SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This triangle symbol will allow the new safety information to be established quickly. Healthcare professionals are expected to report any suspected adverse reactions. See Section 4.8 for how to report adverse reactions?

1. NAME OF THE MEDICINAL PRODUCT

LEDEZLA 30 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each film coated tablet contains 30 mg apremilast.
Excipient(s):
Each film coated tablet contains 180 mg lactose monohydrate (from cow's milk).
For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet
Immediate release, diamond-shaped, beige film coated tablet with "30" engraved on one side

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Psoriatic arthritis

Apremilast, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response to, or are intolerant of, prior DMARD therapy (see section 5.1).

Psoriasis

Apremilast is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who have failed to respond to, have a contraindication to, or are intolerant of other systemic therapies, including cyclosporine, methotrexate, or psoralen and ultraviolet-A light (PUVA).

4.2. Posology and method of administration

Posology/frequency and duration of administration:
Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis.
The recommended dosage of apremilast is 30 mg taken orally twice daily, in the morning and evening, approximately 12 hours apart, without food restrictions. An initial titration schedule is required as shown in Table 1 below. After the initial titration, no further titration is necessary.

Table 1: Dose titration program

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 and thereafter	
Morning	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

If patients miss a dose, the next dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken and the next dose should be taken at the usual time.

During pivotal studies, most improvement was observed within the first 24 weeks of treatment. If a patient does not show evidence of therapeutic benefit after 24 weeks, treatment should be re-evaluated. The patient's response to treatment should be evaluated regularly.

Method of administration:
LEDEZLA is for oral use.
LEDEZLA film coated tablets should be swallowed whole, on an empty or full stomach.

Additional information for special populations:
Renal impairment:
No dose adjustment is needed in patients with mild or moderate renal impairment. The dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance less than 30 mL per minute as calculated by the Cockcroft-Gault equation). For initial dose titration in this group of patients, it is recommended to titrate apremilast only using the MORNING schedule listed in Table 1 and skip EVENING doses (see section 5.2).

Hepatic impairment:
No dose adjustment is needed in patients with hepatic impairment (see section 5.2).

Pediatric population:
The safety and efficacy of apremilast in children aged 0-18 years have not been established. No data is available.

Geriatric population:
No dose adjustment is necessary for this patient population (see sections 4.8 and 5.2).

4.3. Contraindications
- It is contraindicated in the cases of hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- It is contraindicated during pregnancy (see section 4.6).

4.4. Special warnings and precautions for use
Diarrhea , Nausea and Vomiting
There have been post-marketing reports of severe diarrhea, nausea, and vomiting associated with apremilast use. Most events occurred within the first few weeks of treatment. In some cases, patients were hospitalized. Patients aged 65 or older may be at higher risk for complications. If patients develop severe diarrhea, nausea, or vomiting, discontinuation of treatment with apremilast may be necessary.

Psychiatric disorders
Apremilast use is associated with an increased risk of psychiatric disorders such as insomnia and depression. Suicidal ideation and behavior, including suicide, has been observed in patients with or without a history of depression (see section 4.8). If patients report prior or current psychiatric symptoms, or if concomitant treatment with other medicinal products likely to cause psychiatric events is planned, the risks and benefits of initiating or continuing treatment with apremilast should be carefully considered. Patients and their caregivers should be instructed to report any changes in behavior or mood or any thoughts of suicide to their prescribers. It is recommended that treatment

with apremilast be discontinued if patients experience new or worsening psychiatric symptoms or if suicidal ideation or suicide attempts are detected.

Severe renal impairment
The apremilast dose should be reduced to 30 mg once daily in patients with severe renal impairment (see sections 4.2 and 5.2).

Weak patients
The body weight of patients who are underweight at the beginning of treatment should be monitored regularly. In cases of unexplained and clinically significant weight loss, these patients should be evaluated by a physician and discontinuation of therapy should be considered.

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

4.5. Interactions with other medicinal products and other forms of interaction
Concomitant administration of the strong cytochrome P450 3A4 (CYP3A4) enzyme inducer rifampicin resulted in a decrease in the systemic exposure of apremilast, which may result in loss of apremilast efficacy. Therefore, the use of strong CYP3A4 enzyme inducers (e.g., rifampicin, phenobarbital, carbamazepine, phenytoin, and St. John's wort) with apremilast is not recommended. Concomitant administration of apremilast with multiple doses of rifampicin resulted in decreases in the area under the concentration-time curve (AUC) and maximum serum concentration (C_{max}) of apremilast by approximately 72% and 43%, respectively. Apremilast exposure is decreased when administered concomitantly with strong CYP3A4 inducers (e.g., rifampicin) and may result in reduced clinical response.

In clinical studies, apremilast was administered concomitantly with topical therapy (including corticosteroids, coal tar shampoo, and salicylic acid scalp preparations) and UVB phototherapy.

There was no clinically significant drug-drug interaction between ketoconazole and apremilast. Apremilast may be administered concomitantly with a potent CYP3A4 inhibitor such as ketoconazole.

There is no pharmacokinetic drug-drug interaction between apremilast and methotrexate in patients with psoriatic arthritis. Apremilast can be administered concomitantly with methotrexate.

There was no pharmacokinetic drug-drug interaction between apremilast and oral contraceptives containing ethinyl estradiol and norgestimate. Apremilast can be administered concomitantly with oral contraceptives.

Additional information for special populations
Pediatric patients:
No interaction study has been performed on its use in pediatric population.

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category: C

Women of childbearing potential/Birth control (Contraception)
Before starting treatment, it must be checked whether the patient is pregnant or not. Women of

childbearing potential should use effective birth control to prevent pregnancy during treatment.

Pregnancy
Data on the use of apremilast in pregnant women are limited.

Apremilast is contraindicated during pregnancy. Effects of apremilast on pregnancy included embryofetal loss in mice and monkeys and decreased fetal weight and delayed ossification in mice at doses higher than the currently recommended maximum human dose. Such effects were not observed in animals at exposures 1.3 times the clinical exposure (see section 5.3).

Breastfeeding
Apremilast has been detected in the milk of lactating mice (see section 5.3). It is unknown whether apremilast or its metabolites are excreted in human breast milk. A risk to breast-fed infants cannot be excluded, therefore apremilast should not be used in breastfeeding mothers.

Reproduction ability/Fertility
There are no fertility data in humans. In animal studies in mice, no adverse effects were observed in males at exposure levels 3 times the clinical exposure and in females at exposure levels 1 times the clinical exposure. See section 5.3 for pre-clinical fertility data.

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
Summary of the safety profile
The most commonly reported adverse events of apremilast in PsA and PSOR are gastrointestinal (GI) disorders, including diarrhea (15.7%) and nausea (13.9%). Other most frequently reported adverse events included upper respiratory tract infections (8.4%), headache (7.9%), and tension-type headache (7.2%) and were mostly mild to moderate in severity.

Gastrointestinal side effects usually occur within the first 2 weeks of treatment and usually resolve within 4 weeks.

Hypersensitivity reactions were observed rarely in apremilast clinical studies (see section 4.3).

Adverse reactions occurring in patients treated with apremilast are listed by MedDRA organ system in Table 2.

Adverse drug reactions were identified based on data from the apremilast clinical development program. The frequencies of adverse drug reactions are those reported in the apremilast arms of the four Phase III studies in psoriatic arthritis (n=1945) or the two Phase III studies in psoriasis (n=1184) (Table 2 shows the highest frequencies from both data pools).

Adverse drug reactions are listed according to the frequencies defined below:
Classified 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), very rare (<1/10,000), unknown (not established by available data).

Table 2. Summary of adverse reactions in psoriatic arthritis and/or psoriasis

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection[a]
	Common	Bronchitis
		Nasopharyngitis*
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Decreased appetite*
Psychiatric disorders	Common	Insomnia
		Depression
	Uncommon	Suicidal ideation and behavior#
Nervous system disorders	Very common	Headache*
	Common	Migraine*
		Tension-type headache*
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very common	Diarrhea*
		Nausea*
	Common	Vomiting*
		Dyspepsia
		Frequent bowel movements
		Upper abdominal pain*
		Gastrointestinal reflux disease
	Uncommon	Gastrointestinal hemorrhage
Skin and subcutaneous tissue disorders	Uncommon	Rash
		Urticaria
	Unknown	Angioedema
Musculoskeletal, connective tissue, and bone disorders	Common	Back pain*
General disorders and administration site conditions	Common	Fatigue
Investigations	Uncommon	Weight loss

* At least one of these adverse reactions was reported as serious.

Definitions of the selected adverse reactions

Psychological disorders

#Uncommon cases of suicidal ideation and behavior have been reported in clinical studies and post-marketing experience, while suicide has been reported post-marketing. Patients and their caregivers should be instructed to report any suicidal ideation to their physician (see section 4.4).

Weight loss

Patient weight was routinely measured in clinical studies. The mean observed weight loss in patients treated with apremilast for up to 52 weeks was 1.99 kg. A total of 14.3% of patients receiving

apremilast experienced a weight loss of 5-10%, while 5.7% experienced a weight loss of more than 10%. None of these patients developed overt clinical consequences of weight loss. A total of 0.1% of patients treated with apremilast discontinued the drug due to the adverse reaction of decreased weight.

For patients who are weak at the start of treatment, see additional warning in section 4.4.

Additional information for special populations:
Geriatric population:
Based on post-marketing experience, patients aged 65 years and older may be at higher risk for complications of severe diarrhea, nausea, and vomiting.

Hepatic impairment:
The safety of apremilast in patients with psoriatic arthritis or psoriasis and hepatic impairment has not been evaluated.

Renal impairment:
In psoriatic arthritis or psoriasis clinical studies, the safety profile observed in patients with mild renal impairment was similar to that in patients with normal renal function. The safety of apremilast in patients with psoriatic arthritis or psoriasis with moderate or severe renal impairment has not been evaluated in clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals should report any suspected adverse reaction via the national reporting system.

4.9. Overdose and treatment
Apremilast has been investigated in healthy volunteers at a maximum total daily dose of 100 mg (given as 50 mg BID) for 4.5 days without evidence of dose-limiting toxicity. In the event of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse effects and appropriate symptomatic treatment be initiated. Symptomatic and supportive treatment is recommended in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Selective immunosuppressants
ATC code: L04AA32

Mechanism of action
Apremilast, an oral small molecule phosphodiesterase 4 (PDE4) inhibitor, functions intracellularly to regulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and is the predominant PDE in inflammatory cells. PDE4 inhibition increases intracellular cAMP levels, which in turn reduces the inflammatory response by regulating the expression of TNF -α , IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also regulates levels of anti-inflammatory cytokines such as IL-10. These pro-inflammatory and anti-inflammatory mediators have been shown to be involved in psoriatic arthritis and psoriasis.

Pharmacodynamic effects

In clinical studies in patients with psoriatic arthritis, apremilast significantly, but not completely inhibited, plasma protein levels of IL-1 α , IL-6, IL-8, MCP-1, MIP-1ß, MMP-3, and TNF- α. A decrease in plasma protein levels of IL-17 and IL-23 and an increase in IL-10 were seen after 40 weeks of treatment with apremilast. In clinical studies in patients with psoriasis, apremilast reduced lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro-inflammatory genes, including those for inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-17A, IL-22, and IL-8.

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

Clinical trials

Psoriatic arthritis

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

Patients in these studies had a diagnosis of psoriatic arthritis of at least 6 months' duration. In PALACE 3, a qualifying psoriasis skin lesion (at least 2 cm in diameter) was also required. Apremilast was used in combination with stable doses of small molecule DMARDs (65.2%) or as monotherapy (34.8%). 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%). Concomitant treatment with biologic DMARDs, including TNF blockers, was not permitted. Patients with each subtype of psoriatic arthritis were enrolled in these 3 studies, including symmetric polyarthritis (62.0%), asymmetric oligoarthritis (26.9%), distal interphalangeal (DIP) joint arthritis (6.2%), arthritis mutilans (2.7%), and predominantly spondylitis (2.1%). Patients with pre-existing enthesopathy (63%) or dactylitis (42%) were enrolled. A total of 76.4% of patients had been previously treated with small molecule DMARDs only, while 22.4% of patients had been previously treated with biologic DMARDs (7.8% of whom had therapeutic failure with a prior biologic DMARD). Median psoriatic arthritis disease duration was 5 years.

Based on study design, patients whose tender and swollen joint counts did not improve by at least 20% at week 16 were considered non-responders. Placebo patients considered non-responders were re-randomized in a 1:1 blinded manner 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. After 52 weeks of treatment, patients were able to continue open-label apremilast 20 mg or 30 mg for a total treatment duration of up to 5 years (260 weeks) in the long-term extension of the PALACE 1, PALACE 2, and PALACE 3 studies.

The primary endpoint was the percentage of patients achieving an American College of Rheumatology (ACR) 20 response at week 16.

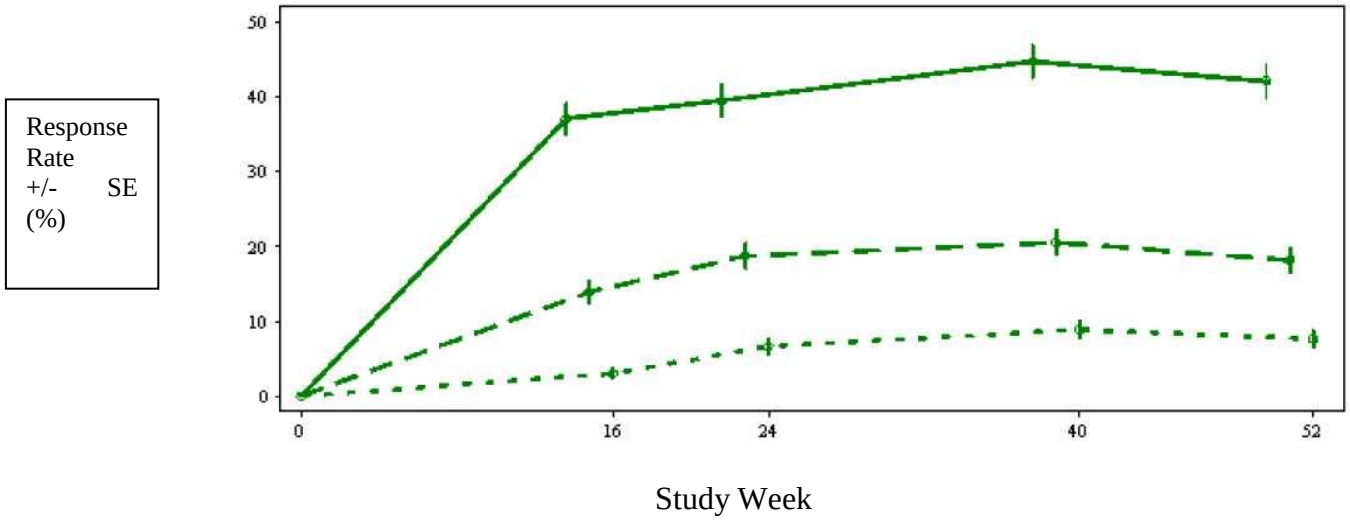
Treatment with apremilast resulted in significant improvements in signs and symptoms of psoriatic arthritis as assessed by ACR 20 response criteria compared to placebo at Week 16. The proportion of patients achieving ACR 20/50/70 for apremilast 30 mg twice daily at Week 16 (responses in Studies PALACE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

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

Table 3. Proportion of patients with ACR responses at week 16 in PALACE 1, PALACE 2, and PALACE 3 studies and combined studies

	PALACE 1		PALACE 2		PALACE 3		COMBINED	
N[a]	Placebo +/- DMARD N=168	Apremilast 30 mg BID ±/- DMARD N=168	Placebo +/- DMARD N=159	Apremilast 30 mg BID +/- DMARD N=162	Placebo +/- DMARD N=169	Apremilast 30 mg BID +/- DMARD N=167	Placebo +/- DMARD N=496	Apremilast 30 mg BID ±/- DMARD N=497
ACR 20[a]								
16. Week	19%	38.1%**	18.9%	32.1%*	18.3%	40.7%**	18.8%	37%**
ACR 50								
Week 16	6%	16.1%*	5%	10.5%	8.3%	15%	6.5%	13.9%**
ACR 70								
Week 16	1.2%	4.2%	0.6%	1.2%	2.4%	3.6%	1.4%	3%
*p ≤ 0.01 for apremilast versus placebo.								
**p ≤ 0.001 for apremilast versus placebo.								
[a] N is the number of patients randomized and treated.								

Figure 1. Proportion of ACR 20/50/70 responders by week 52 in combined analysis of PALACE 1, PALACE 2, and PALACE 3 studies (NRI*)



Endpoint	n/m(%)	n/m(%)	n/m(%)	n/m(%)
ACR 20	184/497 (37)	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)	33/497 (6.6)	44/497 (8.9)	38/497 (7.6)

Endpoint	ACR 20	ACR 50	ACR 70

*NRI: Non-responders Subjects who dropped out before the time point and did not have sufficient data to definitively determine response status at the time point were counted as non-responders.

Of the 497 patients initially randomized to apremilast 30 mg twice daily, 375 patients (75%) were still on this treatment at week 52. ACR 20/50/70 responses at week 52 in these patients were 57%, 25%, and 11%, respectively. Among 497 patients initially randomized to apremilast 30 mg twice daily, 375 patients (75%) entered long-term extension studies, of whom 221 patients (59%) were still receiving this treatment at week 260. ACR responses were maintained for up to 5 years in long-term open-label extension studies.

Responses observed in the apremilast-treated group were similar in patients with and without concomitant DMARD use, including MTX. Patients receiving apremilast who were previously treated with DMARDs or biologics achieved a greater ACR 20 response at Week 16 than patients receiving placebo.

Similar ACR responses were observed in patients with different psoriatic arthritis subtypes, including DIP. The number of patients with arthritis mutilans and predominant spondylitis subtypes was too small to be considered as significant.
Improvements in the proportion of patients achieving Disease Activity Scale (DAS) 28 C-reactive protein (CRP) and modified psoriatic arthritis response criteria (PsARC) in PALACE 1, PALACE 2 and PALACE 3 were greater in the apremilast group compared to placebo at week 16 (nominal p-value $p \leq 0.0017$, $p \leq 0.0004$, respectively). These improvements continued at week 24. Among patients who maintained apremilast treatment to which they were randomized at the start of the study, DAS28(CRP) score and PsARC response were maintained through week 52.

Improvements in parameters characteristic of peripheral activity of psoriatic arthritis (e.g., number of swollen joints, number of painful/tender joints, dactylitis, and enthesitis) and skin manifestations of psoriasis were seen in patients treated with apremilast at weeks 16 and 24. These improvements were maintained through week 52 in patients who remained on apremilast treatment to which they were randomized at the start of the study.

In open-label extension studies, clinical responses in skin manifestations of psoriasis and the same peripheral activity parameters were maintained throughout treatment for up to 5 years.

Physical function and health-related quality of life
Patients treated with apremilast demonstrated a statistically significant improvement in physical function as assessed by change from baseline in the health assessment questionnaire disability index (HAQ-DI) compared to placebo at Week 16 in studies PALACE 1, PALACE 2, and PALACE 3 and the combined studies. Improvement in HAQ-DI scores continued at week 24.

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

In PALACE 1, PALACE 2, and PALACE 3 studies, significant improvements in health-related quality of life were demonstrated in the physical functioning (PF) domain of the Short Form Health Survey version 2 (SF-36v2) and in change from baseline in 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 maintained apremilast treatment to which they were randomized at the start of the study, improvements in physical function and FACIT-fatigue were maintained through week 52.

Improved physical function as assessed by HAQ-DI and SF36v2PF domain and FACIT-fatigue scores was maintained through 5 years of treatment in open-label extension studies.

Psoriasis
The safety and efficacy of apremilast were evaluated in two multicenter, randomized, double-blind, placebo-controlled studies (ESTEEM 1 and ESTEEM 2 Studies) that enrolled a total of 1,257 patients with moderate to severe plaque psoriasis (≥ 10% body surface area (BSA) involvement, Psoriasis Area and Severity Index (PASI) score ≥ 12, static Physician Global Assessment (sPGA) ≥ 3 (moderate or severe), and who were candidates for phototherapy or systemic therapy.

These studies have similar designs up to 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 to 32, all patients received apremilast 30 mg BID (maintenance phase). During the Randomized Treatment Withdrawal Phase (Weeks 32-52), patients initially randomized to apremilast who achieved a 75% reduction in PASI scores (PASI-75) (ESTEEM 1) or a 50% reduction in PASI scores (PASI-50) (ESTEEM 2) were re-randomized to placebo or apremilast 30 mg BID at Week 32. Patients who were re-randomized to placebo and lost PASI-75 response (ESTEEM 1) or 50% of PASI improvement at week 32 (ESTEEM 2) were re-treated with apremilast 30 mg BID. Patients who did not achieve PASI response by Week 32 or were initially randomized to placebo remained on apremilast treatment through Week 52. Low-potency topical corticosteroids, coal tar shampoos, and/or salicylic acid scalp preparations were permitted in the studies for use on the face, axilla, and groin. Additionally, at Week 32, subjects who did not achieve a PASI-75 response in ESTEEM 1 or a PASI-50 response in ESTEEM 2 were allowed to use topical psoriasis treatments and/or phototherapy in addition to apremilast 30 mg BID.

After 52 weeks of treatment, patients were able to continue open-label apremilast 30 mg for a total treatment duration of up to 5 years (260 weeks) in the long-term extension studies ESTEEM 1 and ESTEEM 2.

The primary endpoint in both studies was the proportion of patients achieving PASI-75 at week 16. The major secondary endpoint was the proportion of patients who achieved a clear (0) or nearly clear (1) sPGA score at week 16.

The mean baseline PASI score was 19.07 (median 16.80), and the proportion of patients with sPGA scores of 3 (moderate) and 4 (severe) at baseline were 70.0% and 29.8%, respectively, with a mean BSA involvement of 25.19% (median 21.0%). Approximately 30% of all patients had received prior phototherapy and 54% 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 having a clear (0) or nearly clear (1) sPGA score are presented in Table 4 below. Treatment with apremilast resulted in significant improvement in moderate to severe plaque psoriasis as demonstrated by the proportion of patients with a PASI-75 response at week 16 compared to placebo. Clinical improvement was demonstrated as measured by sPGA, PASI-50, and PASI-90 responses at week 16. In addition, apremilast has demonstrated treatment benefit in a variety of psoriasis manifestations, including pruritus, nail disease, scalp involvement, and quality of life measures.

Table 4. Clinical response at week 16 in ESTEEM 1 and ESTEEM 2 studies (FAS a, LOCFb)

	ESTEEM 1		ESTEEM 2	
	Placebo	**30 mg APR twice a day***	**Placebo**	**30 mg APR twice a day***
N	282	562	137	274
PASI[C] 75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA[d] Clear or Nearly 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)
Percentage 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, mean ± SD	-1.02 ±9.161	2.39 ±9.504	0 ±10.498	2.58 ±10.129

* p<0.0001 for apremilast vs placebo except for Change in ESTEEM 2 PASI 90 and SF-36 MCS with p=0.0042 and p=0.0078 respectively
[a] FAS = Full Analysis Set
[b] LOCF = Last Observation Carried Forward
[c] PASI = Psoriasis Psoriasis Area and Severity Index
[d] sPGA = Static Physician Global Assessment
[e] BSA = Body Surface Area
[f] VS = Visual Analog Scale; o = best, 100 = worst
[g] DLQI = Dermatology Quality of Life Index; o = best, 30 = worst
[h] SF-36 MCS = Medical Outcomes Study Short Form 36-Item Health Survey, Psychological 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 history of psoriatic arthritis). The clinical benefit of apremilast was also demonstrated regardless of prior psoriasis medication use 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 signs and symptoms of psoriasis, including PASI, skin discomfort/pain, and pruritus, compared to placebo by Week 2. In general, PASI responses were obtained by week 16 and continued through week 32.

In both studies, the mean percentage improvement from baseline in PASI remained stable during the Randomized Withdrawal Phase for patients re-randomized to apremilast at Week 32 (Table 5).

Table 5. Durability of efficacy in subjects randomized to APR 30 BID at week 0 and re-randomized to APR 30 BID at week 32 to week 52

	Endpoint	ESTEEM 1	ESTEEM 2
		Patients who achieved PASI-75 at week 32	Patients who achieved PASI-50 at week 32
Percentage Change (%) from Baseline in PASI ± SD[a]	Week 16	-77.7 ± 20.3	-69.7 ± 24.23
	Week 32	-88 ± 8.3	-76.7 ± 13.42
	Week 52	-80.5 ± 12.6	-74.4 ± 18.91
Change from baseline in DLQI, 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 volunteers 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)
	Week 52	35/48 (72.9)	20/37 (54.1)

[a] Includes subjects re-randomized to APR 30 BID at week 32 with baseline and post-baseline values in the study week evaluated.
[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 non-responders .
In the ESTEEM 1 Study, approximately 61% of patients re-randomized to apremilast at week 32 had a PASI-75 response at week 52. Of patients with at least a PASI-75 response at Week 32 who were re-randomized to placebo during the Randomized Withdrawal Phase, 11.7% were PASI-75 responders at Week 52. Among patients re-randomized to placebo, the median time to loss of PASI-75 response was 5.1 weeks.

In the ESTEEM 2 Study, approximately 80.3% of patients re-randomized to apremilast at week 32 had a PASI-50 response at week 52. Of 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 50% loss in week 32 PASI improvements was 12.4 weeks.

Following randomized treatment withdrawal 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 reinitiation of apremilast treatment. Due to study design, the duration of retreatment was variable and ranged from 2.6 to 22.1 weeks.

In Study ESTEEM 1, patients randomized to apremilast at study entry who did not achieve a PASI-75 response at Week 32 were allowed to use concomitant topical treatments and/or UVB phototherapy between Weeks 32 and 52. Of these patients, 12% achieved a PASI-75 response at week 52 with apremilast plus topical therapy and/or phototherapy.

In Studies ESTEEM 1 and ESTEEM 2, significant improvements (reductions) in nail psoriasis, as measured by mean percent change from baseline in the Nail Psoriasis Severity Index (NAPSI), were observed in patients receiving apremilast compared to placebo-treated patients at Week 16 ($p<0.0001$

and p=0.0052, respectively). Additional improvements in nail psoriasis were observed at week 32 in patients continuing to receive treatment with apremilast.

Significant improvements in at least moderate (≥3) scalp psoriasis, as measured by the proportion of patients achieving a Scalp Psoriasis Physician Global Assessment (ScPGA) score of clear (0) or minimum (1) at Week 16, were observed in patients receiving apremilast compared to placebo-treated patients in Studies ESTEEM 1 and ESTEEM 2. Improvements were generally maintained from week 32 to week 52 in subjects re-randomized to apremilast (Table 5).

In Studies ESTEEM 1 and ESTEEM 2, patients receiving apremilast had significant improvements in quality of life as measured by the Dermatology Quality of Life Index (DLQI) and SF-36v2MCS compared to placebo-treated patients (Table 4). Improvements in DLQI were maintained through week 52 in subjects re-randomized to apremilast at week 32 (Table 5). Additionally, in the ESTEEM 1 Study, patients receiving apremilast had significant improvement on the Work Limitations Questionnaire (WLQ-25) compared to placebo.

Among 832 patients initially randomized to apremilast 30 mg twice daily, 443 patients (53%) entered the open-label extension studies of ESTEEM 1 and ESTEEM 2, of whom 115 patients (26%) were still on treatment at Week 260. In the open-label extension of ESTEEM 1 and ESTEEM 2 studies, improvements in PASI score, affected BSA, pruritus, nails, and quality of life measures were generally maintained for up to 5 years for patients who continued on apremilast.

The long-term safety of apremilast 30 mg twice daily in patients with psoriatic arthritis and psoriasis has been evaluated for a total treatment duration of up to 5 years. Long-term experience with apremilast in open-label extension studies was generally similar to that in the 52-week studies.

5.2. Pharmacokinetic properties

General properties

Absorption:

Apremilast is well absorbed with 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 over the dose range of 10 to 100 mg daily. Accumulation was minimal when apremilast was administered once daily and approximately 53% in healthy volunteers and 68% in volunteers with psoriasis when administered twice daily. Apremilast can be administered on an empty or full stomach, as administration with food does not alter bioavailability.

Distribution:

The binding of apremilast to human plasma protein is approximately 68%. The mean apparent volume of distribution (Vd) was 87L, indicating extravascular distribution.

Biotransformation:

Apremilast is extensively metabolized by both CYP-mediated and non-CYP pathways, including oxidation, hydrolysis, and conjugation, suggesting that inhibition of a single clearance pathway is unlikely to cause significant drug-drug interactions. The oxidative metabolism of apremilast is mediated primarily 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 being recovered in the urine and feces, respectively. The major inactive metabolite in circulation is the glucuronide conjugate of O-demethylated apremilast (M12). Consistent with apremilast being a CYP3A4 substrate, apremilast

exposure is reduced when administered concomitantly with rifampicin, a strong CYP3A4 inducer.

In vitro, apremilast is not an inhibitor or inducer of cytochrome P450 enzymes. Therefore, apremilast administered with substrates of CYP enzymes is unlikely to affect the clearance and exposure of active substances metabolized by CYP enzymes.

In vitro, apremilast is a P-glycoprotein substrate and weak inhibitor (IC50>50µM), however, clinically relevant drug interactions via P-gp are not expected to occur.

In vitro, apremilast has little or no inhibitory effects on Organic Anion Transporter (OAT)1 and OAT3, Organic Cation Transporter (OCT)2, Organic Anion Transporter Polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP) and is not a substrate for these transporters. Therefore, clinically relevant drug-drug interactions are unlikely when apremilast is administered concomitantly with substrates or inhibitors of these transporters.

Elimination:
Plasma clearance of apremilast averages approximately 10 L/h in healthy subjects with a terminal elimination half-life of approximately 9 hours. Following oral administration of radiolabeled apremilast, approximately 58% and 39% of the radioactivity was recovered in the urine and feces, respectively, while 3% and 7% of the radioactive dose was recovered as apremilast in the urine and feces, respectively.

Special populations:
Geriatric population:
Apremilast has been studied in young and elderly healthy volunteers. Exposure in elderly subjects (65 to 85 years) was approximately 13% higher in AUC and approximately 6% higher in C_{max} for apremilast compared to young subjects (18 to 55 years). Pharmacokinetic data in volunteers over 75 years of age from clinical studies are limited. No dose adjustment is required in elderly patients.

Renal impairment:
There was no significant difference in the PK of apremilast between subjects with mild or moderate renal impairment and matched healthy volunteers (N=8 each). The findings supports the fact that no dose adjustment is necessary for patients with mild or moderate renal impairment. In patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2 or CLcr < 30 mL/min), reduce the apremilast dose to 30 mg once daily. In 8 subjects with severe renal impairment who received a single 30 mg dose of apremilast, 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 required in patients with hepatic impairment.

5.3. Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. No evidence of immunotoxic potential, dermal irritation or phototoxic potential.

Fertility and early embryonic development
In a male mouse fertility study, apremilast at oral doses of 1, 10, 25, and 50 mg/kg/day had no effects on male fertility; the no observed adverse effect level (NOAEL) for male fertility was greater than 50

mg/kg/day (3 times the clinical exposure).

In a female mouse fertility and embryo-fetal developmental toxicity study combining oral doses of 10, 20, 40, and 80 mg/kg/day, prolonged estrous cycles and increased time to mating were observed at 20 mg/kg/day and above; however, all mice mated and pregnancy rates were unaffected. The no observed adverse effect level (NOEL) for female fertility is 10 mg/kg/day (1.0 times the clinical exposure).

Embryo-fetal development

In a female mouse fertility and embryo-fetal developmental toxicity study combined with oral doses 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 early resorption numbers and decreased ossified tarsal numbers were observed at 20, 40 and 80 mg/kg/day. Delay in ossification of the supraoccipital skull bone and reduced fetal weights were observed at 40 and 80 mg/kg/day. The maternal and developmental NOEL in mice is 10 mg/kg/day (1.3 times the clinical exposure).

In a monkey embryo-fetal developmental toxicity study, oral doses of 20, 50, 200, and 1000 mg/kg/day resulted in a (low) dose-related increase in prenatal loss at doses of 50 mg/kg/day and above; no test substance-related effects on prenatal loss were observed at 20 mg/kg/day (1.4 times the clinical exposure).

Pre-natal and post-natal development

In a pre-natal and post-natal study, apremilast was administered orally to pregnant female mice at doses of 10, 80 and 300 mg/kg/day from gestation day 6 (GD) to lactation day 20. At 300 mg/kg/day, decreases in maternal body weight and weight gain and one death associated with difficulty in delivering the pups were observed. Physical signs of maternal toxicity associated with the birth of pups were also observed in one mouse at each of 80 and 300 mg/kg/day. At ≥80 mg/kg/day (≥4.0 times clinical exposure), increased prenatal and postnatal pup mortality and decreased pup body weights during the first week of lactation were observed. There were no apremilast-related effects on the duration of gestation, the number of pregnant mice at the end of the gestation period, the number of mice giving birth to pups, or any developmental effects in the pups beyond postnatal day 7. Offspring developmental effects observed during the first week of the postnatal period are possibly related to apremilast-associated pup toxicity (decreased pup weight and viability) and/or lack of maternal care (higher incidence of pups not having enough milk in their stomach). All developmental effects were observed during the first week of the postnatal period; no apremilast-related effects were seen during the remainder of the pre- and post-weaning periods, including sexual maturation, behavior, mating, fertility, and uterine parameters. The NOEL in mice for maternal toxicity and the F1 generation was 10 mg/kg/day (1.3 times the clinical AUC).

Carcinogenicity studies

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

Genotoxicity studies

Apremilast is not genotoxic. Apremilast did not induce mutations in the Ames assay or chromosomal 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.

Other studies:
No evidence of immunotoxic, dermal irritation or phototoxic potential was found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate (from cow's milk)
Croscarmellose sodium
Magnesium stearate
Opadry Beige 03B270010

Opadry Beige 03B270010
Hydroxypropyl Methyl Cellulose
Macrogol/PEG
Titanium dioxide
Talc
Iron oxide red
Iron oxide yellow
Iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 30°C.

6.5 Nature and contents of container

The primary packaging material is a blister made of transparent PVC/PVdC and aluminum foil. The blisters are packed in cardboard boxes. 56 film coated tablets and package leaflet are presented in a cardboard box.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

2022/564

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 09.10.2022
Date of renewal of authorization:

10. DATE OF REVISION OF THE TEXT