

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

APREZO (Apremilast Tablets 10 mg, 20 mg, and 30 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Apremilast Tablets 10 mg

Each film coated tablet contains: Apremilast 10 mg

Apremilast Tablets 20 mg

Each film coated tablet contains: Apremilast 20 mg

Apremilast Tablets 30 mg

Each film coated tablet contains: Apremilast 30 mg

Excipients with known effect: Lactose Monohydrate,

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Psoriatic Arthritis

Apremilast Tablets are indicated for the treatment of adult patients with active psoriatic arthritis.

Psoriasis

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

4.2 Posology and Method of Administration

Posology: Dosage in Psoriatic Arthritis and Psoriasis

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

Table 1: Dosage Titration Schedule

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

Dosage Adjustment in Patients with Severe Renal Impairment

No dose adjustment is needed in patients with mild and moderate renal impairment. Apremilast dosage should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance (CL_{cr}) of less than 30 mL per minute estimated by the Cockcroft-Gault equation). For initial dose titration in this group, it is recommended that apremilast be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped.

Patients with hepatic impairment

No dose adjustment is necessary for patients with hepatic impairment.

Pediatric population

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

Method of administration

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

4.3 Contraindications

Apremilast is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients listed in section 6.1.

4.4 Special Warnings and Precautions for Use

Diarrhea, Nausea, and Vomiting

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

Consider apremilast dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

Depression

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

Psoriatic arthritis:

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

Psoriasis:

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

Weight Decrease

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

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

Patients treated with apremilast should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of apremilast should be considered.

Drug Interactions

Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with apremilast is not recommended.

Apremilast tablets contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Strong CYP450 Inducers

Apremilast exposure is decreased when apremilast is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to apremilast during pregnancy.

Risk Summary

Adequate and well-controlled studies with apremilast have not been conducted in pregnant women. In animal embryo-fetal development studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. In mice, there were no apremilast induced malformations up to exposures 4.0- times the MRHD. The incidences of malformations and

pregnancy loss in human pregnancies have not been established for apremilast. However, all pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. Apremilast should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Labor or delivery

The effects of apremilast on labor and delivery in pregnant women are unknown. In mice, dystocia was noted at doses corresponding to ≥ 4.0 -times the MRHD (on an AUC basis at doses ≥ 80 mg/kg/day) of apremilast.

Animal Data

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

Mouse embryo-fetal development: In an embryo-fetal development study, apremilast was administered at doses of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation Day 6 through 15). In a combined fertility and embryo-fetal development study, apremilast was administered at doses of 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation Day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of 2.3-times the MRHD and greater (≥ 20 mg/kg/day). At doses of ≥ 20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose approximately 1.3-times the MRHD (10 mg/kg/day).

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

Breast-feeding

It is not known whether apremilast or its metabolites are present in human milk; however apremilast was detected in milk of lactating mice. Because many drugs are present in human milk, caution should be exercised when apremilast is administered to a nursing woman

Fertility

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

4.7 Effects on ability to drive and use machines

Apremilast has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Psoriatic Arthritis Clinical Trials

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

The majority of the most common adverse reactions presented in Table 2 occurred within the first 2 weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking apremilast were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of patients

with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking apremilast 30 mg twice daily and 1.2% for placebo-treated patients.

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

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

^a Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in apremilast 30 mg twice daily; 1 subject treated with apremilast 20 mg twice daily experienced a serious adverse reaction of diarrhea; 1 patient treated with apremilast 30 mg twice daily experienced a serious adverse reaction of headache. ^b Of the reported adverse drug reactions none were serious. ^c n (%) indicates number of patients and percent.

Other adverse reactions reported in patients on apremilast in clinical studies including extension studies: **Immune system disorders:** Hypersensitivity
Investigations: Weight decrease
Gastrointestinal Disorders: Frequent bowel movement, gastroesophageal reflux disease, dyspepsia **Metabolism and Nutrition Disorders:** Decreased appetite*

Nervous System Disorders: Migraine

Respiratory, Thoracic, and Mediastinal Disorders: Cough

Skin and Subcutaneous Tissue Disorders: Rash

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

Psoriasis Clinical Trials

The safety of apremilast was assessed in 1426 subjects in 3 randomized, double-blind, placebo-controlled trials in adult subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Subjects were randomized to receive apremilast 30 mg twice daily

or placebo twice daily. Titration was used over the first 5 days. Subjects ranged in age from 18 to 83 years, with an overall median age of 46 years.

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

Table 3: Adverse Reactions Reported in $\geq 1\%$ of Subjects on Apremilast and With Greater Frequency Than in Subjects on Placebo; up to Day 112 (Week 16)

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

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

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

To report any side effects: Saudi Arabia

- The National Pharmacovigilance and Drug Safety Center (NCP) • Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Ext: 2317-2356-2340.
- SFDA Call Center: 19999
- E-mail: ncp.drug@sfd.gov.sa • website: www.sfd.gov.sa/npc

other GCC States: Please contact the relevant competent authority.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA32

Mechanism of action

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

Clinical trials experience

Psoriatic Arthritis

The safety and efficacy of apremilast was evaluated in 3 multi-center, randomized, double-blind, placebo-controlled trials (Studies PsA-1, PsA-2, and PsA-3) of similar design. A total of 1493 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite prior or current treatment with disease-modifying antirheumatic drug (DMARD) therapy were randomized. Patients enrolled in these studies had a diagnosis of PsA for at least 6 months. One qualifying psoriatic skin lesion of at least 2 cm in diameter was required in Study PsA3. Previous treatment with a biologic, including TNF-blockers was allowed (up to 10% could be TNF-blocker therapeutic failures). Across the 3 studies, patients were randomly assigned to placebo (n=496), apremilast 20 mg (n=500), or apremilast 30 mg (n=497) given orally twice daily. Titration was used over the first 5 days. Patients were allowed to receive stable doses of concomitant methotrexate [MTX (≤ 25 mg/week)], sulfasalazine [SSZ (≤ 2 g/day)], leflunomide [LEF (≤ 20 mg/day)], low dose oral corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and/or nonsteroidal anti-inflammatory drugs (NSAIDs) during the trial. Treatment assignments were stratified based on small-molecule DMARD use at baseline in Studies PsA-1, PsA-2 and PsA-3. There was an additional

stratification of BSA >3% with psoriasis in study PsA-3. The patients who were therapeutic failures of >3 agents for PsA (small molecules or biologics), or >1 biologic TNF blocker were excluded.

The primary endpoint was the percentage of patients achieving American College of Rheumatology (ACR) 20 response at Week 16. Placebo-controlled efficacy data were collected and analyzed through Week 24. Patients whose tender and swollen joint counts had not improved by at least 20% were considered non-responders at Week 16. Placebo non-responders were re-randomized 1:1 in a blinded fashion to either apremilast 20 mg twice daily or 30 mg twice daily following the titration schema. Apremilast patients remained on their initial treatment. At Week 24, all remaining placebo patients were re-randomized to either 20 mg twice daily or 30 mg twice daily.

Patients with subtypes of PsA were enrolled across the 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (27.0%), distal interphalangeal (DIP) joint arthritis (6.0%), arthritis mutilans (3.0%), and predominant spondylitis (2.1%). The median duration of PsA disease was 5 years. Patients received concomitant therapy with at least one DMARD (65.0%), MTX (55.0%), SSZ (9.0%), LEF (7.0%), low dose oral

corticosteroids (14.0%), and NSAIDs (71.0%). Prior treatment with small-molecule DMARDs only was reported in 76.0% of patients and prior treatment with biologic DMARDs was reported in 22.0% of patients, which includes 9.0% who had failed prior biologic DMARD treatment.

Clinical Response in Patients with Psoriatic Arthritis

The percent of patients achieving ACR 20, 50 and 70 responses in Studies PsA-1, PsA-2, and PsA-3 are presented in Table 4 below. Apremilast ± DMARDs, compared with Placebo ± DMARDs resulted in a greater improvement in signs and symptoms of psoriatic arthritis as demonstrated by the proportion of patients with an ACR 20 response at Week 16.

Table 4: Proportion of Patients with ACR Responses in Studies PsA-1, PsA-2 and PsA-3

	Placebo ± DMARDs N=168	Apremilast 30 mg twice daily ± DMARDs N=168	Placebo ± DMARDs N=159	Apremilast 30 mg twice daily ± DMARDs N=162	Placebo ± DMARDs N=169	Apremilast 30 mg twice daily ± DMARDs N=167
ACR 20 Week 16	19%	38% ^b	19%	32% ^b	18%	41% ^b
ACR 50 Week 16	6%	16%	5%	11%	8%	15%
ACR 70 Week 16	1%	4%	1%	1%	2%	4%

a N is number of randomized and treated patients.

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

Apremilast 30 mg twice daily resulted in improvement for each ACR component, compared to placebo at Week 16 in Study PsA-1 (Table 5). Consistent results were observed in Studies PsA-2 and PsA-3.

Table 5: ACR Components Mean Change from Baseline at Week 16 in Study PsA- 1

Table 5: ACR Components Mean Change from Baseline at Week 16 in Study PsA- 1

	Placebo (N*=168)	Apremilast 30 mg twice daily (N*=168)
Number of tender joints ^a		
Sample Size	166	164
Baseline	23	23
Mean Change at Week 16	-2	-7
Number of swollen joints ^b		
Sample Size	166	164
Baseline	13	13
Mean Change at Week 16	-2	-5
Patient's assessment of pain ^c		
Sample Size	165	159
Baseline	61	58
Mean Change at Week 16	-6	-14
Patient's global assessment of disease activity ^c		
Sample Size	165	159
Baseline	59	56
Mean Change at Week 16	-3	-10
Physician's global assessment of disease activity ^c		
Sample Size	158	159
Baseline	55	56
Mean Change at Week 16	-8	-19
HAQ-DI ^d score		
Sample Size	165	159
Baseline	1.2	1.2
Mean Change at Week 16	-0.09	-0.2
CRPe		
Sample Size	166	167
Baseline	1.1	0.8
Mean Change at Week 16	0.1	-0.1

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

^a Scale 0-78.

^b Scale 0-76.

^c VAS=Visual Analog Scale; 0=best, 100=worst.

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

^e CRP = C-reactive protein; Reference range 0-0.5 mg/dL

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

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

Physical Function Response

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

Psoriasis

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

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

Clinical Response in Subjects with Plaque Psoriasis

The proportion of subjects who achieved PASI -75 responses, and sPGA score of clear (0) or almost clear (1), are presented in Table 6.

Table 6: Clinical response at week 16 in studies PSOR-1 and PSOR-2

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

^a N is number of randomized and treated patients.

^b PASI=Psoriasis Area and Severity Index.

^c sPGA=Static Physician Global Assessment.

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Metabolism

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

Elimination

The plasma clearance of apremilast is on 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.

Specific Populations

Renal impairment

The pharmacokinetics of apremilast is not affected by mild or moderate

renal impairment. In 8 subjects with severe renal impairment administered a single dose of 30 mg apremilast, the AUC and C_{max} of apremilast increased by approximately 88% and 42%, respectively.

Hepatic impairment

The pharmacokinetics of apremilast is not affected by moderate or severe hepatic impairment.

Age:

A single oral dose of 30-mg apremilast was studied in young adults and elderly healthy subjects. The apremilast exposure in elderly subjects (65 to 85 years of age) was about 13% higher in AUC and about 6% higher in C_{max} than in young subjects (18 to 55 years of age).

Gender:

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

Race and Ethnicity:

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

Drug Interactions:

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

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

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

5.3 Preclinical safety data

Carcinogenicity studies

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

Genotoxicity studies

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate,
Crospovidone,
Magnesium Stearate,
Lactose Monohydrate Corn starch dried ,
Opadry White,
Purified Water

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC-Aluminium Blister pack.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Ltd. Glenmark House,
HDO-Corporate Building, Wing – A, B, D. Sawant Marg, Chakala, Off.
western express highway, Andheri (East), Mumbai – 400 099, INDIA.

Manufacturing site

Glenmark Pharmaceuticals Ltd. At: Plot No. 2, Phase –II, Pharma Zone, SEZ, Pithampur, Dist. Dhar Madhya Pradesh – 454775. INDIA.

8. MARKETING AUTHORISATION NUMBER(S)

H2021/CTD8387/17094

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Jul 2018

10. DATE OF REVISION OF THE TEXT

Jul 2018