OTEZLA® Tablet (Apremilast)

[Prescription Drug]

[Ingredients and Amount]

In 10mg 1 tablet (Approximately 104mg)

Active ingredient: Apremilast ---------- 10mg

In 20mg 1 tablet (Approximately 208mg)

Active ingredient: Apremilast ---------- 20mg

In 30mg 1 tablet (Approximately 312mg)

Active ingredient: Apremilast ---------- 30mg

Excipient

- 10mg Tablet: Lactose anhydrous, Microcystaline cellulose, Croscarmellose Sodium, Magensium Stearate, OpadryII Pink
- 20mg Tablet: Lactose anhydrous, Microcystaline cellulose, Croscarmellose Sodium, Magensium Stearate, OpadryII Brown
- 30mg Tablet: Lactose anhydrous, Microcystaline cellulose, Croscarmellose Sodium, Magensium Stearate, OpadryII Beige

[Appearance]

- 10mg Tablet: Pink, diamond shaped film-coated tablet
- 20mg Tablet: Brown, diamond shaped film-coated tablet
- 30mg Tablet: Beige, diamond shaped 30 mg film-coated tablet

[Indication]

1. Psoriatic Arthritis

   The treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior anti-rheumatic therapy (DMARD)

2. Psoriasis

   The treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

[Dose and Administration]

Treatment with Otezla should be initiated by specialists experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis. To reduce adverse events in gasto-intestinal tract, OTEZLA should be administered according to the schedule in Table 1 at initial therapy. The

recommended maintenance dosage is 30 mg twice daily taken orally, approximately 12 hours apart.
No re-titration is required after initial titration.

Table 1. Dosage Titration Schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 and after	
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 can be administered without regard to meals. Do not crush, split, or chew the tablets.
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.

Renal impairment patients

No dose adjustment is needed in patients with mild and moderate renal impairment. The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockcroft-Gault equation). For initial dose 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.
It is recommended to evaluate renal fuction prior to administration.

Hepatic impairment patients

No dose adjustment is necessary for patients with hepatic impairment.

[Precaution in Use]

1. Contraindication

1) Hypersensitivity to the active ingredient or to any of the excipients
2) Pregnant or nursing women
3) Do not administer to patient with genetic disorder (e.g galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption) since OTEZLA contains lactose.

2. Carefully administer to patients in below.

1) Renal impairment patients

3. Advers Events

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.

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 2. 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 most frequently reported TEAEs were gastrointestinal related. The overall incidence of serious adverse events was low and similar to placebo.

Table 2. TEAES with Patient Incidence of at Least 2% in psoriatic arthritis or psoriasis Phase 3 studies

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)
Psoriasis	13 (3.1)	10 (0.8)

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 apremilast clinical development programme and post-marketing experience. 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 3).

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1,000), not known (cannot be estimated from the available data).

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

System Organ Class	Frequency	Preferred Term
Gastrointestinal disorders	Very Common	Diarrhoea
		Nausea
	Common	Vomiting
		Frequent bowel movements
		Abdominal pain upper
		Gastroesophageal reflux disease
		Dyspepsia
	Uncommon	Gastrointestinal Haemorrhage
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

System Organ Class	Frequency	Preferred Term
Nervous system disorders	Common	Migraine
		Tension Headache
		Headache
Psychiatric disorders	Common	Insomnia, Depression
	Uncommon	Suicidal ideation and behaviour
Respiratory, thoracic, and mediastinal disorders	Common	Cough
Skin and subcutaneous tissue disorders	Uncommon	Rash, Urticaria
	Not known	Angioedema

The most commonly reported adverse reactions in Phase 3 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

1) **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.
2) **Depression:** During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials for psoriatic arthritis, 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% (2/1945) 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.

During the 0 to 16 week placebo-controlled period of the 2 controlled clinical trials for Psoriasis, 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.

4. General Precaution

1) **Diarrhoea, Nausea, and Vomiting:** There have been post-marketing reports of severe diarrhoea, 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 may be at a higher risk of complications. If patients develop severe diarrhoea, nausea, or vomiting, discontinuation of treatment with apremilast may be necessary.
2) **Weight Decrease:** In some patient 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 3. Adverse Effects section).
3) **Depression:** Treatment with this drug is associated with an increase in occurrences of insomnia and 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 3. Adverse Effects section). 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 this drug if such events occur.

5. Drug Interaction

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

2) 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.
3) 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. 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 (Cmax) by approximately 72% and 43%, respectively. Co-administration of this drug with a potent CYP3A4 enzyme derivatives is not recommended.
4) Ketoconazole co-administration increased mean apremilast $AUC_{0-\infty}$ and Cmax by approximately 36% and by 5%, respectively, which is not clinically meaningful. Otezla can be co-administered with a potent CYP3A4 inhibitor like ketoconazole.

6. Fertility, pregnancy and lactation

1) **Pregnancy**: 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. 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.
2) **Nursing Mother**: 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.
3) **Women of childbearing potential**: Pregnancy should be excluded before treatment can be initiated. Women of childbearing potential should use an effective method of contraception to prevent pregnancy during treatment.
4) **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-fetal developmental toxicity study, 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).

7. Paediatric use

The safety and effectiveness of Otezla has not been established in paediatric patients.

8. Use in the elderly

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.

9. 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.

10. Overdose

1) 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.
2) Patients should be managed by symptomatic and supportive care should there be an overdose.

11. Storage and Handling

1) Keep this medicine out of the reach of children
2) Storing the medicine in different container after taking out from the original container may result in misuse or negative impact on product quality. Keep the medicine in the original container.

12. Information for Healthcare Professionals

1) 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 and psoriasis.

2) Pharmacokinetics information

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 are 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%. The mean apparent volume of distribution (Vd) is 87 L, indicative of extravascular distribution.

Biotransformation

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 parent compound recovered in urine and faeces, respectively. The major circulating inactive metabolite is the glucuronide conjugate of *O*-demethylated apremilast (M12). Consistent with apremilast being a substrate of CYP3A4, apremilast exposure is decreased when administered concomitantly with rifampicin, a strong inducer of CYP3A4.
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 active substances that are metabolised by CYP enzymes.
In vitro, apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC50>50μM), however clinically relevant drug interactions mediated via P-gp are not expected to occur.
In vitro, apremilast has little to no inhibitory effect (IC50>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.

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. Following oral administration of radiolabelled 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.

Elderly patients

Apremilast 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).

Renal impairment

Reduce apremilast dose to 30 mg once daily in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2 or CLcr < 30 mL/min). In 8 subjects with severe renal impairment to whom a single dose of 30 mg apremilast was administered, the AUC and C_{max} of apremilast increased by approximately 89% and 42%, respectively.

Hepatic impairment

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

3) Clinical trials experience

Psoriatic Arthritis

The safety and efficacy of apremilast were evaluated in 3 multi-center, randomized, double-blind, placebo- controlled studies (Studies PALACE 1, PALACE 2, and PALACE 3) of similar design in adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment with small molecule or biologic DMARDs. A total of 1493 patients were randomised and treated with either placebo, apremilast 20 mg or apremilast 30 mg given orally twice daily.

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. Apremilast was used as a monotherapy (34.8%) or in combination with stable doses of small molecule DMARDs (65.2%). Patients received apremilast in combination with one or more of the following: methotrexate (MTX, ≤ 25 mg/week, 54.5%), sulfasalazine (SSZ, ≤ 2 g/day, 9.0%), and leflunomide (LEF; ≤ 20 mg/day, 7.4%). Patients with each subtype of PsA were enrolled in 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 enthesopathy (63%) or pre-exisitng dactylitis (42%) were enrolled. A total of 76.4% of patients were previously treated with only small-molecule DMARDs and 22.4% of patients were previously treated with biologic DMARDs, which includes 7.8% who had a therapeutic failure with a prior biologic DMARD. The median duration of PsA disease was 5 years.

Based on the study design, patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo patients who were considered non-responders were re- randomized 1:1 in a blinded fashion to either apremilast

20 mg twice daily or 30 mg twice daily. At Week 24, all remaining placebo-treated patients were switched to either apremilast 20 or 30 mg BID. The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16.

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 Weeks 16. The proportion of patients with ACR 20/50/70(responses in Studies PALACE 1, PALACE 2 and PALACE 3, and the pooled data for studies PALACE 1, PALACE 2 and PALACE 3, for apremilast 30 mg twice daily at Week 16, are shown in Table 4.

Among patients who were initially randomized to apremilast 30 mg twice daily treatment, ACR 20/50/70 response rates were maintained through Week 52 in the pooled Studies PALACE 1, PALACE 2 and PALACE 3 (Figure 1).

Table 4. Proportion of patients with ACR responses in studies PALACE 1, PALACE 2 and PALACE 3 and pooled studies at Week 16

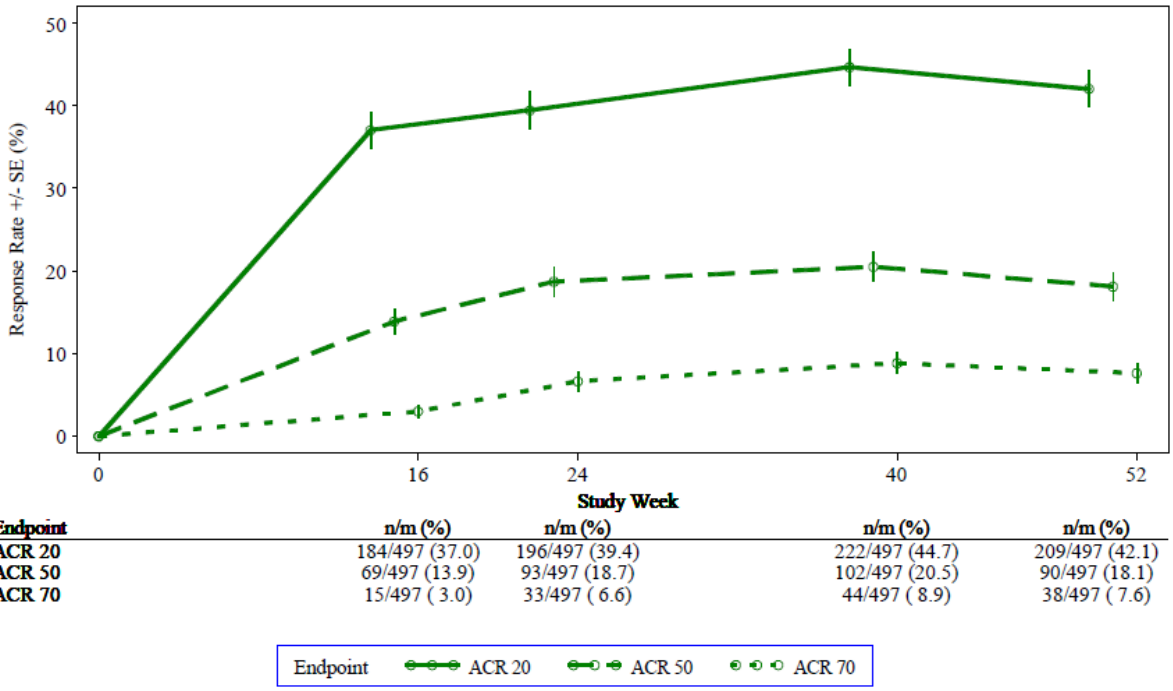
	PALACE 1		**PALACE 2**		**PALACE 3**		**POOLED**	
N[a]	**Placebo +/- DMARDs N=168**	**Apremilast 30 mg BID +/- DMARDs N=168**	**Placebo +/- DMARDs N=159**	**Apremilast 30 mg BID +/- DMARDs N=162**	**Placebo +/- DMARDs N=169**	**Apremilast 30 mg BID +/- DMARDs N=167**	**Placebo +/- DMARDs N=496**	**Apremilast 30 mg BID +/- DMARDs N=497**
ACR 20[a]								
Week 16	19.0%	38.1%**	18.9%	32.1%*	18.3%	40.7%**	18.8%	37.0%**
ACR 50								
Week 16	6.0%	16.1%*	5.0%	10.5%	8.3%	15.0%	6.5%	13.9%**
ACR 70								
Week 16	1.2%	4.2%	0.6%	1.2%	2.4%	3.6%	1.4%	3.0%

*p ≤ 0.01 for apremilast vs. placebo.

**p ≤ 0.001 for apremilast vs. placebo

[a] N is the number of patients as randomized and treated.

Figure 1. Proportion of ACR 20/50/70 responders through Week 52 in the pooled analysis of studies PALACE 1, PALACE 2 and PALACE 3 (NRI*)



Endpoint	n/m (%)	n/m (%)	n/m (%)	n/m (%)
ACR 20	184/497 (37.0)	196/497 (39.4)	222/497 (44.7)	209/497 (42.1)
ACR 50	69/497 (13.9)	93/497 (18.7)	102/497 (20.5)	90/497 (18.1)
ACR 70	15/497 (3.0)	33/497 (6.6)	44/497 (8.9)	38/497 (7.6)

*NRI: None responder imputation. Subjects who discontinued early prior to the time point and subjects who did not have sufficient data for a definitive determination of response status at the time point are counted as non-responders.

Among 497 patients initially randomized to apremilast 30 mg twice daily, 375 (75%) patients were still on this treatment on Week 52. In these patients, ACR 20/50/70 responses at Week 52 were of 57%, 25%, and 11% respectively.

Responses observed in the apremilast treated group were similar in patients receiving and not receiving concomitant DMARDs, including MTX. Patients previously treated with DMARDs or biologics who received apremilast achieved a greater ACR 20 response at Week 16 than patients receiving placebo. Similar ACR responses were observed in patients with different PsA subtypes, including DIP. The number of patients with arthritis mutilans and predominant spondylitis subtypes was too small to allow meaningful assessment.

In PALACE 1, PALACE 2 and PALACE 3, improvements in Disease Activity Scale (DAS) 28 C-reactive protein (CRP) and in the proportion of patients achieving a modified PsA response criteria (PsARC) were greater in the apremilast group, compared to placebo at Week 16 (nominal p-value p≤0.0004, p-value≤0.0017, respectively). These improvements were maintained at Week 24. Among patients who remained on the apremilast treatment to which they were randomized at study start, DAS28(CRP) score and PsARC response were maintained through Week 52.

At Weeks 16 and 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and

enthesitis) and in the skin manifestations of psoriasis were seen in the apremilast-treated patients. Among patients who remained on the apremilast treatment to which they were randomized at study start, these improvements were maintained through Week 52.

Physical function and health-related quality of life

Apremilast-treated patients demonstrated statistically significant improvement in physical function, as assessed by the disability index of the health assessment questionnaire (HAQ-DI) change from baseline, compared to placebo at Weeks 16 in PALACE 1, PALACE 2 and PALACE 3 and in the pooled studies. Improvement in HAQ-DI scores was maintained at Week 24.

Among patients who were initially randomized to apremilast 30 mg twice daily treatment, the change from baseline in the HAQ-DI score at week 52 was -0.333 in the apremilast 30 mg twice daily group in a pooled analysis of the open label phase of studies PALACE 1, PALACE 2 and PALACE 3.

In studies PALACE 1, PALACE 2 and PALACE 3, significant improvements were demonstrated in health- related quality of life, as measured by the changes from baseline in the physical functioning (PF) domain of the Short Form Health Survey version 2 (SF-36v2), and in the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-fatigue) scores in patients treated with apremilast compared to placebo at Weeks 16 and 24. Among patients who remained on the apremilast treatment, to which they were initially randomized at study start, improvement in physical function and FACIT- fatigue was maintained through Week 52.

Psoriasis

The safety and efficacy of apremilast were evaluated in two multicenter, randomized, double-blind, placebo- controlled studies (Studies ESTEEM 1 and ESTEEM 2) which enrolled a total of 1257 patients with moderate to severe plaque psoriasis who had a body surface area (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.

These studies had a similar design through Week 32. In both studies, patients were randomized 2:1 to apremilast 30 mg BID or placebo for 16 weeks (placebo-controlled phase) and from Weeks 16-32, all patients received apremilast 30 mg BID (maintenance phase). During the Randomized Treatment Withdrawal Phase (Weeks 32-52), patients originally randomized to apremilast 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-randomized at Week 32 to either placebo or apremilast 30 mg BID. Patients who were re-randomized 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 apremilast 30 mg BID.

Patients who did not achieve the designated PASI response by Week 32, or who were initially randomized to placebo, remained on apremilast until Week 52. The use of low potency topical corticosteroids on the face, axillae, and groin, coal tar shampoo and/or salicylic acid scalp preparations was permitted throughout the studies. In addition, at Week 32, subjects who did not achieve a PASI-75 response in ESTEEM 1, or a PASI- 50 response in ESTEEM 2, were permitted to use topical psoriasis therapies and/or phototherapy in addition to apremilast 30 mg BID treatment.

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.

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 was 70.0% and 29.8%, respectively with a mean baseline BSA involvement of 25.19% (median 21.0%). 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.

The proportion of patients achieving PASI-50, -75 and -90 responses, and sPGA score of clear (0) or almost clear (1), are presented in Table 5 below. Treatment with apremilast resulted in significant improvement in moderate to severe plaque psoriasis as demonstrated by the proportion of patients with PASI-75 response at Week 16, compared to placebo. Clinical improvement measured by sPGA, PASI-50 and PASI-90 responses were also demonstrated at Week 16. In addition, apremilast demonstrated a treatment benefit across multiple manifestations of psoriasis including pruritus, nail disease, scalp involvement and quality of life measures.

Table 5. Clinical response at week 16 in studies ESTEEM 1 and ESTEEM 2 (FAS[a], LOCF[b])

	ESTEEM 1		ESTEEM 2	
	Placebo	**30 mg BID APR***	**Placebo**	**30 mg BID APR***
N	282	562	137	274
PASI[c] 75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[d] 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[e] (%) mean± SD	- 6.9 ± 38.95	- 47.8 ± 38.48	- 6.1 ± 47.57	- 48.4 ± 40.78
Change in Pruritus VAS[f] (mm), mean± SD	- 7.3 ± 27.08	- 31.5 ± 32.43	- 12.2 ± 30.94	- 33.5 ±35.46
Change in DLQI[g], mean± SD	- 2.1 ± 5.69	- 6.6 ± 6.66	- 2.8 ± 7.22	- 6.7 ± 6.95
Change in SF-36 MCS[h], mean± SD	- 1.02 ± 9.161	2.39 ± 9.504	0.00 ±10.498	2.58 ± 10.129

* p< 0.0001 for apremilast vs placebo, except for ESTEEM 2 PASI 90 and Change in SF-36 MCS where p=0.0042 and p=0.0078, respectively.

[a] FAS = Full Analysis Set

[b] LOCF= Last Observation Carried forward

[c] PASI = Psoriasis Area and Severity Index

[a] sPGA = Static Physician Global Assessment

[e] BSA = Body Surface Area

[l] VAS = Visual Analog Scale; 0 = best, 100 = worst

[g] DLQI = Dermatology Life Quality Index; 0 = best, 30 = worst

[h] SF-36 MCS = Medical Outcome Study Short Form 36-Item Health Survey, Mental Component Summary

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

Response to apremilast was rapid, with significantly greater improvements in the signs and symptoms of psoriasis, including PASI, skin discomfort/pain and pruritus, compared to placebo by Week 2. In general, PASI responses were achieved by Week 16 and were maintained through Week 32.

In both studies, the mean percent improvement in PASI from baseline remained stable during the Randomized Treatment Withdrawal Phase for patients re-randomized to apremilast at Week 32 (Table 6).

Table 6. Persistence of effect among subjects randomized to APR 30 BID at Week 0 and re- randomized to APR 30 BID at Week 32 to Week 52

	Time Point	ESTEEM 1	ESTEEM 2
		Patients who achieved PASI-75 at Week 32	Patients who achieved PASI-50 at Week 32
Percent Change in PASI from baseline, mean (%) ± SD[a]	Week 16	-77.7 ± 20.30	-69.7 ± 24.23
	Week 32	-88 ± 8.30	-76.7 ± 13.42
	Week 52	-80.5 ± 12.60	-74.4 ± 18.91
Change in DLQI from baseline, mean± SD[a]	Week 16	-8.3 ± 6.26	-7.8 ± 6.41
	Week 32	-8.9 ± 6.68	-7.7 ± 5.92
	Week 52	-7.8 ± 5.75	-7.5 ± 6.27
Proportion of subjects with Scalp Psoriasis PGA (ScPGA) 0 or 1, n/N (%)[b]	Week 16	40/48 (83.3)	21/37 (56.8)
	Week 32	39/48 (81.3)	27/37 (73.0)
	Week 52	35/48 (72.9)	20/37 (54.1)

[a] Includes subjects re-randomized to APR 30 BID at Week 32 with a baseline value and a post-baseline value at the evaluated study week.

[b] N is based on subjects with moderate or greater scalp psoriasis at baseline who were re-randomized to APR 30 BID at Week 32. Subjects with missing data were counted as nonresponders.

In Study ESTEEM 1, approximately 61% of patients re-randomized to apremilast at Week 32 had a PASI-75 response at Week 52. Of the patients with at least a PASI-75 response who were re-randomized to placebo at Week 32 during a Randomized Treatment Withdrawal Phase, 11.7% were PASI-75 responders at Week 52. The median time to loss of PASI-75 response among the patients re-randomized to placebo was 5.1 weeks.

In Study ESTEEM 2, approximately 80.3% of patients re-randomized to apremilast 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. The median time to loss of 50% of their Week 32 PASI improvement was 12.4 weeks.

After randomized 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 (ESTEEM 1) or PASI-50 (ESTEEM 2) responses after re-initiation of apremilast treatment. Due to the study design the duration of re-treatment was variable, and ranged from 2.6 to 22.1 weeks.

In Study ESTEEM 1, patients randomized to apremilast at the start of the study who did not achieve a PASI-75 response at Week 32 were permitted to use concomitant topical therapies and/or UVB phototherapy between Weeks 32 to 52. Of these patients, 12% achieved a PASI-75 response at Week 52 with apremilast plus topical and/or phototherapy treatment.
In Studies ESTEEM 1 and ESTEEM 2, significant improvements (reductions) in nail psoriasis, as measured by the mean percent change in Nail Psoriasis Severity Index (NAPSI) from baseline, were observed in patients receiving apremilast compared to placebo-treated patients at Week 16 ($p< 0.0001$ and $p=0.0052$, respectively). Further improvements in nail psoriasis were observed at Week 32 in patients continuously treated with apremilast.
In Studies ESTEEM 1 and ESTEEM 2, 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 observed in patients receiving apremilast compared to placebo-treated patients ($p< 0.0001$ for both studies). The improvements were generally maintained in subjects who were re-randomized to Otezla at Week 32 through Week 52 (Table 6). In Studies ESTEEM 1 and ESTEEM 2, significant improvements in quality of life as measured by the Dermatology Life Quality Index (DLQI) and the SF-36v2MCS were demonstrated in patients receiving apremilast compared with placebo-treated patients (Table 4). Improvements in DLQI were maintained through Week 52 in subjects who were re-randomized to apremilast at Week 32 (Table 5). In addition, in Study ESTEEM 1, significant improvement in the Work Limitations Questionnaire (WLQ-25) Index was achieved in patients receiving apremilast compared to placebo.

Effect on ECG

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

4) Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safetypharmacology and repeated dose toxicity. There is no evidencefor immunotoxic, dermal irritation, or phototoxic potential.

Fertility and early embryonic development

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-fetal 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).

Embryo-fetal development

In a combined female mouse fertility and embryo-fetal developmental toxicity study with oral dosages of 10, 20, 40, and 80 mg/kg/day, absolute and/or relative heart weights of maternal animals were increased at 20, 40, and 80 mg/kg/day. Increased numbers of early resorptions and reduced numbers of ossified tarsals were observed at 20, 40, and 80 mg/kg/day. Reduced fetal weights and retarded ossification of the supraoccipital bone of the skull were observed at 40 and 80 mg/kg/day. The maternal and developmental NOEL in the mouse was 10 mg/kg/day (1.3-fold clinical exposure).
In a monkey embryo-fetal 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).

Pre- and post-natal development

In a pre- and postnatal study, apremilast was administered orally to pregnant female mice at dosages of 10, 80 and 300 mg/kg/day from gestation day (GD) 6 to Day 20 of lactation. Reductions in maternal body weight and weight gain, and one death associated with difficulty in delivering pups were observed at 300 mg/kg/day. Physical signs of maternal toxicity associated with delivering pups were also observed in one mouse at each of 80 and 300 mg/kg/day. Increased peri- and postnatal pup deaths and reduced pup body weights during the first week of lactation were observed at ≥ 80 mg/kg/day (≥ 4.0-fold clinical exposure). There were no apremilast-related effects on duration of pregnancy, number of pregnant mice at the end of the gestation period, number of mice that delivered a litter, or any developmental effects in the pups beyond postnatal day 7. It is likely that pup developmental effects observed during the first week of the postnatal period were related to the apremilast-related pup toxicity (decreased pup weight and viability) and/or lack of maternal care (higher incidence of no milk in the stomach of pups). All developmental effects were observed during the first week of the postnatal period; no apremilast-related effects were seen during the remaining pre- and post-weaning periods, including sexual maturation, behavioural, mating, fertility and uterine parameters. The NOEL in the mouse for maternal toxicity and F1 generation was 10 mg/kg/day (1.3-fold clinical AUC).

Carcinogenicity studies

Carcinogenicity studies in mice and rats showed no evidence of carcinogenicity related to treatment with apremilast.

Genotoxicity studies

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.

[Shelf Life] 36 months

[Storage Condition] Tight container, room temperature (1-30℃)

[Package Configuration]

Starter pack: 10mg 4 tablets, 20mg 4 tablets, 30mg 19 tablets

30mg pack: 28 tablets, 56 tablets

- If products are decomposed, deteriorated, damaged, contaminated or expired, they can be exchanged at the pharmacy, clinic, hospital, or wholesaler where purchased. Please contact the facility where you bought the product for return or exchange.
- You will be compensated for consumers' damages as per the Consumer Injury Compensation Rule.
- Relief of injury from adverse drug reaction: Korea Institute of Drug Safety & Risk Management (Tel: 1644-6223, www.drugsafe.or.kr)
- You can find the latest product information after the following revision date on the MFDS medicines integrated information system (http://nedrug.mfds.go.kr) or the importer website (www.amgen.co.kr).
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