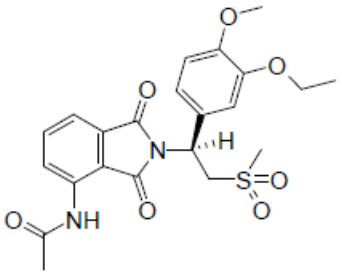
Attachment 1: Product information for AusPAR Apremilast (Otezla) Celgene Pty Ltd PM-2013-04920-1-3 Final 22 October 2015. This Product Information was approved at the time this AusPAR was published.

Product Information

OTEZLA® (apremilast) tablets

i) Name of the medicine

Australian approved name:	apremilast
Molecular formula:	$C_{22}H_{24}N_2O_7S$
Molecular weight:	460.5
CAS number:	608141-41-9
ATC code:	L04AA32
Chemical name:	N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide
Chemical structure:	

ii) Description

Apremilast is a white to pale yellow non-hygroscopic powder with a melting point of approximately 156.1°C. It is practically insoluble in water, slightly soluble in ethanol, and soluble in acetone. Apremilast is the S-enantiomer with a specific rotation of +28.1° in acetonitrile at a concentration of 20 mg/mL.

List of Excipients

Otezla tablets contain microcrystalline cellulose, lactose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide red, iron oxide yellow (20 and 30 mg only) and iron oxide black (30 mg only).

iii) Pharmacology

Pharmacotherapeutic group: Selective immunosuppressants.

Pharmacodynamic properties

Mechanism of action

Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis (PsA) and psoriasis (PSOR).

Clinical Pharmacodynamics

In clinical studies in patients with psoriatic arthritis, apremilast significantly modulated, but did not fully inhibit, plasma protein levels of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, MMP-3, and TNF-α. After 40 weeks of treatment with apremilast, there was a decrease in plasma protein levels of IL-17 and IL-23, and an increase in IL-10. In clinical trials in patients with psoriasis, apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro-inflammatory genes, including inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-17A, IL-22 and IL-8.

Cardiac Electrophysiology

Apremilast administered at doses of up to 50 mg twice daily did not prolong the QT interval in healthy subjects.

Pharmacokinetic properties

Absorption

Apremilast is well absorbed with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours. Apremilast pharmacokinetics is linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 100 mg daily. Accumulation is minimal when apremilast is administered once daily and approximately 53% in healthy subjects and 68% in patients with psoriasis when administered twice daily. Co-administration with food does not alter the bioavailability; therefore, apremilast can be administered with or without food.

Distribution

Human plasma protein binding of apremilast is approximately 68%. Mean apparent volume of distribution (Vd) is 87 L indicative of extra vascular distribution.

Metabolism

Apremilast is extensively metabolised by both CYP and non-CYP mediated pathways including oxidation, hydrolysis, and conjugation, suggesting inhibition of a single clearance pathway is not likely to cause a marked drug-drug interaction. Oxidative metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. Apremilast is the major circulating component following oral administration. Apremilast undergoes extensive metabolism with only 3% and 7% of the administered drug recovered in urine and faeces, respectively. The major circulating metabolite, M12, is the glucuronide conjugate of *O*-demethylated apremilast which is inactive.

Elimination

The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 9 hours. There is approximately 30% reduction in apremilast clearance observed in female subjects compared to male subjects. No dose adjustment is necessary for female patients. Following oral administration of radiolabeled apremilast, about 58% and 39% of the radioactivity is recovered in urine and faeces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and faeces, respectively.

Renal impairment

No formal studies have been conducted in subjects with mild to moderately impaired renal function. 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 89% and 42%, respectively. See Dosage and Administration section for dose adjustments for patients with severe renal impairment.

Hepatic impairment

The pharmacokinetics of apremilast and its major metabolite M12 is not affected by moderate or severe hepatic impairment. No dosage adjustment is necessary for patients with hepatic impairment.

iv) Clinical trials

This section presents data from three (3) multi-centre, randomised, double-blind, placebo-controlled studies in patients with active PsA despite previous treatment with disease modifying antirheumatic drugs (DMARDS) including biologics, one (1) multi-centre, randomised, double-blind, placebo-controlled study in patients with active PsA who were DMARD-naive and two (2) multi-centre, randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis. More details on the individual studies are provided in the sections below.

1. Clinical Trial experience in Psoriatic Arthritis patients previously treated with DMARDS.

The safety and efficacy of Otezla were evaluated in 3 multi-centre, randomised, double-blind, placebo-controlled studies (Studies PALACE 1, PALACE 2, and PALACE 3) of similar design in 1493 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior DMARD treatment, including biologic DMARD treatment (e.g. TNF-blockers), or current treatment with oral DMARD therapy.

Patients in these studies had a diagnosis of PsA for at least 6 months. One qualifying psoriatic skin lesion (at least 2 cm in diameter) was also required in PALACE 3. The patients who were therapeutic failures of > 3 agents for PsA (small molecules or biologics), or > 1 biologic TNF blocker, were excluded. Patients with each subtype of PsA were enrolled across the 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (26.9%), distal interphalangeal (DIP) joint arthritis (6.2%), arthritis mutilans (2.7%), and predominant spondylitis (2.1%). Patients with pre-existing enthesitis (63%) and pre-existing dactylitis (42%) were enrolled. 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; the combination of apremilast with biologic DMARDs was not studied.

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. Treatment assignments were stratified based on small-molecule DMARD use at baseline in Studies PALACE 1, PALACE 2 and PALACE 3. There was an additional stratification of body surface area (BSA ≥ 3% with psoriasis in PALACE 3).

Patients received concomitant therapy with at least one DMARD (total 65.2%), MTX (54.5%), SSZ (9.0%), LEF (7.4%), low dose oral corticosteroids (13.9%), and NSAIDs (70.7%). Prior treatment with only small-molecule DMARDs was reported in 76.4% of patients and prior treatment with biologic DMARDs was reported in 22.4% of patients, which includes 7.8% who had a therapeutic failure with a prior biologic DMARD. The median duration of PsA disease was 5 years.

The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16. 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-randomised 1:1 in a blinded fashion to either Otezla 20 mg twice daily or 30 mg twice daily. Otezla patients remained on their initial treatment. At Week 24, all remaining placebo patients were re-randomised to either Otezla 20 mg twice daily or Otezla 30 mg twice daily. At the end of 52 weeks, patients could enter a long-term open-label extension study for a total duration of up to 5 years. These studies did not investigate the effects of Otezla on structural progression.

Clinical Responses

Treatment with apremilast resulted in significant improvements in the signs and symptoms of PsA, as assessed by the ACR 20 response criteria, compared to placebo at Week 16. The proportion of patients with ACR 20/50/70 responses in Studies PALACE 1, PALACE 2 and PALACE 3, for apremilast 30 mg twice daily at Week 16, are shown in Table 3. ACR 20/50/70 responses were maintained at Week 24.

Table 1 Proportion of Patients with ACR Responses in Studies PALACE 1, PALACE 2 and PALACE 3 at Week 16

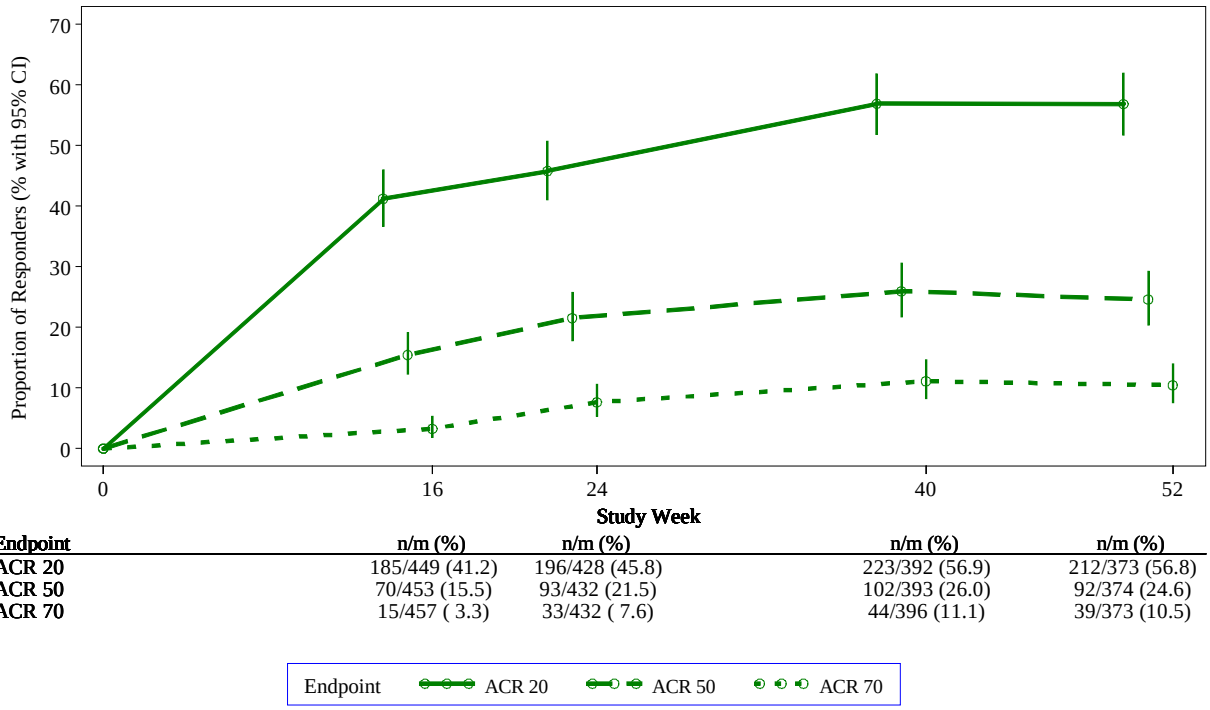
	PALACE 1		PALACE 2		PALACE 3	
N[a]	**Placebo +/- DMARDs N=168**	**Apremilast 30 mg BID +/- DMARDs N=168**	**Placebo +/- DMARDs N=159**	**Apremilast 30 mg BID +/- DMARDs N=162**	**Placebo +/- DMARDs N=169**	**Apremilast 30 mg BID +/- DMARDs N=167**
ACR 20						
Week 16	19.0%	38.1%**	18.9%	32.1%*	18.3%	40.7%**
ACR 50						
Week 16	6.0%	16.1%*	5.0%	10.5%	8.3%	15.0%
ACR 70						
Week 16	1.2%	4.2%	0.6%	1.2%	2.4%	3.6%

*p≤ 0.01 for apremilast vs. placebo.
**p ≤ 0.001 for apremilast vs. placebo.
[a] N is the number of randomised and treated patients at Week 16.

ACR 20/50/70 Response Through Week 52

Among 497 patients initially randomized to apremilast 30 mg twice daily, 373 (75%) patients were still on this treatment at Week 52. In these patients, ACR 20/50/70 responses at week 52 were 57%, 25%, and 11% respectively (**Figure 1**).

Figure 1 Proportion of ACR 20/50/70 Responders Through Week 52 in the Pooled Studies PALACE 1 PALACE 2 and PALACE 3



Endpoint	n/m (%)	n/m (%)	n/m (%)	n/m (%)
ACR 20	185/449 (41.2)	196/428 (45.8)	223/392 (56.9)	212/373 (56.8)
ACR 50	70/453 (15.5)	93/432 (21.5)	102/393 (26.0)	92/374 (24.6)
ACR 70	15/457 (3.3)	33/432 (7.6)	44/396 (11.1)	39/373 (10.5)

Note: n/m is the number of responders/number of subjects with sufficient data for definitive determination of response status at each time point, which includes subjects who discontinued early between the preceding time point and the time point in question.

ACR 20 responses were higher in patients treated with Otezla than in patients treated with placebo when used alone or in combination with DMARDs. In Study PALACE 1, the proportion of patients with an ACR 20 response at Week 16 with concomitant DMARD use was 33.0 % for Otezla 30 mg twice daily and 23.6 % for placebo. The proportion of patients with an ACR 20 response at Week 16 without concomitant DMARD use was 46.8% for Otezla 30 mg twice daily and 10.3% for placebo. Similar results were observed in Studies PALACE 2 and PALACE 3.

A greater proportion of patients achieved an ACR 20 response with the use of Otezla 30 mg twice daily, irrespective of prior small molecule or prior biologic DMARD use. In Study PALACE 1, the proportion of patients with prior treatment of only small-molecule DMARDs (biologic-naïve) with an ACR 20 response at Week 16 were 41.1% for Otezla 30 mg twice daily and 23.3% for placebo and the proportion of patients with prior biologic use with an ACR 20 response at Week 16 were 26.8% for Otezla 30 mg twice daily and 4.9% for placebo. Similar results were observed in Studies PALACE 2 and PALACE 3.

Similar ACR 20 responses were observed in patients with different PsA subtypes including distal interphalangeal (DIP); however, the number of patients with arthritis mutilans and predominant spondylitis subtypes was too small to allow for a meaningful assessment.

Otezla 30 mg twice daily resulted in greater improvement for each ACR component [number of swollen and tender joints, physician and patient assessment of disease activity and patient assessment of pain, Health Assessment Questionnaire-Disability Index (HAQ-DI) scores and CRP values], compared to placebo at Weeks 16 and 24 in Study PALACE 1. Among patients who were continuously treated with Otezla, sustained improvements in individual ACR components were observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

The proportion of patients achieving modified PsA response criteria (PsARC) was significantly greater in the Otezla 30 mg twice daily group compared to placebo at Week 16 (46.4% and 29.8% respectively; $p < 0.01$) in Study PALACE 1. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, a PsARC response of 73.6% was observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

A greater proportion of patients treated with Otezla 30 mg twice daily achieved remission, as measured by a DAS28 (CRP) less than 2.6, compared to placebo at Weeks 16 (13.1% and 3.6% respectively; $p < 0.01$) in Study PALACE 1. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, a DAS28 (CRP) response of 23.3% was observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

In patients with pre-existing enthesitis or dactylitis, treatment with Otezla 30 mg twice daily resulted in improvement in enthesitis and dactylitis. Among patients who were continuously treated with Otezla, improvement in enthesitis and dactylitis continued through Week 52.

Physical function responses and health-related quality of life

Patients treated with Otezla 30 mg twice daily demonstrated a significantly greater improvement in physical function compared to placebo treated patients, as shown in the mean change from Baseline in HAQ-DI score at Week 16 (-0.244 and -0.086 respectively; $p < 0.01$) and Week 24 (-0.258 vs, -0.076, respectively; $p<0.001$) in Study PALACE 1. Among patients who were continuously treated with Otezla, a mean change from Baseline in HAQ-DI score of -0.318 was observed at Week 52. In addition, there was a greater proportion of HAQ-DI responders who showed improvement (≥ 0.3 improvement from Baseline) at Week 16 for the Otezla 30 mg twice daily group compared to the placebo group (38.1% vs 26.8% respectively, $p<0.05$). The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the proportion of HAQ-DI responders was 44.7% at Week 52. Similar results in the mean change from Baseline in HAQ-DI and in the proportion of HAQ-DI responders were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

Patients treated with Otezla 30 mg twice daily demonstrated a significantly greater improvement compared to placebo treated patients in the mean change from Baseline in the SF-36v2 Physical Functioning (PF) Domain Score at Week 16 (4.23 and 1.81 respectively; $p < 0.01$) in Study PALACE 1. A greater improvement, compared to placebo, in the mean change from Baseline was also observed in the Physical Component Summary (PCS) Score at Week 16 (4.59 and 2.39 respectively; $p < 0.01$). The responses were maintained at Week 24. Among patients who were continuously treated with Otezla, mean changes from baseline in SF-36v2 PF and PCS scores of 5.69 and 6.45, respectively, were observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

There was no worsening observed in the mean change from Baseline in the Mental Component Summary score (MCS) in patients treated with Otezla 30 mg twice daily in comparison to placebo patients at Week 16 (0.69 and 0.07 respectively) and Week 24 in Study PALACE 1. Among patients who were continuously treated with Otezla, a mean change from baseline in the MCS score of 0.34 was observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

A greater improvement was observed in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-fatigue) scores in the patients treated with Otezla 30 mg twice daily when compared with the placebo group at Weeks 16 (3.88 and 1.55 respectively; $p < 0.05$) in Study PALACE 1. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, a mean change from baseline in the FACIT-fatigue score of 3.67 was observed at Week 52. Similar results were observed in Studies PALACE 2 and PALACE 3 at Weeks 16, 24 and 52.

PASI-75 Response

Treatment with Otezla 30 mg twice daily resulted in improvement in the skin manifestations of psoriasis. Patients with psoriasis involvement of at least 3% BSA were evaluated using the PASI-75 responses. In Study PALACE 3, a significantly greater proportion of patients achieved a PASI-75 in the Otezla group compared to the placebo group (22.2% and 7.9%, respectively; $p < 0.01$) at Week 16. The response was maintained at Week 24. There were more patients with PASI-75 responses in the Otezla group than in patients treated with placebo, with or without concomitant DMARD treatment. Among patients who were continuously treated with Otezla, a PASI-75 response of 39.1% was observed at Week 52. Similar responses were observed in Studies PALACE 1 and PALACE 2 at Weeks 16, 24 and 52.

2. Clinical Trial experience in DMARD naive Psoriatic Arthritis patients

The safety and efficacy of Otezla were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (Study PALACE 4) in 527 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) who were DMARD-naive. Patients enrolled in this study had a diagnosis of PsA for at least 3 months. Previous treatment with DMARDs or biologics was not allowed.

Patients were randomly assigned to placebo (n = 176), Otezla 20 mg (n = 175), or Otezla 30 mg (n = 176) given orally twice daily. Patients were allowed to receive stable doses of prednisone (equivalent to ≤ 10 mg/day) and/or nonsteroidal anti-inflammatory drugs (NSAIDs). The use of other DMARDs including methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), or biologics was prohibited. Patients with each subtype of PsA were enrolled, including symmetric polyarthritis (61.3%), asymmetric oligoarthritis (30%), distal interphalangeal (DIP) joint arthritis (6.6%), arthritis mutilans (0.8%), and predominant spondylitis (1.3%). Patients with pre-existing enthesitis (65%) and pre-existing dactylitis (50%) were enrolled. The median duration of PsA disease was 1.1 years.

Patients received concomitant therapy including low dose oral corticosteroids (7.2%) and NSAIDs (73.1%); the combination of apremilast with small molecule or biologic DMARDs was not studied.

The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16. 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-randomised 1:1 in a blinded fashion to either Otezla 20 mg twice daily or 30 mg twice daily. Otezla patients remained on their initial treatment. At Week 24, all remaining placebo patients were re-randomised to either Otezla 20 mg twice daily or Otezla 30 mg twice daily. At the end of 52 weeks, patients could enter a long-term open-label extension study for a total duration of up to 5 years. This study did not investigate the effects of Otezla on structural progression.

Clinical Responses:

The percent of patients achieving ACR 20/50/70 responses at Week 16 in Study PALACE 4 is presented below in **Table 2**. Otezla, compared with placebo, resulted in significantly greater improvement in signs and symptoms of psoriatic arthritis, as demonstrated by the proportion of patients with ACR 20 response at Week 16. Improvement in ACR 50/70 responses were also demonstrated at Week 16. ACR 20/50/70 responses were maintained at Week 24.

Table 2 Proportion of Patients with ACR Responses at Week16 in Study PALACE 4

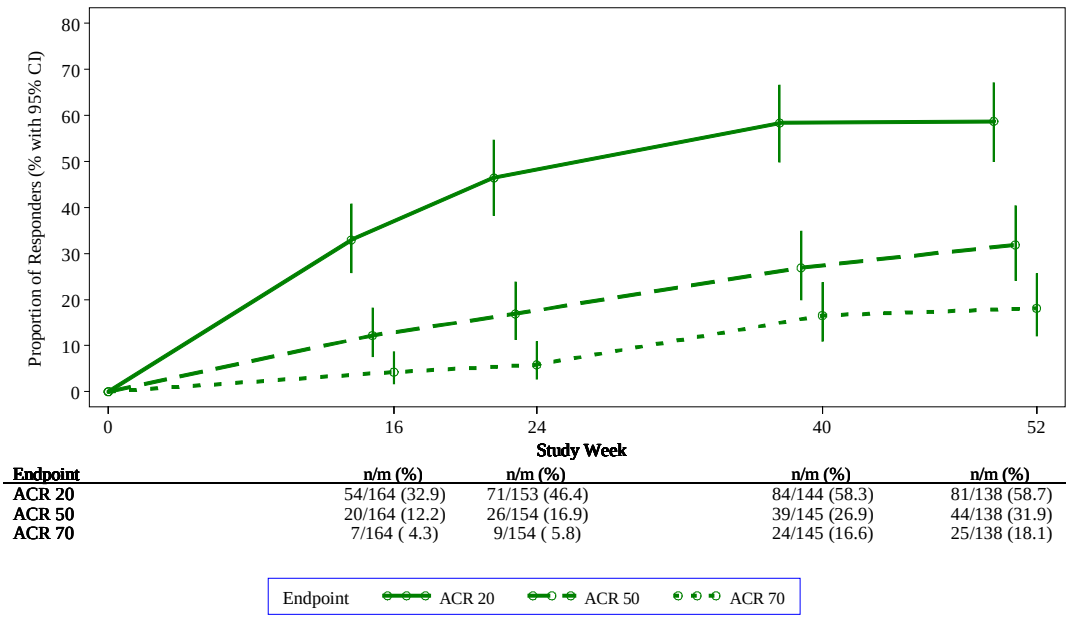
PALACE 4		
	Placebo	**Otezla 30 mg twice daily**
N[a]	176	176
ACR 20		
Week 16	16%	31%**
ACR 50		
Week 16	5%	11%*
ACR 70		
Week 16	1%	4%

[a]N is number of randomised and treated patients
*p ≤ 0.05 for Otezla vs. placebo.
**p ≤0.001 for Otezla vs. placebo.

ACR 20/50/70 Response Through Week 52

Among 176 patients initially randomized to apremilast 30 mg twice daily, 138 (78%) patients were still on this treatment at Week 52. In these patients, ACR 20/50/70 responses at week 52 were 57%, 25%, and 11% respectively (**Figure 2**).

Figure 2 Proportion of ACR 20/50/70 Responders Through Week 52 in Study PALACE 4 (Data as Observed)



Endpoint	n/m (%)	n/m (%)	n/m (%)	n/m (%)
ACR 20	54/164 (32.9)	71/153 (46.4)	84/144 (58.3)	81/138 (58.7)
ACR 50	20/164 (12.2)	26/154 (16.9)	39/145 (26.9)	44/138 (31.9)
ACR 70	7/164 (4.3)	9/154 (5.8)	24/145 (16.6)	25/138 (18.1)

Note: n/m is the number of responders/number of subjects with sufficient data for definitive determination of response status at each time point, which includes subjects who discontinued early between the preceding time point and the time point in question.

Treatment with Otezla 30 mg twice daily resulted in greater improvement for each ACR component [number of swollen and tender joints, physician and patient assessment of disease activity and patient assessment of pain, HAQ-DI score and CRP value], compared to placebo at Weeks 16 and 24 in Study

PALACE 4. Among patients who were continuously treated with Otezla, sustained improvements in individual ACR components were observed at Week 52.

The proportion of patients achieving a modified PsARC was significantly greater in the Otezla 30 mg twice daily group compared with placebo at Week 16 (45.5% and 24.4% respectively; $p < 0.001$) in Study PALACE 4. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the modified PsARC response was 75.9% at Week 52.

In patients with pre-existing enthesitis or dactylitis, treatment with Otezla 30 mg twice daily resulted in improvement in enthesitis and dactylitis, compared to placebo at Week 16. The responses were maintained at Week 24. Among patients who were continuously treated with Otezla, sustained improvement in enthesitis and dactylitis was observed through Week 52.

Physical function response and health-related quality of life

Patients treated with Otezla 30 mg twice daily demonstrated a significantly greater improvement in physical function compared to placebo treated patients, as shown in the mean change from Baseline in HAQ-DI score at Week 16 (-0.205 and -0.012, respectively; $p < 0.001$) and Week 24 (-0.207 vs. -0.012, respectively; $p < 0.001$) in Study PALACE 4. Among patients who were continuously treated with Otezla, the mean change from baseline in HAQ-DI score was -0.392 at Week 52. In addition, there was a greater proportion of HAQ-DI responders who showed improvement (≥ 0.3 improvement from baseline) at Week 16 for the Otezla 30 mg twice daily group compared to the placebo group (34.7% and 19.3%, respectively). The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the proportion of HAQ-DI responders was 48.9% at Week 52.

Treatment with Otezla 30 mg twice daily demonstrated a significantly greater improvement, compared to placebo, in the mean change from Baseline in the SF-36v2 PF at Week 16 (3.19 and 0.01 respectively; $p < 0.001$) in Study PALACE 4. In addition, treatment with Otezla 30 mg twice daily demonstrated a greater improvement, compared to placebo in the mean change from Baseline in the PCS at Week 16 (4.20 and 0.93 respectively; $p < 0.001$). The responses were maintained at Week 24. Among patients who were continuously treated with Otezla, the mean change from baseline in SF-36v2 PF and PCS scores of 6.41 and 6.67, respectively, were observed at Week 52.

There was no worsening observed in the mean change from Baseline in the SF-36v2 MCS at Week 16 and Week 24 in Study PALACE 4. Among patients who were continuously treated with Otezla 30 mg twice daily, the mean change from baseline in the SF-36v2 MCS score was 2.19 at Week 52.

There was greater improvement in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-fatigue) scores in the Otezla group when compared with placebo at Week 16 (2.62 and 0.07 respectively; $p < 0.01$) in Study PALACE 4. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the mean change from baseline in the FACIT-fatigue score was 5.89 at Week 52.

PASI-75 Response

Treatment with Otezla 30 mg twice daily resulted in improvement in the skin manifestations of psoriasis. Patients with psoriasis involvement of at least 3% BSA were evaluated using the PASI-75 response. At Week 16, there was a greater proportion of patients achieving a PASI-75 in the Otezla 30 mg twice daily group compared to the placebo group (26.6% and 10.8% respectively; $p < 0.01$) in Study PALACE 4. The response was maintained at Week 24. Among patients who were continuously treated with Otezla, the PASI-75 response was 31.9% at Week 52.

3. Clinical Trial experience in Psoriasis patients

The safety and efficacy of Otezla were evaluated in two multi-centre, randomised, double-blind, placebo-controlled studies (Studies ESTEEM 1 and ESTEEM 2) which enrolled a total of 1257 patients 18 years of age and older with moderate to severe plaque psoriasis who had a BSA involvement of ≥ 10%, Psoriasis Area and Severity Index (PASI) score ≥ 12, static Physician Global Assessment (sPGA) of ≥ 3 (moderate or severe), and who were candidates for phototherapy or systemic therapy. The studies did not include an active comparator arm.

These studies had a similar design through Week 32. In both studies, patients were randomised 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks (placebo-controlled phase) and from Weeks 16-32, all patients received Otezla 30 mg twice daily (maintenance phase). During the Randomised Treatment Withdrawal Phase (Weeks 32-52), patients originally randomised to Otezla who achieved at least a 75% reduction in their PASI score (PASI-75) (ESTEEM 1) or a 50% reduction in their PASI score (PASI-50) (ESTEEM 2) were re-randomised at week 32 to either placebo or Otezla 30 mg twice daily. Patients who were re-randomised to placebo and who lost PASI-75 response (ESTEEM 1) or lost 50% of the PASI improvement at Week 32 compared to Baseline (ESTEEM 2) were retreated with Otezla 30 mg twice daily. Patients who did not achieve the designated PASI response by Week 32, or who were initially randomised to placebo, remained on Otezla until Week 52.

In both studies, the primary endpoint was the proportion of patients who achieved PASI-75 at Week 16. The major secondary endpoint was the proportion of patients who achieved a sPGA score of clear (0) or almost clear (1) at Week 16. Other endpoints included BSA, Pruritus VAS, nail disease (NAPSI), scalp involvement (ScPGA), and quality of life measures (DLQI and SF-36 MCS).

Across both studies, patients ranged in age from 18 to 83 years, with an overall median age of 45.8 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 patients with sPGA score of 3 (moderate) and 4 (severe) at Baseline were 70.0% and 29.8%, respectively. Approximately 30% of all patients had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis (including treatment failures), with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one-third of patients had not received prior phototherapy, conventional systemic or biologic therapy. A total of 18% of patients had a history of psoriatic arthritis.

Clinical Response

The proportion of patients achieving PASI-50, -75 and -90 responses, and sPGA score of clear or almost clear, are presented in **Table 3** below. Otezla resulted in significant improvements in moderate to severe plaque psoriasis as demonstrated by the proportion of patient with PASI-75 response at Week 16 compared with placebo. Clinical improvement measured by sPGA, PASI-50 and PASI-90 responses were also demonstrated at Week 16. In addition, Otezla demonstrated a treatment benefit across multiple manifestations of psoriasis including pruritus, nail disease, scalp involvement and quality of life measures.

Table 3. Clinical Response at Week 16 in Studies ESTEEM 1 and ESTEEM 2[a]

	ESTEEM 1		ESTEEM 2	
	Placebo	**30 mg twice daily APR[#]**	**Placebo**	**30 mg twice daily APR[#]**
N	282	562	137	274
PASI 75[b], 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)
PASI 50, n (%)	48 (17.0)	330 (58.7)	27 (19.7)	152 (55.5)
PASI 90, n (%)	1 (0.4)	55 (9.8)	2 (1.5)	24 (8.8)
Percent Change BSA[d,h] (%)	- 6.9 ± 38.95	- 47.8 ± 38.48	- 6.1 ± 47.57	-48.4 ± 40.78
Change in Pruritus VAS[e,h] (mm)	- 7.3 ± 27.08	- 31.5 ± 32.43	- 12.2 ± 30.94	- 33.5 ±35.46
Change in DLQI[f,h]	- 2.1 ± 5.69	- 6.6 ± 6.66	-2.8 ± 7.22	-6.7 ± 6.95
Change in SF-36 MCS[g,h]	- 1.02 ± 9.161	2.39 ± 9.504	0 ±10.498	2.58 ± 10.129

[#] p< 0.0001 for all comparisons vs. placebo, except for ESTEEM 2 PASI 90 and Change in SF-36 MCS where p = 0.0042 and p = 0.0078, respectively.
[a] Full Analysis Set, Last Observation Carried Forward
[b] PASI = Psoriasis Area and Severity Index
[c] sPGA = Static Physician Global Assessment
[d] BSA = Body Surface Area
[e] VAS = Visual Analog Scale; 0 = best, 100 = worst
[f] DLQI = Dermatology Life Quality Index; 0 = best, 30 = worst
[g] SF-36 MCS = Medical Outcome Study Short Form 36-Item Health Survey, Mental Component Summary
[h] mean +/- standard deviation

The clinical benefit of Otezla was demonstrated across multiple subgroups defined by baseline demographics, baseline clinical disease characteristics (including psoriasis disease duration and patients with a history of psoriatic arthritis), prior psoriasis medication usage and response to prior psoriasis treatments. Similar response rates were observed across all weight ranges.

Significantly greater improvements compared to placebo in mean % change in PASI from baseline, skin discomfort/pain and pruritus were observed at Week 2. In general, PASI responses were achieved by Week 16 and were sustained through Week 32.

During the Randomized Treatment Withdrawal Phase (Weeks 32 – 52) in Study ESTEEM 1, the mean percent improvement in PASI from Baseline remained stable (81-88%) for patients re-randomized to Otezla at Week 32. Approximately 61% of these patients had a PASI-75 response at Week 52. Of the patients re-randomized to placebo at Week 32, 11.7% achieved PASI-75 response at Week 52. Patients who were re-randomized to placebo lost PASI-75 response faster than patients re-randomized to Otezla. The median time to first loss of PASI-75 response for patients re-randomized to placebo and Otezla at Week 32 was 5.1 and 17.7 weeks, respectively.

In Study ESTEEM 2, 80.3% of patients re-randomized to Otezla at Week 32 had a PASI-50 response at Week 52. Of the patients with at least a PASI-50 response who were re-randomized to placebo at Week 32, 24.2% were PASI-50 responders at Week 52. Patients who were re-randomized to placebo lost 50% of their Week 32 PASI response significantly faster than patients re-randomized to Otezla. The median time to first loss of PASI-50 response for patients re-randomized to placebo and Otezla at Week 32 was 12.4 and 21.9 weeks, respectively.

After randomised withdrawal from therapy at Week 32, approximately 70% of patients in Study ESTEEM 1, and 65.6% of patients in Study ESTEEM 2, regained PASI-75 (Study ESTEEM 1) or PASI-50 (Study ESTEEM 2) responses after re-initiation of Otezla treatment. The duration of re-treatment was variable, and ranged from 3.4 to 22.1 weeks in Study ESTEEM 1 and from 2.6 to 18.3 weeks in Study ESTEEM 2.

Nail Psoriasis

In Study ESTEEM 1, significant improvements (reductions) in nail psoriasis, as measured by the mean percent change in Nail Psoriasis Severity Index (NAPSI) from Baseline, were detected in patients receiving Otezla compared with placebo-treated patients at Week 16 (Otezla 30 mg twice daily: -22.5%; placebo: +6.5%; $p < 0.0001$). Similar improvements were observed in Study ESTEEM 2 (Otezla 30 mg twice daily: -29.0%; placebo: -7.1%, $p = 0.0052$). Further improvements in nail psoriasis were observed in patients continuously treated with Otezla, with mean percent changes from Baseline in NAPSI at Week 32 of -43.6% in Study ESTEEM 1 and -60.0% in Study ESTEEM 2.

Scalp Psoriasis

In Study ESTEEM 1, significant improvements in scalp psoriasis of at least moderate severity (≥ 3), measured by the proportion of patients achieving Scalp Psoriasis Physician's Global Assessment (ScPGA) of clear (0) or minimal (1) at Week 16, were detected in patients receiving Otezla compared with placebo-treated patients (46.5% and 17.5%, respectively, $p < 0.0001$). Similar results were observed in Study ESTEEM 2 (APR 30 twice daily 40.9%; placebo 17.2%, $p < 0.0001$).

Quality of Life

In Studies ESTEEM 1 and 2, significant improvements in quality of life as measured by the Dermatology Life Quality Index (DLQI) and the SF-36v2 MCS were demonstrated in patients receiving Otezla compared with placebo-treated patients. In addition, in Study ESTEEM 1, significant improvement in the Work Limitations Questionnaire (WLQ-25) Index was achieved in patients receiving Otezla compared with placebo.

v) Indications

Otezla is indicated for:

- The treatment of signs and symptoms of active psoriatic arthritis in adult patients.
- The treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

vi) Contraindications

Otezla is contraindicated:

- In patients with known hypersensitivity to the active substance or to any of the excipients.
- During pregnancy and in nursing women.

vii) Precautions

1. Effects on fertility

No fertility data is available in humans.

In a male mouse fertility study, apremilast at oral dosages of 1, 10, 25, and 50 mg/kg/day produced no effects on male fertility; the no observed adverse effect level (NOAEL) for male fertility was greater than 50 mg/kg/day (3-fold clinical exposure).

In a combined female mouse fertility and embryo-foetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, a prolongation of oestrous cycles and increased time to mating were observed at 20 mg/kg/day and above; despite this, all mice mated and pregnancy rates were unaffected. The no observed effect level (NOEL) for female fertility was 10 mg/kg/day (1.0-fold clinical exposure).

2. Use in pregnancy (Pregnancy Category B3)

There are no adequate and well controlled studies of Otezla in pregnant women.

Otezla is contraindicated in pregnant women, and should not be used in women attempting to become pregnant.

Apremilast was not teratogenic in mice or monkeys. Other effects of apremilast on pregnancy included embryofoetal loss in mice and monkeys, and reduced foetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. No such effects were observed when exposure in animals was at 1.3-fold the clinical exposure.

In a combined female mouse fertility and embryofoetal developmental toxicity study, the maternal and developmental NOEL observed was 10 mg/kg/day (1.3-fold clinical exposure). No treatment-related developmental malformations were observed up to the highest dosage of 80 mg/kg/day (4.0-fold clinical exposure).

In a monkey embryofoetal developmental toxicity study, oral dosages of 20, 50, 200, and 1000 mg/kg/day resulted in a dose-related increase in prenatal loss (abortions) at dosages of 50 mg/kg/day and above; no test article-related effect in prenatal loss was observed at 20 mg/kg/day (1.4-fold clinical exposure). No treatment-related foetal developmental effects or malformations were observed in the monkey up to the highest dosage of 1000 mg/kg/day in the study (3.5-fold clinical exposure).

In a pre- and postnatal study, in which apremilast was administered orally to pregnant female mice, clinical signs of maternal toxicity associated with delivering pups were observed in one mouse at each of 80 and 300 mg/kg/day. Increased pre- and postnatal pup mortality and reduced pup body weights

during the first week of lactation were observed at ≥ 80 mg/kg/day (≥ 4.0-fold clinical exposure). The NOEL in the mouse for maternal toxicity and F1 generation was 10 mg/kg/day (1.3-fold clinical AUC).

3. Use during lactation

Apremilast was detected in milk of lactating mice.

It is not known whether apremilast or its metabolites are excreted in human milk. Therefore, the use of Otezla is contraindicated in mothers who are breast-feeding.

4. Paediatric use

The safety and effectiveness of Otezla has not been established in patients under the age of 18 years.

5. Use in the elderly

Otezla was studied in young and elderly healthy subjects. The exposure in elderly subjects (65 to 85 years of age) is about 13% higher in AUC and about 6% higher in C_{max} for apremilast than that in young subjects (18 to 55 years of age).

No overall differences were observed in the safety or efficacy profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

No dosage adjustment is necessary for elderly patients.

6. Weight Decrease

In some patients treatment with Otezla has been associated with 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 Adverse Effects section).

7. Depression

Before using Otezla in patients with a history of depression and/or suicidal thoughts or behaviour, prescribers should carefully weigh the risks and benefits of treatment with Otezla in such patients (see Adverse Effects section).

8. Renal Function

Assessment of renal function is recommended prior to initiation of Otezla.

9. Genotoxicity

Apremilast is not genotoxic. Apremilast did not induce mutations in an Ames assay or chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of metabolic activation. Apremilast was not clastogenic in an in vivo mouse micronucleus assay at doses up to 2000 mg/kg/day.

10. Carcinogenicity

Carcinogenicity studies showed no evidence of treatment-related tumours following oral treatment with apremilast at plasma exposure levels (AUC) that were 7 to 10-fold (mice) and 0.1 to 1-fold (rats) than anticipated clinically.

11. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use of machines have been performed.

12. Use in patients with Lactose Intolerance

Otezla tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

viii) Interaction with other medicines

Otezla has not been studied in combination with cyclosporin or biologic therapies.

Effect of Otezla on other medicinal products

There was no pharmacokinetic drug-drug interaction between Otezla and methotrexate. Otezla can be co-administered with methotrexate.

There was no pharmacokinetic drug-drug interaction between Otezla and oral contraceptives containing ethinyl estradiol and norgestimate. Otezla can be taken with oral contraceptives without clinically relevant drug-drug interaction.

In vitro, apremilast is not an inhibitor or inducer of cytochrome P450 enzymes. Hence, apremilast co-administered with substrates of CYP enzymes is unlikely to affect the clearance and exposure of drugs that are metabolized by CYP enzymes.

In vitro, apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC>50µM).

In vitro, apremilast has little to no inhibitory effect (IC_{50}>10µM) on 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) and is not a substrate for these transporters. Hence, clinically relevant drug-drug interactions are unlikely when apremilast is co-administered with drugs that are substrates or inhibitors of these transporters.

Effect of other medicinal products on Otezla

Co-administration of Otezla with multiple doses of rifampicin resulted in a decrease in apremilast area-under-the concentration time curve (AUC) and maximum serum concentration (C_{max}) by approximately 72% and 43%, respectively. Apremilast exposure is decreased when administered concomitantly with strong inducers of CYP3A4 (e.g. rifampicin, phenobarbitone, carbamazepine, phenytoin and St. John's Wort) and may result in reduced clinical response.

Ketoconazole co-administration increased mean apremilast AUC $_{0-\infty}$ and C_{max} by approximately 36% and by 5%, respectively, which is not clinically meaningful. Otezla can be co-administered with a potent CYP3A4 inhibitor like ketoconazole.

ix) Adverse effects

Otezla was evaluated in 4 multi-centre, randomised, double-blind, placebo-controlled trials (Studies PALACE 1, PALACE 2, PALACE 3 and PALACE 4) of similar design in adult patients with active psoriatic arthritis. Across the 4 studies, there were 1945 patients who received at least one dose of Otezla 20 mg twice daily or Otezla 30 mg twice daily.

Otezla was evaluated in 2 multi-centre, randomised, double-blind, placebo-controlled trials (Studies ESTEEM 1 and ESTEEM 2) of similar design in adult patients with moderate to severe plaque psoriasis. Across the two studies, 1184 psoriasis patients were exposed to Otezla 30 mg twice daily.

Hypersensitivity reactions were observed infrequently in clinical studies with Otezla.

Tabulated list of Treatment Emergent Adverse Events:

The observed Treatment Emergent Adverse Events (TEAEs) with patient incidence of at least 2% in any treatment group during clinical studies is presented in **Table 4**. The frequencies of TEAEs are based on those reported in the Otezla 30 mg twice daily arm in either psoriatic arthritis or psoriasis Phase 3 studies during weeks 0-16 of therapy. The highest incidence from either indication is shown below. The most frequently reported TEAEs were gastrointestinal related. The overall incidence of serious adverse events was low and similar to placebo.

Table 4 Otezla Data Pool: TEAES with Patient Incidence of at Least 2% in psoriatic arthritis or psoriasis Phase 3 studies in any Treatment Group (highest incidence from either indication) During Weeks 0-16

Preferred Term[a]	Placebo n (%)	Otezla 30 mg twice daily n (%)
Diarrhoea	28 (6.7)	186 (15.7)
Nausea	28 (6.7)	164 (13.9)
Upper respiratory tract infection	27 (6.5)	100 (8.4)
Headache	24 (3.6)	77 (7.9)
Nasopharyngitis	29 (6.9)	89 (7.5)
Tension headache	14 (3.3)	85 (7.2)
Vomiting	7 (1.7)	39 (3.3)
Fatigue	6 (1.4)	32 (2.7)
Dyspepsia	4 (1.0)	31 (2.6)
Hypertension	15 (2.2)	25 (2.6)
Decreased appetite	4 (1.0)	28 (2.4)
Arthralgia	7 (1.7)	25 (2.1)
Back pain	4 (1.0)	25 (2.1)
Migraine	4 (1.0)	25 (2.1)
Sinusitis	6 (1.4)	25 (2.1)
Abdominal discomfort	6 (1.4)	24 (2.0)
Frequent bowel movements	1 (0.2)	24 (2.0)
Gastroenteritis	9 (2.2)	20 (1.7)
Urinary tract infection	9 (2.2)	17 (1.4)

Preferred Term[a]	Placebo n (%)	Otezla 30 mg twice daily n (%)
Psoriasis	13 (3.1)	10 (0.8)

[a] Preferred Terms are coded using the MedDRA (Version 14.0)

Tabulated list of adverse reactions:

The adverse reactions observed in patients treated with Otezla are listed below by system organ class (SOC) and frequency for all adverse reactions. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The adverse drug reactions were determined based on data from the Otezla Phase 3 clinical development program. The frequencies of adverse drug reactions are those reported in the Otezla arms of the four Phase 3 studies in psoriatic arthritis (n = 1945) or the two Phase 3 studies in psoriasis (n = 1184) (highest frequency from either data pool is represented in **Table 5**).

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100) or rare (≥ 1/10,000 to < 1/1,000).

Table 5. Summary of Adverse Reactions in Phase 3 Psoriatic Arthritis and Psoriasis Clinical Studies

System Organ Class	Frequency	Preferred Term [a]
Gastrointestinal disorders	Very Common	Diarrhoea
		Nausea
	Common	Vomiting
		Frequent bowel movements
		Abdominal pain upper
		Gastroesophageal reflux disease
		Dyspepsia
General disorders and administrative site conditions	Common	Fatigue
Immune System disorders	Uncommon	Hypersensitivity
Infections and infestations	Common	Bronchitis
		Upper respiratory tract infection
		Nasopharyngitis
Investigations	Uncommon	Weight decrease
Metabolism and nutrition disorders	Common	Decreased appetite
Musculoskeletal and connective tissue	Common	Back pain
Nervous system disorders	Common	Migraine
		Tension Headache
		Headache
Psychiatric disorders	Common	Insomnia

System Organ Class	Frequency	Preferred Term [a]
Respiratory, thoracic, and mediastinal disorders	Common	Cough
Skin and subcutaneous tissue disorders	Uncommon	Rash

[a] Preferred Terms are coded using the MedDRA (Version 14.0)

The most commonly reported adverse reactions in Phase 3 (Studies PALACE 1, PALACE 2, PALACE 3, PALACE 4 and ESTEEM 1 and ESTEEM 2) clinical studies have been gastrointestinal (GI) disorders including diarrhoea (15.7%) and nausea (13.9%). These GI adverse reactions were mostly mild to moderate in severity, with 0.3% of patients reporting severe diarrhoea and 0.3% of patients reporting severe nausea. These adverse reactions generally occurred within the first 2 weeks of treatment and usually resolved within 4 weeks. The other most commonly reported adverse reactions included upper respiratory tract infections (8.4%), headache (7.9%), and tension headache (7.2%). Overall, most adverse reactions were considered to be mild or moderate in severity. The most common adverse reactions leading to discontinuation during the first 16 weeks of treatment were diarrhoea (1.7%), and nausea (1.5%).

Description of selected adverse reactions:

Weight Decrease:

Patient weight was measured routinely in clinical studies.

The mean observed weight loss in patients treated for up to 52 weeks with apremilast was 1.99 kg. A total of 14.3% of patients receiving apremilast had observed weight loss between 5-10% while 5.7% of the patients receiving apremilast had observed weight loss greater than 10%. None of these patients had overt clinical consequences resulting from weight loss. A total of 0.1% of patients treated with apremilast discontinued due to adverse reaction of weight decreased. Weight decreases of greater than 5% of baseline body weight were observed more frequently in women than in men.

Depression:

Psoriatic arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 0.9% (18/1945) of subjects treated with Otezla reported depression or depressed mood compared to 0.7% (5/671) treated with placebo. During the clinical trials, 0.1% (4/1945) of subjects treated with Otezla discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/671). Depression was reported as serious in 0.2% (3/1945) of subjects exposed to Otezla, compared to none in placebo-treated subjects (0/671). Instances of suicidal ideation and behaviour have been observed in 0.2% (3/1945) of subjects while receiving Otezla, compared to none in placebo treated subjects (0/671). 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, 1.2% (14/1184) of subjects treated with Otezla reported depression compared to 0.5% (2/418) treated with placebo. During the clinical trials, 0.1% (1/1184) of subjects treated with Otezla discontinued treatment due to depression compared with none in placebo-treated subjects (0/418). Depression was reported as serious in 0.1% (1/1184) of subjects exposed to Otezla, compared to none in placebo-treated subjects (0/418). Instances of suicidal behaviour have been observed in 0.1% (1/1184) of subjects while receiving Otezla, compared to 0.2% (1/418) in placebo-treated subjects. In the clinical trials, one subject treated with Otezla attempted suicide while one who received placebo committed suicide.

Safety in elderly patients

No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

x) Dosage and Administration

Treatment with Otezla should be initiated by specialists experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis.

The recommended dose of Otezla is 30 mg twice daily taken orally approximately 12 hours apart. An initial titration schedule is required as shown below in **Table 6**. No re-titration is required after initial titration.

Table 6: Dose Titration Schedule

Day 1	Day2		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

Otezla tablets should be swallowed whole, either with or without food. The tablets should not be crushed, split or chewed.

If patients miss a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose, the missed dose should not be taken and the next dose should be taken at the regular time.

No dosage adjustment is necessary for elderly patients.

No dose adjustment is needed in patients with mild renal impairment. There are limited data on moderate renal impairment. Otezla should be dose reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockroft-Gault equation). For initial dosage titration in this group, it is recommended that apremilast be titrated using only the AM schedule listed in **Table 6** and the PM doses be skipped.

Dose adjustment is not required in patients with hepatic impairment. The safety of Otezla was not evaluated in PsA or PSOR patients with hepatic impairment.

In the event of intolerable adverse events, interruption or discontinuation of Otezla should be considered.

xi) Overdosage

Otezla was studied in healthy subjects at a maximum total daily dose of 100 mg (given as 50 mg twice daily) for 4.5 days without evidence of dose limiting toxicities. Patients should be managed by symptomatic and supportive care should there be an overdose.

Contact the Poisons Advisory Centre on 13 11 26 for advice on management.

xii) Presentation and storage conditions

Presentation[#]

A two-week titration pack (4 x 10 mg, 4 x 20 mg and 5 x 30 mg for the first week for dose titration and 14 x 30 mg tablets for the second week).

A four-week pack (56 x 30 mg tablets)

A 12 week pack (168 x 30 mg tablets)

[#] Not all pack sizes are marketed in Australia

Otezla 10 mg Tablets: Pink, diamond shaped 10 mg film-coated tablet with “APR” engraved on one side and “10” on the opposite side.

Otezla 20 mg Tablets: Brown, diamond shaped 20 mg film-coated tablet with “APR” engraved on one side and “20” on the opposite side.

Otezla 30 mg Tablets: Beige, diamond shaped 30 mg film-coated tablet with "APR" engraved on one side and "30" on the opposite side.

Composition

Active

Apremilast

Excipients

See Description section, for a list of the excipients.

Storage conditions

Store below 30°C.

Container type

The tablets are provided in polyvinylchloride (PVC) blisters with push through aluminium foil.

xiii) Name and address of the sponsor

Sponsored in Australia by:

Celgene Pty Limited
Level 7, 607 St Kilda Road,
Melbourne, VIC 3004,
Australia.
Telephone: 1800 CELGENE (1800 235 4363)

xiv) Poison Schedule of the medicine

Schedule 4 (Prescription Only Medicine)

xv) Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

19 March 2015