1. NAME OF THE MEDICINAL PRODUCT

Otezla 10 mg
Otezla 20 mg
Otezla 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of apremilast.
Each film-coated tablet contains 20 mg of apremilast.
Each film-coated tablet contains 30 mg of apremilast.

Excipient(s) with known effect

Each film-coated tablet contains 60 mg lactose monohydrate
Each film-coated tablet contains 120 mg lactose monohydrate
Each film-coated tablet contains 180 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Otezla 10 mg film-coated tablets
Pink, diamond shaped 10 mg film-coated tablet of 8 mm length with "APR" engraved on one side and "10" on the opposite side.
Otezla 20 mg film-coated tablets
Brown, diamond shaped 20 mg film-coated tablet of 10 mm length with "APR" engraved on one side and "20" on the opposite side.
Otezla 30 mg film-coated tablets
Beige, diamond shaped 30 mg film-coated tablet of 12 mm length with "APR" engraved on one side and "30" on the opposite side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Otezla is indicated:

- For treatment of adult patients with active psoriatic arthritis (PsA).
- For adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy (PSOR).
- For the treatment of adult patients with oral ulcers associated with Behçet's disease (BD).

4.2 Posology and method of administration

Treatment with apremilast should be initiated by specialists experienced in the diagnosis and treatment of psoriasis, psoriatic arthritis or Behçet's disease.

Posology
The recommended dose of apremilast is 30 mg taken orally twice daily, approximately 12 hours apart (morning and evening), with no food restrictions. An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration.

Table 1: Dose 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
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 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.

During pivotal trials the greatest improvement was observed within the first 24 weeks of treatment. If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis.

Special populations

Elderly patients
No dose adjustment is required for this patient population (see sections 4.8 and 5.2).

Patients with renal impairment
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 apremilast be titrated using only the AM schedule listed in Table 1 and the PM doses be skipped (see section 5.2).

Patients with hepatic impairment
No dose adjustment is necessary for patients with hepatic impairment (see section 5.2).

Pediatric population
The safety and efficacy of apremilast in children aged 0 to 17 years have not been established. No data are available.

Method of administration
Apremilast is for oral use. The film-coated tablets should be swallowed whole, and can be taken either with or without food.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

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 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 may be at a higher risk of complications. If patients develop severe diarrhea, nausea, or vomiting, discontinuation of treatment with apremilast may be necessary.

Psychiatric disorders
Apremilast is associated with an increased risk of psychiatric disorders such as insomnia and depression. Instances of suicidal ideation and behavior, including suicide, have been observed in patients with or without history of depression (see section 4.8). The risks and benefits of starting or continuing treatment with apremilast should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended. Patients and caregivers should be instructed to notify the prescriber of any changes in behavior or mood and of any suicidal ideation. If patients suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with apremilast.

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

Underweight patients
Patients who are underweight at the start of treatment should have their body weight monitored regularly. In the event of unexplained and clinically significant weight loss, these patients should be evaluated by a medical practitioner and discontinuation of treatment should be considered.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

There was no clinically meaningful interaction between ketoconazole and apremilast. Apremilast can be co-administered with a potent CYP3A4 inhibitor such as ketoconazole.

There was no pharmacokinetic interaction between apremilast and methotrexate in psoriatic arthritis patients. Apremilast can be co-administered with methotrexate.

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

4.6 Fertility, pregnancy and lactation

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.

Pregnancy
There are limited data about the use of apremilast in pregnant women.

Apremilast is contraindicated during pregnancy (see section 4.3). Effects of apremilast on pregnancy included embryofetal loss in mice and monkeys, and reduced fetal 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 (see section 5.3).

Breast-feeding
Apremilast was detected in milk of lactating mice (see section 5.3). It is not known whether apremilast, or its metabolites, are excreted in human milk. A risk to the breastfed infant cannot be excluded, therefore apremilast should not be used during breast-feeding.

Fertility
No fertility data is available in humans. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels 3-fold clinical exposure and in females at exposure levels 1-fold clinical exposure. For pre-clinical fertility data see section 5.3.

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 reactions with apremilast in PsA and PSOR are gastrointestinal (GI) disorders including diarrhea (15.7%) and nausea (13.9%). The other most commonly reported adverse reactions include upper respiratory tract infections (8.4%), headache (7.9%), and tension headache (7.2%) and are mostly mild to moderate in severity.

The most commonly reported adverse drug reactions with apremilast in BD are diarrhea (41.3%), nausea (19.2%), headache (14.4%), upper respiratory tract infection (11.5%), upper abdominal pain (8.7%), vomiting (8.7%) and back pain (7.7%) and are mostly mild to moderate in severity.

The gastrointestinal adverse reactions generally occurred within the first 2 weeks of treatment and usually resolved within 4 weeks.

Hypersensitivity reactions are uncommonly observed (see section 4.3).

Tabulated list of adverse reactions
The adverse reactions observed in patients treated with apremilast 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 program and post-marketing experience. The frequencies of adverse drug reactions are those reported in the apremilast arms of the four Phase III studies in PsA (n = 1945) or the two Phase III studies in PSOR (n=1184), and in the phase III study in BD (n=207) the highest frequency from either data pool is represented in Table 2.

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 2. Summary of adverse reactions in psoriatic arthritis (PsA), psoriasis (PSOR) and Behçet's disease (BD)

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* [a]
	Common	Migraine*
		Tension headache*
Respiratory, thoracic, and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very Common	Diarrhea*
		Nausea*
	Common	Vomiting*
		Dyspepsia
		Frequent bowel movements
		Upper abdominal pain *
		Gastroesophageal reflux disease
	Uncommon	Gastrointestinal hemorrhage
Skin and subcutaneous tissue disorders	Uncommon	Rash Urticaria
	Not known	Angioedema
Musculoskeletal and connective tissue disorders	Common	Back pain*
General disorders and administration site conditions	Common	Fatigue
Investigations	Uncommon	Weight decrease

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

[a] Frequency reported as common in PSA and PSOR

Description of selected adverse reactions

Psychiatric disorders

In clinical studies and post-marketing experience, uncommon cases of suicidal ideation and behavior, were reported, while completed suicide was reported post-marketing. Patients and caregivers should be instructed to notify the prescriber of any suicidal ideation (see section 4.4).

Body weight loss

Patient weight was measured routinely in clinical studies. The mean observed weight loss in PsA and PSOR 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. The mean observed weight loss in BD patients treated with apremilast for 52 weeks was 0.52 kg. A total of 11.8% of patients receving apremilast had observed weight loss between 5-10% while 3.8% of the patients receiving apremilast had observed weight loss greater than 10%. None of these patients had overt clinical consequences from weight loss. None of the patients discontinued the study due to adverse reaction of weight decreased.

Please see additional warning in section 4.4 for patients who are underweight at beginning of treatment.

Special populations

Elderly patients
From post-marketing experience, elderly patients ≥ 65 years of age may be at a higher risk of complications of severe diarrhea, nausea and vomiting (see section 4.4).

Patients with hepatic impairment
The safety of apremilast was not evaluated in PsA, PSOR or BD patients with hepatic impairment.

Patients with renal impairment
In the PsA, PSOR or BD clinical studies, the safety profile observed in patients with mild renal impairment was comparable to patients with normal renal function. The safety of apremilast was not evaluated in PsA, PSOR or BD patients with moderate or severe renal impairment in the clinical studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

Apremilast 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. In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment is instituted. In the event of overdose, symptomatic and supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

Pharmacodynamic effects

In clinical studies in patients with psoriatic arthritis, apremilast significantly modulated, but did not fully inhibit, plasma protein levels of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, MMP-3, and TNF-α. After 40 weeks of treatment with apremilast, there was a decrease in plasma protein levels of IL-17 and IL-23, and an increase in IL-10. In clinical studies in patients with psoriasis, apremilast decreased 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 of up to 50 mg twice daily did not prolong the QT interval in healthy subjects.

Clinical efficacy and safety

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 randomized 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%). Concomitant treatment with biologic DMARDs, including TNF blockers, was not allowed. 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-existing 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 twice daily Following 52 weeks of treatment, patients could continue on open-label apremilast 20 mg or 30 mg within the long-term extension of the PALACE 1, PALACE 2, and PALACE 3 studies for a total duration of treatment up to 5 years (260 weeks).

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 3. ACR 20/50/70 responses were maintained at week 24.

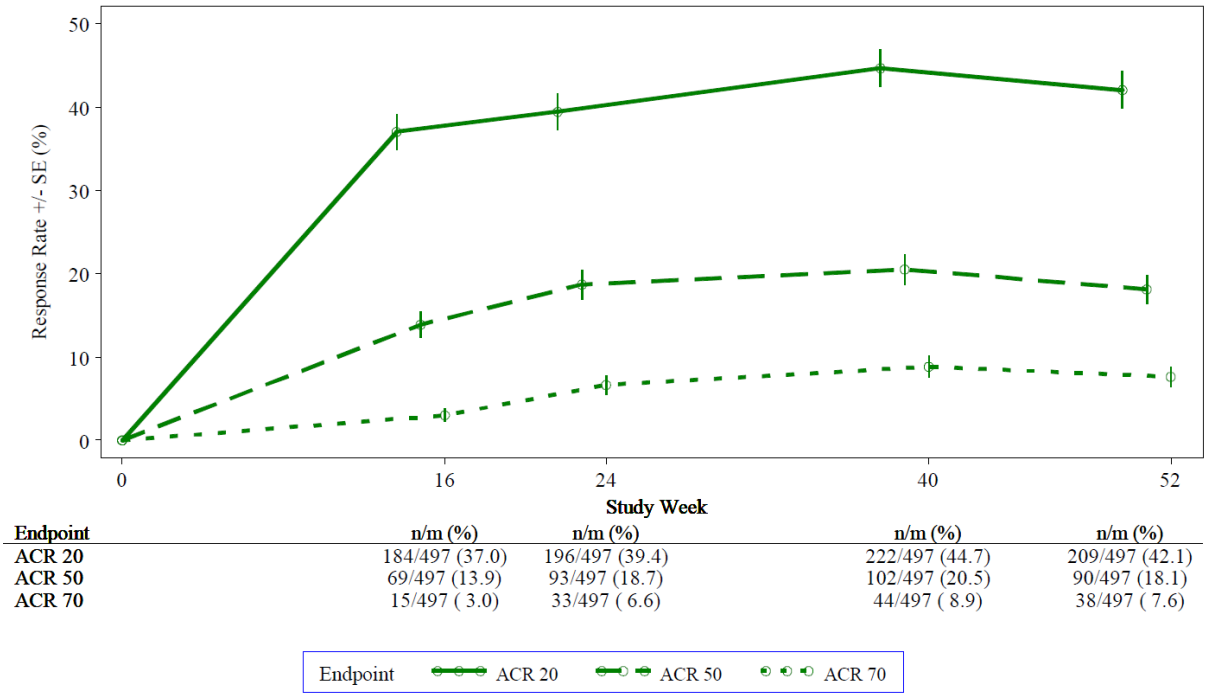
Among patients who were initially randomized to apremilast 30 mg twice daily treatment, ACR 20/50/70 response rates were maintained through week 52 in the pooled Studies PALACE 1, PALACE 2 and PALACE 3 (Figure 1).

Table 3. 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 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	Placebo +/- DMARDs N=496	Apremilast 30 mg twice daily +/- 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. Among 497 patients initially randomized to apremilast 30 mg twice daily, 375 (75%) patients entered

the long-term extension studies, and of these, 221 patients (59%) were still on this treatment at week 260. ACR responses were maintained in the long-term open label extension studies for up to 5 years.

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.

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

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.

Improved physical function as assessed by the HAQ-DI and the SF36v2PF domain, and the FACIT-fatigue scores were maintained in the open-label extension studies for up to 5 years of treatment.

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 $\geq 10\%$, 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 twice daily or placebo for 16 weeks (placebo-controlled phase) and from weeks 16-32, all patients received

apremilast 30 mg twice daily (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 twice daily. 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 twice daily. 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 twice daily treatment.

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

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

	ESTEEM 1		**ESTEEM 2**	
	Placebo	**30 mg twice daily APR***	**Placebo**	**30 mg twice daily 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
[d] sPGA = Static Physician Global Assessment
[e] BSA = Body Surface Area
[f] 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 5).

Table 5. Persistence of effect among subjects randomized to APR 30 twice daily at week 0 and re-randomized to APR 30 twice daily 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 twice daily 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 twice daily at week 32. Subjects with missing data were counted as non-responders.

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 apremilast at week 32 through week 52 (Table 5).

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.

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, and of these 115 patients (26%) were still on treatment at week 260. For patients who remained on apremilast in the open-label extension of ESTEEM 1 and ESTEEM 2 studies, improvements were generally maintained in PASI score, affected BSA, itch, nail and quality of life measures for up to 5 years.

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

Oral Ulcers Associated with Behçet's disease

A multicenter, randomized, placebo-controlled trial (BCT-002) enrolled a total of 207 adult patients with BD with active oral ulcers. Patients were previously treated with at least one nonbiologic BD medication and were candidates for systemic therapy. Patients met the International Study Group (ISG) Criteria for BD. Patients had at least 2 oral ulcers at screening and at least 2 oral ulcers at randomization and without currently active major organ involvement. Concomitant treatment for BD was not allowed.

Patients were randomized 1:1 to receive either apremilast 30 mg twice daily (n=104) or placebo (n=103) for 12 weeks. After week 12, all patients received apremilast 30 mg twice daily.

Efficacy was assessed based on the number and pain of oral ulcers.

Patients ranged in age from 19 to 72, with a mean age of 40 years. The mean duration of BD was 6.84 years. All subjects had a history of recurrent oral ulcers that were currently active. Subjects had a history of skin lesions (98.6%), genital ulcers (90.3%), musculoskeletal manifestations (72.5%), ocular manifestations (17.4%), central nervous system (9.7%), gastrointestinal (GI) manifestations (9.2%) and vascular involvement (1.4%). The mean baseline oral ulcer counts were 4.2 and 3.9 in the apremilast and placebo groups, respectively.

Measures of Oral Ulcers

Improvements in measures of oral ulcers at week 12 are presented in Table 6.

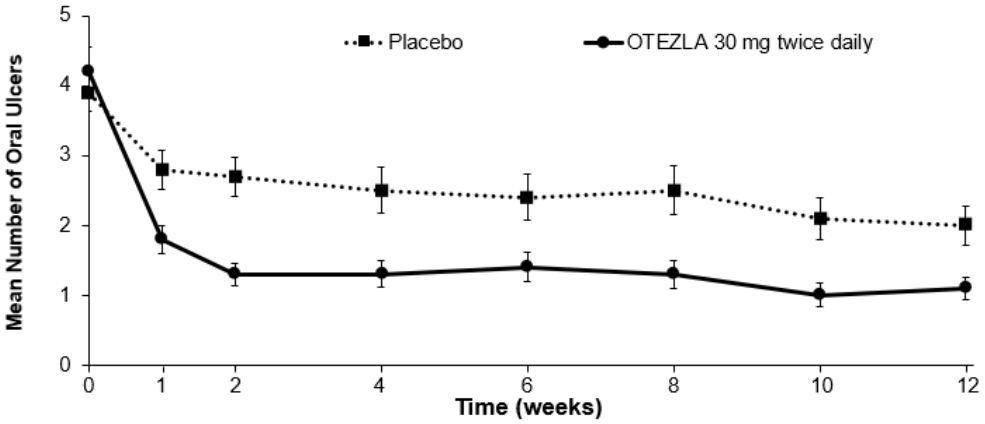
Table 6: Clinical Response of Oral Ulcers at Week 12 in the BCT-002 Study (ITT[a] Population)

Endpoint	**Placebo N=103**	**OTEZLA 30 mg twice daily N=104**	**Treatment Difference[b] (95% CI[c])**
Change[d] from baseline in the pain of oral ulcers as measured by VAS[e] at week 12	-18.7	- 42.7	-24.1 (-32.4, -15.7)
Proportion[f] of subjects achieving oral ulcer complete response (oral ulcer-free) at week 12	22.3%	52.9%	30.6%[g] (18.1%, 43.1%)
Proportion[f] of subjects achieving oral ulcer complete response (oral ulcer-free) by week 6, and who remained oral ulcer-free for at least 6 additional weeks during the 12-week Placebo-controlled Treatment Phase	4.9%	29.8%	25.1%[g] (15.5%, 34.6%)
Daily average[h,i] number of oral ulcers during the 12-week Placebo-controlled Treatment Phase	2.6	1.5	-1.1 (-1.6, -0.7)

[a] ITT=intent to treat.
[b] OTEZLA – Placebo.
[c] CI=confidence interval.
[d] Mean changes from baseline are least square means from mixed-effects model for repeated measures, adjusting for sex, region, and baseline pain of oral ulcers as measured by the visual analog scale.
[e] VAS=visual analog scale; 0=no pain, 100=worst possible pain.
[f] Patients for whom data are not available to determine response status are considered non-responders.
[g] Adjusted difference in proportions is the weighted average of the treatment differences across the 4 strata of combined sex and region factors with the Cochran-Mantel-Haenszel weights.
[h] Mean daily averages are least squares means from analysis of covariance, after adjusting for sex, region, and baseline number of oral ulcers.
[i] Based on oral ulcer counts measured at baseline and at weeks 1, 2, 4, 6, 8, 10, and 12.

Figure 2 displays the mean number of oral ulcers for each treatment group at each visit, while Figure 3 displays the mean oral ulcer pain on a visual analog scale for each treatment group at each visit.

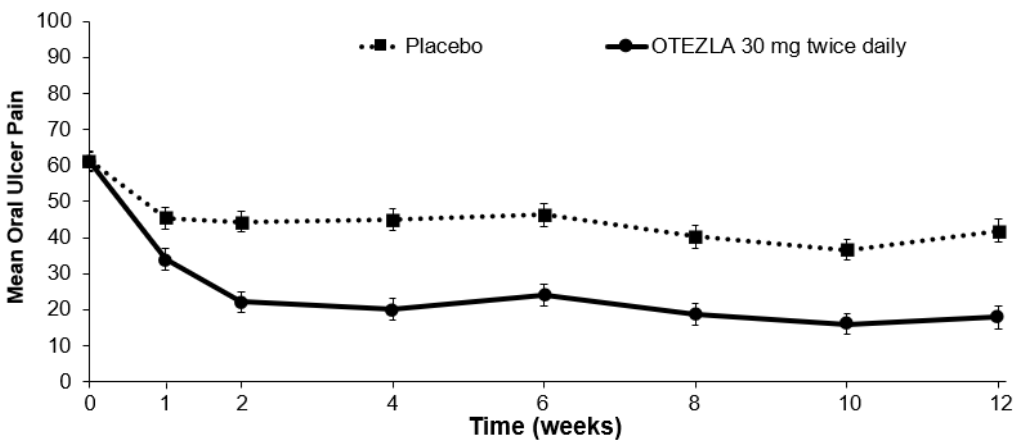
Figure 2: Mean (± SE) Number of Oral Ulcers by Time Point Through Week 12 (ITT Population)



Weeks	0	1	2	4	6	8	10	12
Placebo, n	103	98	97	93	91	86	83	82
OTEZLA 30 mg twice daily, n	104	101	101	101	98	94	94	97

ITT = intent-to-treat; SE = standard error.

Figure 3: Mean (± SE) Oral Ulcer Pain on a Visual Analog Scale by Time Point Through Week 12 (ITT Population)



Weeks	0	1	2	4	6	8	10	12
Placebo, n	101	95	96	91	90	85	82	81
OTEZLA 30 mg twice daily, n	102	95	97	99	97	92	93	95

ITT=intent-to-treat; SE=standard error.
Oral ulcer pain was assessed on a 100-mm Visual Analog Scale with 0 = no pain and 100 = worst possible pain. Mean baseline Visual Analog Scale pain scores were 61.2 and 60.8 in the OTEZLA 30 mg twice daily treatment group and placebo treatment group, respectively.

5.2 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 (V_d) is 87 L, indicative of extravascular distribution.

Biotransformation
Apremilast is extensively metabolized 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 feces, 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 metabolized by CYP enzymes.

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

In vitro, apremilast has little to no inhibitory effect (IC50>10 µM) 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 feces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and feces, 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). There is limited pharmacokinetic data in subjects over 75 years of age in clinical trials. No dosage adjustment is necessary for elderly patients.

Renal impairment
There is no meaningful difference in the PK of apremilast between mild or moderate renally impaired subjects and matched healthy subjects (N = 8 each). The results support that no dose adjustment is needed in patients with mild and moderate renal impairment. Apremilast dose should be reduced 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.

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. There is no evidence of 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 estrous 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, behavioral, 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.

Other studies
There is no evidence of immunotoxic, dermal irritation, or phototoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate.

Film-coating
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc
Iron oxide red

The 20 mg tablets also contain iron oxide yellow

The 30 mg tablets also contain iron oxide yellow and iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30℃.

6.5 Nature and contents of container

The treatment initiation pack contains 27 film-coated tablets (4 × 10 mg, 4 × 20 mg, 19 × 30 mg).
The 30 mg pack contains 56 film-coated tablets (4 × PVC/aluminum foil blisters containing 14 film-coated tablets).

6.6 Special precautions for disposal

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

7. MANUFACTURER

Amgen Europe B.V., Minervum 7061, Breda, The Netherlands.

8. REGISTRATION HOLDER

Amgen Europe B.V., P.O. BOX 53313, Tel - Aviv.

Revised in August 2021 according to MoHs guidelines.