FAQs for Reinitiating Otezla

Otezla® (apremilast) 30mg tablets

The information below is from the ESTEEM 1 Phase 3 study looking at adult patients with moderate to severe plaque psoriasis. It is intended to provide additional context on data for patients on Otezla® (apremilast) who were re-randomized to placebo at week 32 and subsequently reinitiated Otezla without dose titration after losing PASI-75 response no later than week 52.*

- These data are based on the treatment withdrawal phase between weeks 32 and 52. Please note that dose titration after reinitiating Otezla should be based on individual clinical assessments*
- **US Prescribing Information: Dosage** Following a 5-day titration, the recommended maintenance dose of Otezla is 30 mg twice daily. The titration schedule is as follows: Day 1 (AM: 10 mg); Day 2 (AM: 10 mg, PM 10 mg); Day 3 (AM: 10 mg, PM: 20 mg); Day 4 (AM: 20 mg; PM: 20 mg); Day 5 (AM: 20 mg, PM: 30 mg). This titration is intended to reduce the gastrointestinal symptoms associated with initial therapy[1]
  - The dose of Otezla should be reduced to 30 mg once daily in patients with severe renal impairment. For initial dosage titration, it is recommended that Otezla be titrated using only the AM schedule shown above and the PM doses be skipped[1]
- Data on reinitiating Otezla after discontinuation was not studied in the PALACE Phase 3 PsA studies, ACTIVE Phase3b PsA study, and RELIEF Phase 3 oral ulcers associated with Behçet's Disease study

*Please note that Amgen does not recommend the use of Otezla in any manner inconsistent with that described in the Prescribing Information.

Can I reinitiate patients on Otezla who have stopped therapy?

- Data on treatment reinitiation with Otezla after discontinuation is available from the ESTEEM 1 Phase 3 study in adults with moderate to severe plaque psoriasis. In ESTEEM 1, a portion of patients initially randomized to Otezla and achieved a PASI-75 response at week 32, were re-randomized to placebo (n=77). In these patients who were re-randomized to placebo at week 32, and subsequently lost their PASI-75 response, resumed treatment with Otezla 30 mg BID no later than week 52[2]

How was Otezla studied in moderate to severe plaque psoriasis patients who stopped therapy and subsequently reinitiated?

- In a Phase 3 study (ESTEEM 1) in adults with moderate to severe plaque psoriasis, a portion of patients initially receiving Otezla who were responders (patients who attained a PASI-75 response in ESTEEM 1; n=77) were re-randomized to placebo at week 32, and then restarted treatment with Otezla 30 mg BID, no later than week 52, after loss of PASI-75 response with placebo[2,3]

ESTEEM 1 overview

- Patients with moderate to severe plaque psoriasis (N=844) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day dose titration[1,2]
- Patients originally randomized to Otezla who achieved ≥PASI-75 response at week 32 were re-randomized 1:1 to either placebo or Otezla. Patients re-randomized to placebo at week 32 who lost their PASI-75 response were re-treated with Otezla 30 mg BID no later than week 52. Patients originally randomized to placebo switched to Otezla at week 16 and continued Otezla if ≥PASI-75 response at week 32 was achieved. In a separate arm, patients were originally randomized to Otezla or placebo who did not achieve PASI-75 by week 32, concomitant topicals and/or UVB therapy could have been added based on the discretion of the investigator[1]
- Selected inclusion criteria: age ≥18 years; BSA involvement ≥10%; sPGA ≥3; PASI score ≥12; candidates for phototherapy or systemic therapy[1]
- **Primary endpoint:** In ESTEEM 1, 33% PASI-75 response with Otezla 30 mg twice daily (n=562) vs 5% with placebo (n=282) at week 16 (P<0.0001)[1]
- **Safety profile:** The most common adverse reactions (≥5%) were diarrhea, nausea, upper respiratory tract infection, tension headache, and headache[1]
- Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) subjects following discontinuation of treatment with Otezla[1]

Please see next page for more information.

INDICATIONS

Otezla® (apremilast) is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

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

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

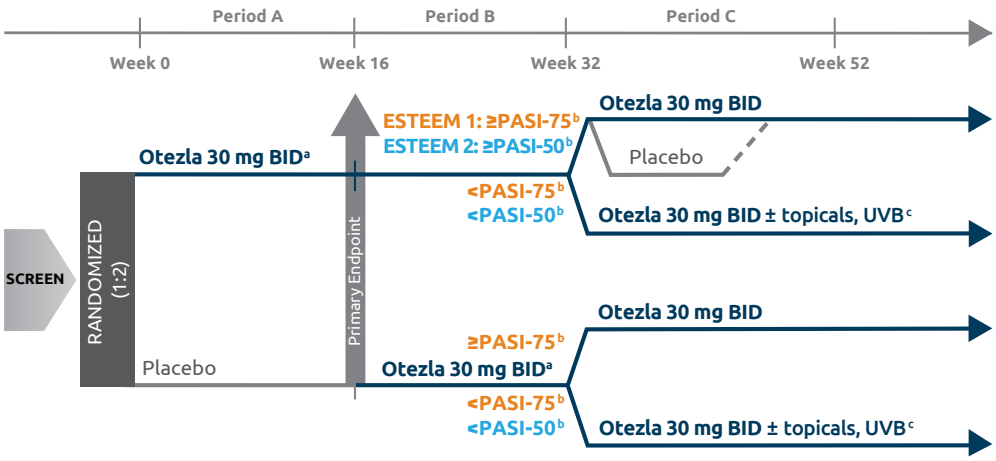
IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Please see Important Safety Information presented throughout, and Full Prescribing Information here.

ESTEEM 1 and 2 study design (N=1257)[2,3]



Adapted from Bissonnette et al, 2015.
[a]Dose titration for apremilast occurred during the initial week of administration and at week 16 during placebo crossover.
[b]Patients restarted apremilast at loss of effect (PASI-75 loss [ESTEEM 1]; loss of 50% of PASI improvement seen at week 32 [ESTEEM 2]), but no later than week 52.
[c]Patients not achieving predefined response were permitted to add UVB and/or topicals at investigator discretion.
BID, twice daily; ESTEEM, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PASI, Psoriasis Area and Severity Index; UVB, ultraviolet B.

Were patients required to dose titrate after reinitiating Otezla during the treatment withdrawal phase (weeks 32-52)?

- There was no dose titration when reinitiating patients on therapy with Otezla[2]
- Dose titration for apremilast occurred during the initial week of administration and at week 16 during placebo crossover

Please note that dose titration after reinitiating Otezla should be based on individual clinical assessments.*

*Please note that Amgen does not recommend the use of Otezla in any manner inconsistent with that described in the Prescribing Information.

Please see next page for more information.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions

- Diarrhea, Nausea, and Vomiting: Cases of severe diarrhea, nausea, and vomiting were 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; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
- Depression: Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, 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 they should contact their healthcare provider if such changes occur
  - Psoriasis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.3% (12/920) of patients reported depression compared to 0.4% (2/506) on placebo. Depression was reported as serious in 0.1% (1/1308) of patients exposed to Otezla, compared to none in placebo-treated patients (0/506). Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. One patient treated with Otezla attempted suicide; one patient on placebo committed suicide
  - Psoriatic Arthritis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.0% (10/998) reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. Suicidal ideation and behavior was observed in 0.2% (3/1441) of patients on Otezla, compared to none in placebo-treated patients. Depression was reported as serious in 0.2% (3/1441) of patients exposed to Otezla, compared to none in placebo-treated patients (0/495). Two patients who received placebo committed suicide compared to none on Otezla
  - Behçet's Disease: Treatment with Otezla is associated with an increase in depression. During the clinical trial, 1% (1/104) reported depression or depressed mood compared to 1% (1/103) treated with placebo. No instances of suicidal ideation or behavior were reported in patients treated with Otezla or treated with placebo

Please see Important Safety Information presented throughout, and Full Prescribing Information here.

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What is the safety data?

Pooled ESTEEM 1 and 2: Incidence of adverse events during the initial 16 weeks of Otezla treatment vs the 16-week treatment period following Otezla® (apremilast) reinitiation[3]

	Initially randomized to APR (week 0) → Re-randomized to placebo (week 32) → Resumed APR (weeks 32 to 52)	
	Initial 16 weeks of APR (weeks 0 to 16)	First 16 weeks after restarting APR
	n (%)	n (%)
≥1 adverse event	88 (67.7)	59 (45.4)
URTI	10 (7.7)	5 (3.8)
Nasopharyngitis	11 (8.5)	4 (3.1)
Diarrhea	27 (20.8)	4 (3.1)
Nausea	24 (18.5)	4 (3.1)
Tension headache	12 (9.2)	2 (1.5)

APR, apremilast; URTI, upper respiratory tract infection.

Please see next page for more information.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

- Weight Decrease: Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla
  - Psoriasis: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Body weight loss of ≥10% occurred in 2% (16/784) of patients treated with Otezla compared to 1% (3/382) of patients treated with placebo
  - Psoriatic Arthritis: Body weight loss of 5-10% was reported in 10% (49/497) of patients taking Otezla and in 3.3% (16/495) of patients taking placebo
  - Behçet's Disease: Body weight loss of >5% was reported in 4.9% (5/103) of patients taking Otezla and in 3.9% (4/102) of patients taking placebo
- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended

Adverse Reactions

- Psoriasis: Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4)
- Psoriatic Arthritis: Adverse reactions reported in at least 2% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 16 weeks (after the initial 5-day titration), were (Otezla%, placebo%): diarrhea (7.7, 1.6); nausea (8.9, 3.1); headache (5.9, 2.2); upper respiratory tract infection (3.9, 1.8); vomiting (3.2, 0.4); nasopharyngitis (2.6, 1.6); upper abdominal pain (2.0, 0.2)
- Behçet's Disease: Adverse reactions reported in ≥5% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 12 weeks, were (Otezla%, placebo%): diarrhea (41.3, 20.4); nausea (19.2, 10.7); headache (14.4, 10.7); upper respiratory tract infection (11.5, 4.9); upper abdominal pain (8.7, 1.9); vomiting (8.7, 1.9); back pain (7.7, 5.8); viral upper respiratory tract infection (6.7, 4.9); arthralgia (5.8, 2.9)

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IMPORTANT SAFETY INFORMATION (cont'd)

Use in Specific Populations

- Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. 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/
- Lactation: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. 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 child from Otezla or from the underlying maternal condition
- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

Please see Full Prescribing Information here.

References: 1. Otezla [package insert]. Thousand Oaks, CA: Amgen Inc. **2.** Papp K, Reich K, Leonardi CL, et al. *J Am Acad Dermatol.* 2015;73(1):37-49. **3.** Data on file, Amgen Inc.