reales de Otezla. No todas las personas responden a Otezla, y quienes responden, pueden hacerlo de distintas maneras.

Vea más fotos del antes y del después en otezla.com

Se demostró en estudios una piel más clara con Otezla

Se demostró en estudios que después de solo 4 meses con Otezla, en algunas personas, se logra una reducción del 75% de la psoriasis en placas de moderada a grave.

¿Lo sabía?

La gravedad de la psoriasis no solo se mide según los síntomas físicos de la piel. También es importante pensar en el impacto emocional que tiene en su vida (especialmente al considerar sus opciones de tratamiento).

Efectos secundarios comunes de Otezla

Los efectos secundarios más comunes de Otezla fueron diarrea, náuseas, infección de las vías respiratorias superiores, dolor de cabeza por tensión y dolor de cabeza común.

Información Seleccionada de Seguridad

No debe tomar Otezla si es alérgico al apremilast o a alguno de los componentes de Otezla.

Otezla puede causar diarrea, náuseas y vómitos intensos, sobre todo en las primeras semanas de tratamiento. El uso de este medicamento en pacientes de edad avanzada, así como el uso simultáneo con determinados medicamentos, podría aumentar el riesgo de tener diarrea, náuseas o vómitos. Dígale a su médico si tiene alguno de estos síntomas.

Consulte la Información Importante de Seguridad en la página 14.

Comprender los efectos secundarios

Otezla *en* los estudios clínicos

En los estudios clínicos con Otezla participaron 1426 adultos con psoriasis en placas de moderada a grave que eran candidatos para recibir fototerapia o terapia sistémica.

En cada estudio, algunas personas tomaron 30 mg de Otezla dos veces al día, y otras tomaron un placebo (tableta de azúcar).

Efectos secundarios

La siguiente tabla incluye los efectos secundarios más comunes informados por las personas que tomaron Otezla, en comparación con los informados por las personas que tomaron placebo (tableta de azúcar).

Efectos secundarios más comunes (hasta la semana 16)*	**Otezla** (920 personas)	**Placebo** (506 personas)
Diarrea	17% de los pacientes	6% de los pacientes
Náuseas	17%	7%
Infección de las vías respiratorias superiores	9%	6%
Dolor de cabeza por tensión	8%	4%
Dolor de cabeza común	6%	4%

*Datos del Día 6 al Día 112 (el período de ajuste de la dosis fue del Día 1 al Día 5, durante los cuales se aumentó gradualmente la dosis hasta alcanzar la dosis recomendada de 30 mg dos veces al día).

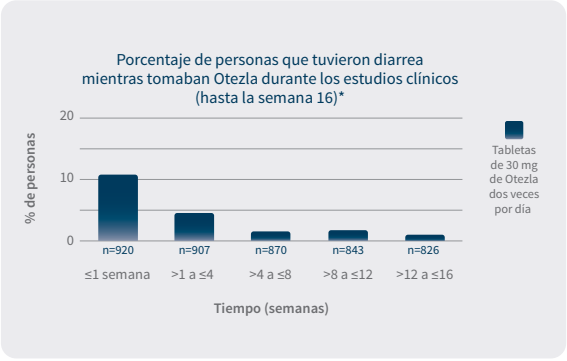
Estos no son todos los efectos secundarios posibles de Otezla. Indíquele a su médico cualquier efecto secundario que le cause molestias o que no desaparezca. Si tiene algún efecto secundario, consulte a su médico. Para conocer la lista completa de los efectos secundarios posibles, consulte la Información sobre la Prescripción en la contratapa de este folleto.

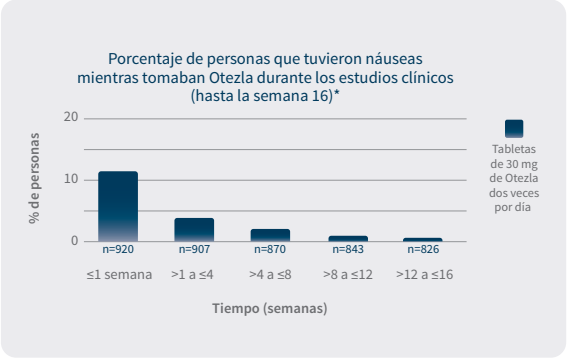
"He probado cremas, lociones y limpiadores. He probado todo. Algunos me daban resultado durante un tiempo, pero nunca atacaban la raíz del problema".

–Janice B., Gilbert, AZ
Paciente real de Otezla

Efectos secundarios gastrointestinales más *comunes* con el tiempo

En la mayoría de las personas, los efectos secundarios de diarrea y náuseas ocurrieron dentro de las primeras 2 semanas de tratamiento y tendieron a desaparecer con el transcurso del tiempo, sin la interrupción de Otezla. En algunos casos, los pacientes con diarrea o náuseas intensas tuvieron que ser hospitalizados. Dígale a su médico si tiene alguno de estos efectos secundarios.





***En estos estudios participaron 920 adultos** con psoriasis en placas de moderada a grave que inicialmente recibieron 30 mg de Otezla dos veces por día.

"n" representa la cantidad de personas que participaron en los estudios durante las semanas indicadas.

Consulte la Información Importante de Seguridad en la página 14.

La historia de Errin con Otezla: *Ahora se siente nuevamente ella*

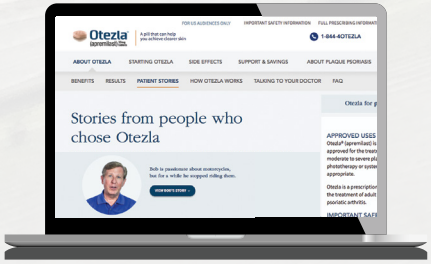
Errin es una historiadora con trabajos publicados y estudiante de doctorado en historia europea. También es bailarina, jugadora de softball, esposa y dueña de un perro. En otras palabras, Errin lleva una vida ajetreada, que es el motivo por el cual ella no quería que la psoriasis en placas se interpusiera en su camino.

Errin empezó con tratamientos de uso externo, pero no le resultaron (teniendo en cuenta el tiempo que demandaban y los resultados que tuvo, simplemente no valían la pena). La fototerapia y el tratamiento con láser le dieron resultado un tiempo, pero las placas siempre volvían.

Por qué eligió Otezla

Después de ver un anuncio de Otezla, Errin quedó intrigada; le gustaba el hecho de que Otezla fuera una tableta que actúa diferente. "Sabía que existían posibles efectos secundarios, pero igual quería hablar con mi doctor sobre Otezla. Llamé inmediatamente al consultorio de mi dermatólogo para pedir una cita. Me reuní con mi dermatólogo, y juntos decidimos que Otezla sería una buena opción para mí".

Finalmente, Errin siente que recuperó parte de su confianza nuevamente. Después de tomar Otezla durante más de un año, está satisfecha con los resultados. Y explica: "Cada persona tendrá un resultado distinto, pero para mí, Otezla me da un resultado que ningún otro tratamiento me dio".



Escuche a más personas que toman Otezla en OtezlaStories.com

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"Mi piel no ha estado tan clara en mucho tiempo".

—ERRIN S., NORTHVILLE, MI
Historiadora y estudiante de doctorado

Consulte la Información Importante de Seguridad en la página 14.

Resultados comprobados en la artritis psoriásica

Otezla es la única tableta aprobada para la artritis psoriásica o la psoriasis en placas de moderada a grave que no requiere controles de laboratorio de rutina.

En algunas personas, después de solo 4 meses, Otezla demostró lo siguiente:

Reduce la inflamación, la sensibilidad y el dolor de las articulaciones.

Mejora la capacidad de realizar las actividades físicas de la vida diaria.

Efectos secundarios comunes de Otezla

Los efectos secundarios más comunes de Otezla fueron diarrea, náuseas y dolor de cabeza común.

Información Seleccionada de Seguridad

Otezla está relacionado con un aumento de la depresión. En estudios clínicos, algunos pacientes reportaron depresión o comportamientos suicidas mientras tomaban Otezla. Algunos pacientes interrumpieron la administración de Otezla debido a la depresión. Antes de comenzar a tomar Otezla, indíquele a su médico si ha tenido sentimientos de depresión, o pensamientos o comportamientos suicidas. Asegúrese de avisarle a su médico si alguno de estos síntomas u otros cambios en su estado de ánimo aparecen o empeoran durante el tratamiento con Otezla.

Algunos pacientes que toman Otezla perdieron peso. Su médico debe monitorear su peso regularmente. Si se produce una pérdida de peso significativa o inexplicable, su médico decidirá si debe continuar con la administración de Otezla.

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¿Está bajo tratamiento con metotrexato o AINE* *(un tipo común de analgésico)*?

Otezla es otro tipo de tableta

¿Lo sabía?

Hasta un **30% de las personas** que tienen psoriasis **desarrollan artritis psoriásica**, que causa **dolor**, **rigidez** e **inflamación** en las articulaciones y a su alrededor.

Hable con su médico si tiene alguno de estos síntomas

un poco de ayuda

una gran impresión

*Medicamentos antinflamatorios no esteroideos.

Consulte la Información Importante de Seguridad en la página 14.

Comprender los efectos secundarios

Otezla se probó en estudios clínicos, en 1493 adultos con artritis psoriásica activa. A todos los pacientes de estos estudios se les había diagnosticado artritis psoriásica desde hacía al menos 6 meses. Tenían entre 18 y 83 años.

En cada estudio, algunas personas tomaron 30 mg de Otezla dos veces al día, y otras tomaron un placebo (tableta de azúcar).

Efectos secundarios comunes de Otezla

La siguiente tabla incluye los efectos secundarios más comunes informados por las personas que tomaron Otezla, en comparación con los informados por las personas que tomaron placebo (tableta de azúcar).

Efectos secundarios más comunes (hasta la semana 16)*	**Otezla** (493 personas)	**Placebo** (490 personas)
Náuseas	9% de los pacientes	3% de los pacientes
Diarrea	8%	2%
Dolor de cabeza común	6%	2%

*Datos del Día 6 al Día 112 (el período de ajuste de la dosis fue del Día 1 al Día 5, durante los cuales se aumentó gradualmente la dosis hasta alcanzar la dosis recomendada de 30 mg dos veces al día).

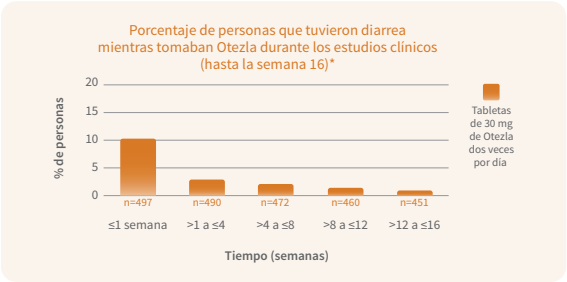
Estos no son todos los efectos secundarios posibles de Otezla. Indíquele a su médico cualquier efecto secundario que le cause molestias o que no desaparezca. Si tiene algún efecto secundario, consulte a su médico.

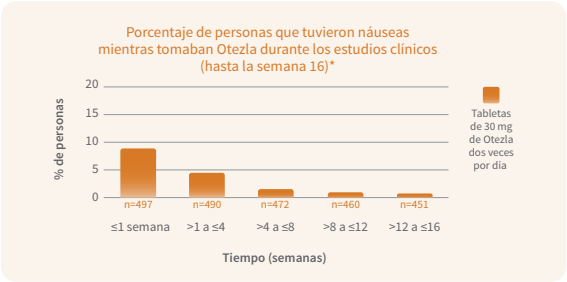
"Cuando no veía ninguna mejora con los medicamentos que tomaba, empecé a buscar algo que actuara diferente".

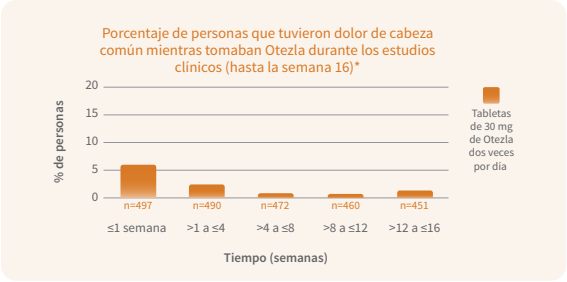
–Cindy C., Jamaica, NY
Paciente real de Otezla

Los efectos secundarios más *comunes* con el tiempo

En la mayoría de las personas, estos efectos secundarios comunes de dolor de cabeza común, diarrea y náuseas ocurrieron dentro de las primeras 2 semanas de tratamiento y tendieron a desaparecer con el transcurso del tiempo, sin la interrupción de Otezla. En algunos casos, los pacientes con diarrea o náuseas intensas tuvieron que ser hospitalizados. Avísele a su médico si tiene alguno de estos síntomas.







*__En estos estudios participaron 497 adultos__ con artritis psoriásica activa que inicialmente recibieron 30 mg de Otezla dos veces por día.

"n" representa la cantidad de personas que participaron en los estudios durante las semanas indicadas.

Consulte la Información Importante de Seguridad en la página 14.

La historia de Anne con Otezla: *Abriéndose camino*

Anne es una aficionada apasionada; hace lo que a usted se le ocurra. Cose, cocina, hace jardinería, restaura y tapiza muebles antiguos, e incluso hace podas artísticas. Durante muchos años ignoró los síntomas de artritis psoriásica que tenía, hasta que estuvo tan mal que incluso le costaba vestirse. Finalmente, fue al médico, quien pudo confirmar que Anne tenía artritis psoriásica.

Algo distinto al metotrexato

Anne probó varios tratamientos diferentes a lo largo del tiempo, incluyendo el metotrexato. Pero ninguno le dio los resultados que quería, y cuando lograba algún resultado, este no duraba. Entonces, el médico de Anne mencionó Otezla como una opción distinta. Después de conversar sobre los posibles riesgos y beneficios, Anne decidió probarlo.

Si bien no todos logran los mismos resultados, en el caso de Anne, después de 4 meses de tratamiento con Otezla, el dolor y la inflamación en las muñecas empezaron a desaparecer.

Nota: En estudios clínicos, algunas personas con artritis psoriásica activa tuvieron menos dolor e inflamación de las articulaciones después de tomar Otezla durante 4 meses.

Escuche a Anne:
Vea su video en OtezlaPsAStories.com

Consulte la Información Importante de Seguridad en la página 14.

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Obtenga más información sobre el programa SupportPlus de Otezla

El programa SupportPlus™ de Otezla es un **conjunto de servicios** disponible para usted desde el día que empieza el tratamiento, e incluso antes.

Otezla SUPPORTPLUS™

Aspectos más notables de afiliarse al programa SupportPlus

Ayuda con preguntas sobre el seguro: Ayuda o asistencia en la cobertura de seguro al trabajar con una farmacia especializada para obtener Otezla.

Programa de copago* de $0: La mayoría de las personas no tiene ningún gasto de bolsillo por Otezla con el programa de copago de $0.

Programa Bridge de Otezla: Si tiene seguro privado y tiene demoras, o su seguro privado no cubre Otezla, es posible que sea elegible para recibir **medicamentos sin cargo** a través del Programa Bridge de Otezla.†

Ayuda para los pacientes sin seguro o con seguro insuficiente: Si tiene seguro del gobierno (Medicare o Medicaid), o no tiene seguro o tiene seguro insuficiente, puede ser elegible para recibir el **Programa de asistencia para pacientes**.

Acceso a enfermeros las 24 horas del día, los 7 días de la semana: Los enfermeros de Otezla están disponibles las 24 horas del día, los 7 días de la semana, de manera que siempre tendrá alguien con quien hablar cuando lo necesite.

Recursos y asistencia constante: Acceso a recursos, a herramientas útiles y a toda la información que necesite sobre Otezla, incluyendo la aplicación GOtezla® para ayudarlo a lograr sus objetivos de tratamiento.

*Se aplican ciertas restricciones; la elegibilidad no se basa en los ingresos; la persona debe tener 18 años o más. Esta oferta no es válida para personas elegibles para el reembolso de este producto, en forma total o parcial, a través de Medicaid, Medicare o programas estatales o federales similares. Oferta no válida para pacientes que paguen en efectivo. Las personas que no sean elegibles pueden llamar al 1-844-4OTEZLA para analizar otras oportunidades de asistencia financiera.

†Para recibir un suministro gratuito de Otezla a través del Programa Bridge, debe tener un diagnóstico recogido en la ficha técnica y le deben negar la cobertura o estar a la espera de esta. Los planes federales, estatales o similares no son elegibles para el Programa Bridge. Una vez que su plan de seguro comercial apruebe Otezla, ya no será elegible para acceder al Programa Bridge.

3 maneras fáciles de *inscribirse*

Inscribirse en SupportPlus es fácil, y los servicios son gratuitos para todos los inscriptos. Para afiliarse:

1. **Visite otezla.com/supportplus**.
2. Llame al **1-844-4OTEZLA** (1-844-468-3952).
3. Solicite a su médico que lo inscriba cuando le recete Otezla.

Consulte la Información Importante de Seguridad en la página 14.

Ahorros y *ayuda con los gastos* de Otezla

La mayoría de las personas que tienen seguro privado no tienen gastos de bolsillo por la receta. Una vez que le receten Otezla, usted tendrá la misma oportunidad de ahorrar.

Cómo obtener la oferta de copago de $0:

1. **Visite otezla.com/copay**.
2. Llame al **1-844-4OTEZLA** (1-844-468-3952).
3. **Pregunte a su médico** sobre la tarjeta de copago de $0.

Otras formas de *ahorrar*

Si tiene seguro privado y tiene demoras, o su seguro privado no cubre Otezla, es posible que sea elegible para recibir **medicamentos sin cargo** a través del **Programa Bridge de Otezla**.

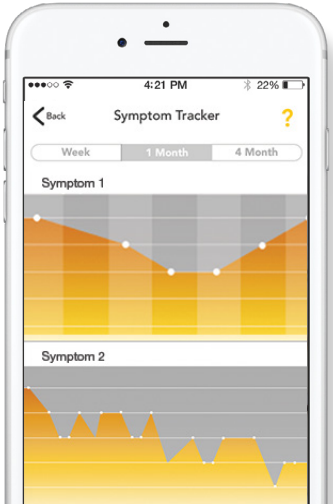
Si tiene seguro del gobierno (Medicare o Medicaid), o no tiene seguro o tiene seguro insuficiente, puede ser elegible para recibir el **Programa de asistencia para pacientes**.

Otezla SUPPORTPLUS™

Por preguntas sobre ahorros en Otezla: *Llame al* **1-844-4OTEZLA** (1-844-468-3952)

Descargue GOtezla®

La aplicación GOtezla tiene herramientas para realizar un seguimiento de su progreso, consejos sobre qué esperar durante el tratamiento y recordatorios de los medicamentos; **y la puede descargar gratis**.



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Cómo trabajar con su equipo de atención médica

La psoriasis en placas y la artritis psoriásica son enfermedades crónicas, lo que significa que están siempre ahí (incluso cuando usted no tiene ningún síntoma). Por eso es extremadamente importante tener un diálogo abierto y honesto con su equipo de atención médica.

Asegúrese de estar recibiendo el tratamiento adecuado para usted:

Pregúntese

¿Estoy satisfecho con mi tratamiento actual?

¿Cuánto tiempo dedico diariamente a mi tratamiento actual?

¿Tengo que alejarme de las cosas que amo?

¿Estoy listo para algo diferente?

Pregunte a su médico

¿Qué es lo que hace que Otezla sea diferente?

¿Cuánto tiempo demora Otezla en actuar?

¿Cuáles son los síntomas que Otezla trata?

¿Cómo puedo ahorrar con Otezla?

¿Cuáles son los efectos secundarios más comunes?

¿El uso de Otezla requiere algún análisis de sangre?

"Voy a las consultas con mi médico con preguntas, entonces siempre recibo la información que necesito para sentirme cómoda".

–Errin S., Northville, MI
Paciente real de Otezla

Vea a una paciente, una dermatóloga y una especialista en SupportPlus de Otezla hablar sobre lo que hace que Otezla sea diferente en otezla.com/learn

Otezla® (apremilast) 30mg tablets | otezla.com

Consulte la Información Importante de Seguridad en la página 14.

INFORMACIÓN IMPORTANTE DE SEGURIDAD

No debe tomar Otezla si es alérgico al apremilast o a alguno de los componentes de Otezla.

Otezla puede causar diarrea, náuseas y vómitos intensos, sobre todo en las primeras semanas de tratamiento. El uso de este medicamento en pacientes de edad avanzada, así como el uso simultáneo con determinados medicamentos, podría aumentar el riesgo de tener diarrea, náuseas o vómitos. Avísele a su médico si tiene alguno de estos síntomas.

Otezla está relacionado con un aumento de la depresión. En estudios clínicos, algunos pacientes reportaron depresión o comportamientos suicidas mientras tomaban Otezla. Algunos pacientes interrumpieron la administración de Otezla debido a la depresión. Antes de comenzar a tomar Otezla, indíquele a su médico si ha tenido sentimientos de depresión, o pensamientos o comportamientos suicidas. Asegúrese de avisarle a su médico si alguno de estos síntomas u otros cambios de estado de ánimo aparecen o empeoran durante el tratamiento con Otezla.

Algunos pacientes que toman Otezla perdieron peso. Su médico debe monitorear su peso regularmente. Si se produce una pérdida de peso significativa o inexplicable, su médico decidirá si debe continuar con la administración de Otezla.

Es posible que algunos medicamentos reduzcan la eficacia de Otezla y, por lo tanto, no se deben administrar junto con Otezla. Comuníquele a su médico todos los medicamentos que toma, incluidos los medicamentos de venta con y sin receta.

Los efectos secundarios de Otezla incluyen diarrea, náuseas, vómitos, infección de las vías respiratorias superiores, secreción nasal, estornudos o congestión, dolor abdominal, dolor de cabeza por tensión y dolor de cabeza común. Estos no son todos los efectos secundarios posibles de Otezla. Pregúntele a su médico acerca de otros efectos secundarios potenciales. Indíquele a su médico cualquier efecto secundario que le cause molestias o que no desaparezca.

Informe a su médico si está embarazada, planea quedar embarazada o planea amamantar. Otezla no se ha estudiado en mujeres embarazadas o que estén amamantando.

Se recomienda informar los efectos secundarios negativos de los medicamentos de venta con receta a la FDA. Visite www.fda.gov/medwatch, o llame al 1-800-332-1088.

Consulte la Información Completa sobre la Prescripción que empieza en la página 15.

Otezla® (apremilast) 30mg tablets

¿Necesita ayuda? *Llámenos.*

Nuestro equipo está disponible de lunes a viernes, de 8 AM a 8 PM, hora del Este, al **1-844-4OTEZLA** (1-844-468-3952).

Pregúntele a su médico acerca de *Otezla*. ¡Con el *Starter Pack para 2 semanas* puede comenzar de inmediato!

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

----------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*

*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 ≥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)

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

[a] 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.
[b] Of the reported adverse drug reactions none were serious.
[c] 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)

Preferred Term	Placebo (N=506) n (%)	OTEZLA 30 mg BID (N=920) n (%)
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[a]	21 (20.4)	43 (41.3)
Nausea[a]	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[a]	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)

[a] 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 ≥4.0-times the MRHD (on an AUC basis at doses ≥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 than18 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 ≥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 ≥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.

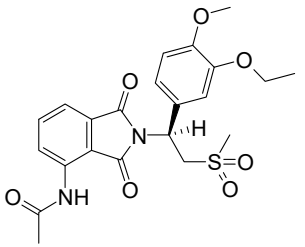
10 OVERDOSAGE

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-1,3-dioxo-1H-isoindol-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 (Vd) 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 ≥1.8-times the MRHD (≥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 (≥3 swollen joints and ≥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 (≤25 mg/week)], sulfasalazine [SSZ (≤2 g/day)], leflunomide [LEF (≤20 mg/day)], low dose oral corticosteroids (equivalent to ≤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[a]	**N=168**	**N=168**	**N=159**	**N=162**	**N=169**	**N=167**
ACR 20 Week 16	19%	38% [b]	19%	32% [b]	18%	41% [b]
ACR 50 Week 16	6%	16%	5%	11%	8%	15%
ACR 70 Week 16	1%	4%	1%	1%	2%	4%

[a] N is number of randomized and treated patients.
[b] 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[a]		
Sample Size	166	164
Baseline	23	23
Mean Change at Week 16	-2	-7
Number of swollen joints[b]		
Sample Size	166	164
Baseline	13	13
Mean Change at Week 16	-2	-5
Patient's assessment of pain[c]		
Sample Size	165	159
Baseline	61	58
Mean Change at Week 16	-6	-14

Patient's global assessment of disease activity[c]		
Sample Size	165	159
Baseline	59	56
Mean Change at Week 16	-3	-10
Physician's global assessment of disease activity[c]		
Sample Size	158	159
Baseline	55	56
Mean Change at Week 16	-8	-19
HAQ-DI[d] score		
Sample Size	165	159
Baseline	1.2	1.2
Mean Change at Week 16	-0.09	-0.2
CRP[e]		
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.
[a] Scale 0-78.
[b] Scale 0-76.
[c] VAS=Visual Analog Scale; 0=best, 100=worst.
[d] 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.
[e] 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 (≥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 ≥10%, static Physician Global Assessment (sPGA) of ≥3 (moderate or severe disease), Psoriasis Area and Severity Index (PASI) score ≥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**
N[a]	**N=282**	**N=562**	**N=137**	**N=274**
PASI[b] -75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[c] of Clear or Almost Clear, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)

[a] N is number of randomized and treated patients.
[b] PASI=Psoriasis Area and Severity Index.
[c] 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[a] Population)

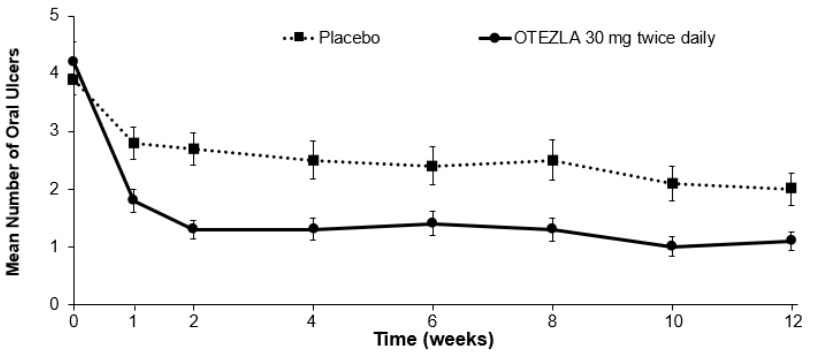
Endpoint	**Placebo N=103**	**OTEZLA 30 mg twice daily N=104**	**Treatment Difference[b] (95% CI[c])**
Change[d] from baseline in the pain of oral ulcers as measured by VAS[e] at Week 12	-18.7	- 42.7	-24.1 (-32.4, -15.7)
Proportion[f] of subjects achieving oral ulcer complete response (oral ulcer-free) at Week 12	22.3%	52.9%	30.6%[g] (18.1%, 43.1%)
Proportion[f] 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%[g] (15.5%, 34.6%)

Daily average[h,i] number of oral ulcers during the 12-week Placebo-controlled Treatment Phase	2.6	1.5	-1.1 (-1.6, -0.7)

[a] ITT=intent to treat.
[b] OTEZLA – Placebo.
[c] CI=confidence interval.
[d] 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.
[e] VAS=visual analog scale; 0=no pain, 100=worst possible pain.
[f] Patients for whom data are not available to determine response status are considered non-responders.
[g] 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.
[h] Mean daily averages are least squares means from analysis of covariance, after adjusting for sex, region, and baseline number of oral ulcers.
[i] 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.

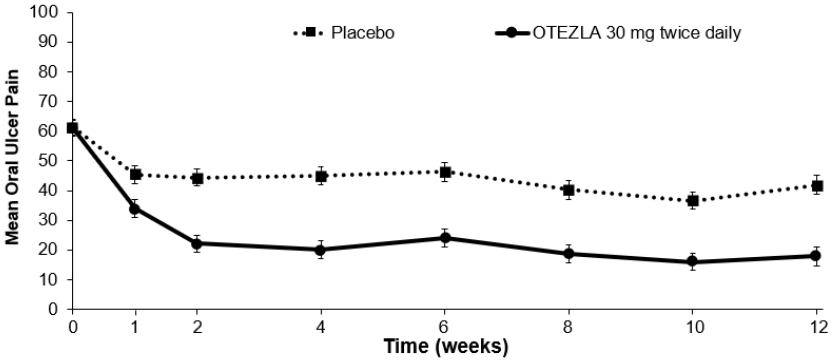
Figure 1: Mean (± SE) Number of Oral Ulcers by Time Point Through Week 12 (ITT Population)



Weeks	0	1	2	4	6	8	10	12
Placebo, n	103	98	97	93	91	86	83	82
OTEZLA 30 mg twice daily, n	104	101	101	101	98	94	94	97

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

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



Weeks	0	1	2	4	6	8	10	12
Placebo, n	101	95	96	91	90	85	82	81
OTEZLA 30 mg twice daily, n	102	95	97	99	97	92	93	95

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.

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Summit, NJ 07901

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