Apremilast (OTEZLA)

National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Apremilast is an oral first-in-class phosphodiesterase 4 inhibitor that was approved by the FDA for the treatment of adults with active psoriatic arthritis and adults with moderate to severe plaque psoriasis.
- The recommended daily dose is 30 mg twice daily and initial doses should be titrated over the course of about a week to reduce gastrointestinal adverse reactions.
- Apremilast was shown to be moderately effective in clinical trials at reducing symptoms of psoriatic arthritis including tender and swollen joints and physical functioning (ACR20) in patients who have failed previous treatments. Concomitant treatment with methotrexate or other conventional systemic disease-modifying antirheumatic drugs (DMARDs) was allowed. Results from 4 clinical trials showed NNTs ranging from 4-10 with 30 mg twice daily dosing.
- Apremilast was shown to be moderately effective in clinical trials at improving symptoms and quality of life for patients with plaque psoriasis. Results from two clinical trials showed statistically significant improvements in 75% improvement in Psoriasis Area and Severity Index (PASI-75) with 20 mg twice daily and 30 mg twice daily dosing.
- Depression may develop or worsen during therapy; educate patients and use caution in patients with a history of depression or suicidality. The most common adverse reactions reported were diarrhea, headache, nausea, and upper respiratory tract infection.
- **Conclusion:** There is moderate quality evidence consistently showing apremilast to be a safe and effective medication in the treatment of adults with moderate to severe psoriatic arthritis or plaque psoriasis. For psoriatic arthritis, the clinical trials showed improvement in clinical symptoms such as tender or swollen joints, however they did not evaluate improvements in or slowed progression of radiographic damage to affected joints. Therefore, apremilast cannot be considered a DMARD. For plaque psoriasis, the clinical trials showed a consistent improvement in patient reported outcomes. Clinical trials for both psoriatic arthritis and plaque psoriasis included patients that failed previous treatment and patients that continued other treatments, therefore apremilast should not be considered as a first line agent. While there are no studies currently available to assess the long-term safety of apremilast, it appears to have a more favorable safety profile when compared to conventional synthetic DMARDs and biologics. To date there have been no head-to-head trials comparing apremilast with DMARDs or biologics, though indirect comparisons of placebo-controlled trial results suggest that apremilast may be more effective in treating psoriatic arthritis than methotrexate, and less effective than TNF inhibitors. Apremilast costs more than both the oral DMARDS and the biologic agents, therefore, it may be considered as an add-on or alternative therapy for patients with active psoriatic arthritis who have failed to show clinical improvement or have not tolerated conventional synthetic DMARDs and biologic agents. To date, there is insufficient evidence to determine apremilast's place in therapy for psoriasis since there were only phases 2 and 2b trials. In summary, the main advantages of apremilast are convenient administration and lack of monitoring. Apremilast appears to be safe in short-term studies. These advantages need to be weighed against cost, lack of long-term safety data, and lack of radiographic evaluation. Direct comparisons with active therapies, long-term studies beyond 1 year and radiographic outcome measures are needed to determine its role in therapy.

Introduction

Apremilast is the first drug in the phosphodiesterase 4 (PDE4) inhibitor drug class approved for the treatment of psoriatic arthritis and plaque psoriasis. It is also the first oral medication approved for treatment of adult patients with active psoriatic arthritis since the commonly used disease modifying anti-rheumatic drugs (DMARDs) do not carry an FDA approved indication for psoriatic arthritis. Apremilast cannot be considered a DMARD because the clinical trials to date have not addressed radiographic improvements in patients with psoriatic arthritis.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating apremilast for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Mechanism of Action

Apremilast inhibits PDE4, which results in increased intracellular cAMP levels in inflammatory cells. As a result, inhibition of PDE4 leads to a persistent elevation of cAMP and subsequently diminished T-cell secretion of proinflammatory cytokines and other mediators, including TNF-alpha, IFN-γ, nitric oxide synthase, IL-2, IL-17, and IL-23. Through modulation of cAMP levels, PDE4 may regulate the proinflammatory actions of monocytes, T-cells, and neutrophils. Mesenchymal cells that express PDE4 include keratinocytes within the dermis, smooth muscle, and vascular endothelium.[2]

Pharmacokinetics

Table 1 Pharmacokinetics of Apremilast

Parameter	Description
Absorption	Tmax: 2.5 hours Extent of absorption not affected by food
Metabolism	In vitro, CYP 3A4 (major), CYP 1A2 and CYP 2A6 (minor)
Elimination	Renal excretion: 3% unchanged Fecal excretion: 7% unchanged
Half-life	6–9 hours
Protein Binding	68%
Bioavailability	73%

FDA-approved Indication(s)

Apremilast is FDA-approved for the following indications[i]:

- Treatment of adult patients with **active psoriatic arthritis**.
- Treatment of patients with **moderate to severe plaque psoriasis** who are candidates for phototherapy or systemic therapy.

Potential Off-label Uses

- Ankylosing spondylitis
  - One RCT compared apremilast 30 mg BID to placebo in 38 patients for 12 weeks.[3] The primary endpoint, which was mean change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at week 12 compared to baseline, was not significant. Further studies are needed to recommend apremilast for this indication.

- Rosacea
    - One open –label pilot study evaluated apremilast 20 mg twice daily in 12 patients for a total of 12 weeks.[4] Significant improvements compared to baseline were seen in the following secondary endpoints: Physician Global 7-Point Assessment, Patient Global Assessment (PGA), Physician Overall Erythema Severity, and physician-rated variable scales. Further studies are needed to recommend apremilast for this indication.
- Atopic dermatitis
    - One open-label pilot study compared apremilast 20 mg BID for a total of three months with apremilast 30 mg BID for a total of six months in 16 patients.[5] Overall, patients in both groups experienced significant reductions in pruritus VAS and Dermatology Life Quality Index (DLQI) compared to baseline. Further studies are needed to recommend apremilast for this indication.
- Discoid lupus erythematosus
    - One phase 2, open-label, single-arm, pilot study evaluated apremilast 20 mg twice daily for 85 days in 8 patients.[6] The primary outcome was change in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) from baseline to day 85. Significant reduction in median CLASI scores were seen. Further studies are needed to recommend apremilast for this indication.
- Lichen planus
    - One open-label, non-randomized, pilot study evaluated apremilast 20 mg twice daily for 12 weeks in 10 patients.[7] Three of the ten patients achieved a 2-grade or more improvement in the PGA score compared to baseline. Further studies are needed to recommend apremilast for this indication.

Current VA National Formulary Alternatives

Oral conventional synthetic DMARDs on national formulary are the following:

- Methotrexate
- Hydroxychloroquine
- Leflunomide
- Cyclosporine
- Sulfasalazine
- Azathioprine
- Cyclophosphamide

Nonformulary Alternatives

Biologic DMARDs are nonformulary.

- Adalimumab
- Etanercept
- Golimumab
- Infliximab
- Ustekinumab

Key exclusion criteria for biologics include contraindication to biologic therapy, such as active or severe infection or administration of live vaccine concomitantly with or during biologic therapy.

Inclusion criteria for use of biologics are extensive and differ for each agent, but generally require patients to have inadequate response, hypersensitivity, serious adverse event, or contraindication to methotrexate.

Dosage and Administration

Film-coated tablet, oral: 30 mg twice daily is the recommended daily dose.

A therapy pack with 10 mg, 20 mg, and 30 mg tablets is available for initial titration of therapy. Patients should receive four doses of 10 mg tablets, followed by four doses of 20 mg tablets, and then 30 mg tablets thereafter. See package insert for detailed information.

Administer without regard to food.

Swallow tablets whole; do not crush, chew, or split.

Dosage in Specific Populations

Renal Impairment: For patients with CrCl <30 mL/min, the evening doses should be skipped during titration. It is recommended that the daily dose should be reduced to 30 mg once daily. No specific recommendations for patients on dialysis.

Hepatic Impairment: No dosage adjustment necessary.

Storage

Store tablets below 30°C (86°F).

Efficacy

Efficacy Measures

The psoriatic arthritis (PsA) studies used 20% improvement in the modified American College of Rheumatology response criteria (ACR20), which was developed to measure changes in rheumatoid arthritis symptoms and found to be useful for discriminating treatment effects in PsA clinical trials. The ACR score is more commonly used in clinical trials than in doctor-patient relationships, as it allows a common standard between researchers.[8] An ACR score of 20 means that the patient's symptoms have improved by 20%, an ACR score of 50% means the patient's symptoms have improved by 50%, etc. To qualify for an ACR20 score, a person must have at least 20% fewer tender joints and at least 20% fewer swollen joints, as well as a 20% improvement in at least three of the five following areas: the person's overall assessment of his or her own PsA, the physician's global assessment of the person's PsA, the person's assessment of his or her own pain, the person's assessment of his or her own physical functioning, and the results of an erythrocyte sedimentation rate or C-reactive protein blood test.[9]

Health Assessment Questionnaire Disability Index (HAQ-DI) is one of the most widely used tools to address functional capacity of patients with rheumatic diseases. It addresses the patient's ability to perform any of 20 activities in his or her daily life, with one of four responses available: without any difficulty (score 0), with some difficulty (score 1), with much difficulty (score 2), and unable to do (score 3). The 20 activities are classified into eight categories: dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and other activities, with two or three activities per category. A score is then assigned to each category based on the highest score for any activity within that category. The total HAQ-DI score is the mean of the representative scores for each category.[10]The FDA states that the minimal clinically important difference (MCID) is a decrease $\geq$ 0.22 units.[11]

The Short Form (36) Health Survey (SF-36) is a patient-reported survey of patient health. It can be used to monitor and compare disease burden as well as other health aspects. It consists of eight scaled scores, which are the weighted sums of the questions in their section. The eight sections are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Each scale is directly transformed into a 0-100 scale, assuming that each question carries equal weight. A lower score indicates greater disability.[12]

The current gold standard for assessment of extensive psoriasis has been the Psoriasis Area and Severity Index (PASI). The PASI is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale), weighted by the area of involvement. A 75% improvement in PASI (PASI 75) is a well-established clinically meaningful endpoint for clinical trials, and there is strong evidence demonstrating that 50% improvement in PASI (PASI 50) is also a clinically meaningful endpoint.[13]

The Psoriatic Arthritis Response Criteria (PsARC) assesses the following: (1) 20% or more improvement in physician global assessment of disease activity; (2) 20% or more improvement in patient global assessment of disease activity; (3) 30% or more improvement in tender joint count; and (4) 30% or more improvement in swollen joint count. In order to achieve response, patient must meet at least two of the criteria and one of the criteria met must be either a tender or swollen joint count. The patient also cannot have any worsening in any of the four criteria.[14]

Summary of efficacy findings

Psoriatic Arthritis

One high-quality Phase 2 RCT,[15] one high-quality Phase 3 RCT[16] and two unpublished RCTs[17,18] showed apremilast to be superior to placebo in the treatment of psoriatic arthritis, measured in percentage of patients achieving ACR20 (Table 2).

Table 2 ACR20 Responder Rates, Psoriatic Arthritis Trials

Reference	Time Point (wk)	APR 20 BID % (N)	APR 30 BID % (N)	APR 40 QD % (N)	PBO % (N)
Schett, et al.(2012)[15]	12	43.5% (55) NNT 3 (2–7)		35.8% (60) NNT 4 (3–13)	11.8% (50)
Kavanaugh, et al. (2014)[16]	16	31.3% (163) NNT 9 (5–40)	39.8% (161) NNT 5 (4–10)		19.4% (165)
Cutolo, et al. (2013), abstract[17]	16	38.4% NNT 5	34.4% NNT 7		19.5%
Edwards, et al. (2013), abstract[18]	16	29.4% NNT 10	42.8% NNT 4		18.9%

All differences in rates between apremilast groups versus placebo groups were statistically significant ($p \leq 0.0235$). NNT, Number needed to treat (95% CI).

Overall, the results showed that apremilast had small to moderate effects in terms of ACR20 responder rates at 12 or 16 weeks. Differences in diagnostic criteria and study populations (e.g., number of tender joints, CRP concentrations, and percentages of patients on methotrexate) may explain the higher responder rates in the Schett (2012) trial[15] relative to those in the Kavanaugh (2014)[16] trial.

A follow-on publication by Strand, Schett, et al. (2013)[19] on the Phase 2 RCT (by Schett, et al. 2012)[15] reported that apremilast was superior to placebo in terms of patient reported outcomes (PROs).[19] For APR20 vs. APR40 vs. PBO:

- Mean change in Global VAS: -10.3 ($p<0.05$) vs. -10.4 ($p<0.05$) vs. 1.0 (MCID=10.0)
- Mean change in Pain VAS: -11.2 ($p<0.05$) vs. -11.5 ($p<0.05$) vs. -1.3 (MCID=10.0)
- Mean change in FACIT-F: 4.1 ($p<0.05$) vs. 4.3 ($p<0.05$) vs. 0.5 (MCID=4.0)
- Mean change in SF-36 MCS: 3.4 ($p<0.05$) vs. 1.1 vs. -0.8 (MCID=2.5)
- Mean change in SF-36 PCS: 2.4 ($p<0.05$) vs. 2.1 vs. 0.8 (MCID=2.5)

Although these results were statistically significant, the expected clinical benefits would be minimal since all results for apremilast were slightly above the MCID.

Plaque Psoriasis

- Two moderate quality RCT showed apremilast to be superior to placebo in the treatment of plaque psoriasis.[20,21]
    - Papp, Cather, et al. (2012), Phase 2b RCT[20]:
        - Percentage of patients achieving PASI-75 at week 16: APR 20 BID 29% of 87 patients, (OR 6.69; 95% CI 2.43-18.5; p<0.0001), APR 30 BID 41% of 88 patients (OR 11.5; 4.24-31.16; p<0.0001) compared with PBO 6 % of 88 patients
        - APR 10 BID results that did not significantly differ when compared with PBO are not presented here.
    - Papp, Kaufmann, et al. (2013),.Phase 2 RCT[21]:
        - Proportion of patients achieving PASI-75 at week 12: APR20 BID: 24.4% (p=0.023) vs. PBO : 10.3%
    - Strand, Fiorentino, et al. (2013)[22] reported patient-reported outcomes at Week 16 for the Phase 2b RCT authored by Papp, Cather, et al. (2012)[20]:
        - Mean percent change in DLQI: APR 20 BID: -5.9 (p<0.001), APR 30 BID: -4.4 (p=0.005) PBO: -1.9 (MCID=5.0)
        - Mean percent change in pruritus VAS: APR 20 BID: -35.5 (p=0.005) vs. APR 30 BID: -43.7 (p<0.05) vs. PBO: -6.1 (MCID=10.0)
        - Mean change in SF-36 MCS: APR 10 BID: 2.8 (p=0.008) vs. APR 20 BID: 3.3 (p=0.007) vs. APR 30 BID: 3.0 (p=0.005) vs. PBO -0.5 (MCID=2.5)
        - APR 10 BID results that did not significantly differ when compared with PBO are not presented here.
- Two unpublished, 52-week (including 16-week placebo-controlled phases), Phase 3 RCTs are ongoing under the ESTEEM (Efficacy and Safety Trial Evaluating the Effects of apreMilast in psoriasis) clinical trial program. Study NCT01690299 will compare apremilast with etanercept for treatment of psoriasis.

Table 3 Assessment of Evidence Base for Psoriatic Arthritis

Category	Summary
Overall Quality of Studies (GRADE)	GRADE: Moderate. Two studies were high quality. Two other studies were unable to be rated because they were reported as abstracts.
Consistency of Results	The 2 published studies showed a small to moderate benefit in reducing signs and symptoms of psoriatic arthritis, with a NNT ranging from 4-10 for apremilast 30mg twice daily dosing.
Directness of Evidence	These studies showed a direct improvement in symptoms of psoriatic arthritis such as tender and swollen joints, however they did not evaluate radiographic improvement, which, long-term, is the more desired outcome.
Precision of Results	The 95% CI around the between-group difference in achievement of an ACR20 was fairly wide, indicating imprecision of results and some degree of uncertainty in effect size. The widest 95% CI was 0.16-0.46 for apremilast 20mg BID vs. placebo (Schett G, et al. 2012).[15] The narrowest 95% CI was 0.01-0.20 for apremilast 20mg BID vs. placebo (Edwards CJ, et al. 2013, abstract).[17]

Table 3 Assessment of Evidence Base for Plaque Psoriasis

Category	Summary
Overall Quality of Studies (GRADE)	GRADE: Moderate. Evidence available from two phase 2 trials.
Consistency of Results	Both (2 of 2) studies showed a significant benefit in reducing signs and symptoms of plaque psoriasis.
Directness of Evidence	These studies showed a direct improvement in symptoms of plaque psoriasis, as well as an improvement in patient reported outcomes. Plaque psoriasis is generally a cosmetic condition and can affect a patient's quality of life; therefore using patient reported outcomes is a direct method for addressing the efficacy of apremilast in this condition.
Precision of Results	The 95% CI around the between-group difference in proportion of patients achieving PASI-75 at week 16 was fairly wide, indicating imprecision of results and uncertainty in effect size. A 95% CI of 4.24-31.16 was found for an Odds Ratio of 11.5 when comparing apremilast 30mg BID to placebo (Papp, Cather, et al. 2012).

Indirect Efficacy Comparisons with Alternative Therapies

In crude indirect comparisons using ACR20 responder rates from psoriatic arthritis placebo-controlled trials, apremilast (NNTs 4–10, Table 2) seems to be less efficacious than TNF inhibitors (NNTs 2–3) and similar to ustekinumab (NNT 4) (Table 4).

Table 4 ACR20 NNTs for Biologic Agents in Psoriatic Arthritis

Drug	Study	Population	Duration of Treatment	NNT
Infliximab	Antoni 2005 (IMPACT 1)	Previous failure of treatment with ≥1 DMARDs. At enrollment, patients were required to have active peripheral polyarticular arthritis, defined as the presence of ≥5 swollen and tender joints in conjunction with at least 1 of the following criteria: ESR ≥28 mm/hour, CRP level ≥15 mg/liter, and/or morning stiffness lasting 45 minutes or longer. Patients also were required to have negative results of serum tests for rheumatoid factor.	16 weeks	2
	Antoni 2005 (IMPACT 2)	Active PsA diagnosed at least 6 months before the first infusion of study drug. Active articular disease was defined as ≥5 swollen joints and ≥5 tender joints and either CRP ≥15 mg/l and/ or morning stiffness lasting 45 minutes or longer. Patients were required to have had an inadequate response to current or previous DMARDs or NSAIDs. In addition, patients had to have active plaque psoriasis with at least one qualifying target lesion at least 2 cm in diameter. Patients also were required to have a negative test for rheumatoid factor in their serum.	14 weeks	
	Vander Cruyssen 2007	The study population consisted of 18 patients with PsA, previously enrolled in a RCT with the following inclusion criteria: Patients had to fulfill the European Spondylarthropathy Study Group criteria. At the time of enrollment, all patients had active SpA defined as the presence of ≥1 swollen joint or 1 current episode of active tendinitis or dactylitis and/or inflammatory spinal pain. DMARDs, such as SSZ, MTX, and cyclosporine, were not allowed during the study and were discontinued at least 4 weeks prior to baseline.	12 weeks	
Adalimumab	Genovese 2007	At study entry, patients were required to have ≥3 swollen joints and ≥3 tender or painful joints, and either an active cutaneous lesion of chronic plaque psoriasis or a documented history of chronic plaque psoriasis diagnosed by the investigator or a dermatologist. All patients enrolled in the study were receiving concomitant DMARD therapy or had a history of DMARD therapy with an inadequate response, as defined by the investigator. Oral corticosteroids were allowed if the equivalent dose was ≤ 10 mg of prednisone/day and had been stable during the 4 weeks preceding the baseline visit. Concomitant treatment with MTX or other DMARDs, with the exception of cyclosporine and tacrolimus (oral or topical) received within 4 weeks of	12 weeks	3

		the baseline visit, was allowed if the patient had received ≥3 months of therapy and the dosage had been stable during the 4 weeks preceding the baseline visit. The maximum allowable MTX dosage was 30 mg/week.		
	Mease 2005	Patients with moderately to severely active PsA, defined as ≥3 swollen joints and ≥3 tender or painful joints and a history of inadequate response to NSAIDS. MTX use was allowed during the study if it had been used for ≥3 months and at a stable dose for ≥4 weeks. MTX dose had to be ≤30 mg/week. Corticosteroids (prednisone ≤10mg/day) were allowed. All other DMARDs, topicals other than low-potency steroids, and anti-TNF were discontinued prior to trial.	12 weeks	
Golimumab	Kavanaugh 2008	Patients enrolled in the study had active PsA despite therapy with DMARDs or NSAIDs. Active PsA was defined by the presence of ≥3 swollen and ≥3 tender joints, negative rheumatoid factor, at least 1 subset of PsA, and the presence of plaque psoriasis with a qualifying lesion at least 2 cm in diameter. Previous use of anti-TNF agents, rituximab, natalizumab, or cytotoxic agents was prohibited. Stable doses of MTX, NSAIDs, and corticosteroids (prednisone ≤10mg/day) were allowed.	14 Weeks	3
Etanercept	Mease 2000	Eligible patients had active PsA, defined as ≥3 swollen and ≥3 tender or painful joints at study enrollment and an inadequate response to NSAIDs. Patients previously achieving partial benefit from methotrexate were allowed to continue its use and a stable dose of ≤25 mg/week. Background use of prednisone ≤10mg/day was allowed. All other DMARDs and topical medicines for psoriasis were discontinued.	12 weeks	2
	Mease 2004	Eligible patients had active PsA, defined as ≥3 swollen and ≥3 tender joints at screening and a previous inadequate response to NSAID therapy. Patients had at least 1 of the clinical subtypes of PsA, as described by Moll and Wright. Patients had stable plaque psoriasis with a qualifying target lesion (≥2 cm in diameter). Concomitant methotrexate therapy, which had been stable for 2 months, could be continued at a stable dosage of ≤25 mg/week. Other DMARDs were discontinued at least 4 weeks before the study start. Corticosteroids, which had been stable for 4 weeks, could be continued at the equivalent of ≤10 mg/day of prednisone.	12 weeks	
Ustekinumab	Gottlieb 2009	Patients had active psoriatic arthritis defined as ≥3 swollen joints and ≥3 tender joints and either CRP ≥15 mg/L or morning stiffness for at least 45 min—and were diagnosed at least 6 months before receipt of study agent. Patients also had to have active plaque psoriasis, with a qualifying target lesion of 2 cm or larger, and an inadequate response to DMARDs, NSAIDs, antiTNF agents, or a combination of these. This study permitted—but did not require—stable regimens of methotrexate (up to 25 mg per week), corticosteroids (up to 10 mg per day prednisone or equivalent), NSAIDS, or a combination of these drugs. This study excluded patients who received biological treatment for psoriasis within 3 months, systemic drugs for psoriasis or phototherapy within 4 weeks, or topical agents for psoriasis within 2 weeks of randomization.	12 weeks	4

Source: Meta-analysis by Ash et al.[26]

No ACR20 data was available for conventional synthetic DMARDs; therefore, indirect comparisons could not be made.

Safety

Psoriatic Arthritis

Adverse reaction data is available from three 52 week, multicenter, randomized, double-blind, placebo-controlled trials that included a total of 1493 patients randomized equally to placebo, apremilast 20 mg twice daily, and apremilast 30 mg twice daily. Titration occurred over the first five days. The median (range) age of patients was 51 (18 to 83) years. Long-term safety data (up to 5 years) is currently being assessed in active-treatment phase of the PALACE 1 trial.

Deaths and Other Serious Adverse Reactions, Psoriatic Arthritis

Serious adverse reactions included decreased appetite, nausea and vomiting, and headache. Each of these reactions occurred in one patient being treated with apremilast 30 mg twice daily. One patient being treated with apremilast 20 mg twice daily experienced a serious adverse reaction of diarrhea.

Common Adverse Reactions, Psoriatic Arthritis

Table 5 shows the adverse reactions reported in ≥2% of patients with psoriatic arthritis on apremilast 30 mg twice daily and ≥1% than that observed in patients on placebo for up to day 112 (week 16).

Table 5 Adverse Reactions: Psoriatic Arthritis Clinical Trials

	Placebo		Apremilast 30 mg twice daily	
Adverse Reaction	**Day 1-5 (N=495) n (%)**	**Day 6-112 (N=490) n (%)**	**Day 1-5 (N=497) n (%)**	**Day 6-112 (N=493) n (%)**
Diarrhea	6 (1.2)	8 (1.6)	46 (9.3)	38 (7.7)
Nausea	7 (1.4)	15 (3.1)	37 (7.4)	44 (8.9)
Headache	9 (1.8)	11 (2.2)	24 (4.8)	29 (5.9)
Upper respiratory tract infection	3 (0.6)	9 (1.8)	3 (0.6)	19 (3.9)
Vomiting	2 (0.4)	2 (0.4)	4 (0.8)	16 (3.2)
Nasopharyngitis	1 (0.2)	8 (1.6)	1 (0.2)	13 (2.6)
Upper abdominal pain	0 (0.0)	1 (0.2)	3 (0.6)	10 (2.0)

The most common adverse reactions were diarrhea, nausea and headache. The majority of common adverse reactions resolved during continued therapy over time.

Other Adverse Reactions, Psoriatic Arthritis

- Immune system disorders: hypersensitivity
- Gastrointestinal disorders: frequent bowel movement, gastroesophageal reflux disease, dyspepsia
- Metabolism and nutrition disorders: decreased appetite, weight loss
- Respiratory, thoracic, and mediastinal disorders: cough
- Skin and subcutaneous tissue disorders: rash

Tolerability, Psoriatic Arthritis

Of 1493 patients, 4.6% of patients taking apremilast 30 mg twice daily discontinued treatment due to an adverse reaction, compared with 1.2% of patients in the placebo group. The most common adverse reactions that resulted in treatment discontinuation in the apremilast-treated patients included nausea (1.8%), diarrhea (1.8%), and headache (1.2%).

Plaque Psoriasis

Adverse event data is available from three phase 2, randomized, double-blind, placebo-controlled trials that included a total of 1426 patients randomized equally to placebo, apremilast 30 mg twice daily and placebo. Titration occurred over the first five days. The median age of patients included was 46 years, with patients ranging from 18 to 83 years.

Deaths and Other Serious Adverse Reactions, Plaque Psoriasis

Two patients experienced serious adverse reactions of abdominal pain.

Common Adverse Reactions, Plaque Psoriasis

Table 6 shows the adverse reactions reported in ≥1% of subjects on apremilast and with greater frequency than in subjects on placebo; up to day 112 (week 16) in psoriasis clinical trials.

Table 6 Adverse Reactions: Psoriasis Clinical Trials

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

Diarrhea, nausea, upper respiratory tract infection, tension headache, and headache were the most common adverse reactions reported during the psoriasis clinical trials.

Other Adverse Events, Plaque Psoriasis

- Rebound psoriasis occurred in 0.3% of patients after discontinuing apremilast therapy.

Tolerability, Plaque Psoriasis

Of 1426 patients, 6.1% of patients taking apremilast 30 mg twice daily discontinued treatment due to an adverse reaction, compared to 4.1% of patients in the placebo group. The most common adverse reactions that resulted in treatment discontinuation in the apremilast-treated patients included nausea (1.6%), diarrhea (1.0%), and headache (0.8%).

Safety of Alternative Agents Used to Treat Psoriatic Arthritis and Plaque Psoriasis

- Methotrexate
    - Common side effects of methotrexate include upset stomach, sore mouth, myelosuppression, which can cause fever, infections, swollen lymph nodes, and easy bruisability and bleeding. It can also cause liver or lung damage, even with low doses, and, therefore, requires monitoring. People using methotrexate are

strongly discouraged from drinking alcoholic beverages because of the increased risk of liver damage with this combination.[23]

- Hydroxychloroquine
  - Taking a high dose of hydroxychloroquine for prolonged periods of time may increase the risk of damage to the retina, though high doses are not usually required for treatment of rheumatoid conditions or lupus. An eye examination is recommended before starting treatment and periodically thereafter.[23]
- Leflunomide
  - Side effects include rash, temporary hair loss, liver damage, nausea, diarrhea, weight loss, and abdominal pain. Regular testing to monitor for liver damage is required.[23]
- Cyclosporine
  - Side effects include high blood pressure, swelling, kidney damage, increased hair growth, nausea, diarrhea, and heartburn. Patients should have blood pressure and kidney function monitoring on a regular basis.[23]
- Sulfasalazine
  - Side effects of sulfasalazine include changes in blood counts, nausea or vomiting, sensitivity to sunlight, skin rash, and headaches. People who are allergic to sulfa drugs may have a cross reaction to sulfasalazine and should, therefore, not take it. Periodic blood tests are recommended to monitor the blood count on a regular basis.[23]
- Azathioprine
  - The most common side effects of azathioprine include nausea, vomiting, decreased appetite, liver function abnormalities, low white blood cell counts, and infection. It is usually taken by mouth once to four times daily. Blood testing is recommended during treatment with azathioprine.[23]
- Cyclophosphamide
  - Side effects include bone marrow suppression, cardiotoxicity, impaired fertility, nausea and vomiting, hyponatremia, immunosuppression, pulmonary toxicity, urinary/renal toxicity, secondary malignancies, and impairment of wound healing.[24]
- TNF Inhibitor Biologics (Adalimumab, Etanercept, Golimumab, Infliximab)
  - Serious infections may develop, and diagnosis may be delayed by an atypical spectrum of signs and symptoms. Patients may experience reactivation of latent tuberculosis, hepatitis B or C or opportunistic infections. Biologic therapy may also modestly increase the risk of lymphoma and some solid tumors. During biologic therapy, demyelinating disorders of the CNS have been noted, and pre-existing disease manifestations may be aggravated. Hepatic transaminase levels may increase. Hyperlipidemia can occur. Patients with congestive heart failure may experience symptom exacerbation.[25]

Overall, apremilast has a favorable safety profile relative to the currently available medications used to treat psoriatic arthritis and plaque psoriasis.

Contraindications

Known hypersensitivity to apremilast or any excipients in formulation

Warnings and Precautions

Depression

Apremilast is associated with an increased risk of depression. The risks and benefits of apremilast use should be carefully considered for patients with a history of depression and/or suicidal thoughts or behaviors. Patients should report increased depression, suicidal thoughts, or other mood changes to a healthcare provider.

Weight Decrease

A weight decrease of 5-10% of body weight was reported in 10% of patients treated with apremilast in controlled clinical studies. Patients treated with apremilast should have their weight monitored regularly. Consider discontinuation of apremilast if unexplained weight loss occurs.

Drug Interactions

The use of cytochrome P450 enzyme inducers with apremilast is not recommended as their concomitant use may result in decreased systemic exposure and efficacy of apremilast.

Special Populations

Hepatic Impairment: The pharmacokinetics of apremilast are not affected by moderate or severe hepatic impairment.

Renal Impairment: Increases in AUC and Cmax have been observed in patients with severe renal impairment, therefore, dosing reduction is recommended in these patients.

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

Gender: Results of pharmacokinetic studies indicate that Cmax was about 8% higher and extent of exposure was about 31% higher in healthy females compared to healthy males

Pregnancy: Pregnancy Category C. Adequate and well-controlled studies with apremilast have not been conducted in pregnant woman.

Lactation: It is unknown whether apremilast or its metabolites are present in human milk.

Sentinel Events

No data

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Table 7 Look-alike / Sound-alike Drug Names

NME Drug Name	Lexi-Comp	First Databank	ISMP	Clinical Judgment	
Apremilast 10, 20, 30 mg tab	None	None	None	Roflumilast Aprepitant	Apresazide Apresoline
Otezla	None	None	None	Otrexup Orencia	

Drug Interactions

Drug-Drug Interactions

Co-administration of strong cytochrome P450 enzyme inducers (rifampin, phenobarbital, carbamazepine, phenytoin) may result in reduced efficacy of apremilast.

Drug-Lab Interactions

None have been identified.

Pharmacoeconomic Analysis

There are no published pharmacoeconomic evaluations of this drug.

Conclusions

There is moderate quality evidence consistently showing apremilast to be a safe and effective medication in the treatment of adults with moderate to severe psoriatic arthritis or plaque psoriasis. For psoriatic arthritis, the clinical trials showed improvement in clinical symptoms such as tender or swollen joints, however they did not evaluate improvements in or slowed progression of radiographic damage to affected joints. Therefore, apremilast cannot be considered a DMARD. For plaque psoriasis, the clinical trials showed a consistent improvement in patient reported outcomes. Clinical trials for both psoriatic arthritis and plaque psoriasis included patients that failed previous treatment and patients that continued other treatments, therefore apremilast should not be considered as a first line agent. While there are no studies currently available to assess the long-term safety of apremilast, it appears to have a more favorable safety profile when compared to conventional synthetic DMARDs and biologics. To date there have been no head-to-head trials comparing apremilast with DMARDs or biologics, though indirect comparisons of placebo-controlled trial results suggest that apremilast may be more effective in treating psoriatic arthritis than methotrexate, and less effective than TNF inhibitors. Apremilast costs more than both the oral DMARDS and the biologic agents, therefore, it may be considered as an add-on or alternative therapy for patients with active psoriatic arthritis who have failed to show clinical improvement or have not tolerated conventional synthetic DMARDs and biologic agents. To date, there is insufficient evidence to determine apremilast's place in therapy for psoriasis since there were only phases 2 and 2b trials. In summary, the main advantages of apremilast are convenient administration and lack of monitoring. Apremilast appears to be safe in short-term studies. These advantages need to be weighed against cost, lack of long-term safety data, and lack of radiographic evaluation. Direct comparisons with active therapies, long-term studies beyond 1 year and radiographic outcome measures are needed to determine its role in therapy.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2004) using the search terms apremilast and Otezla. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Abbreviations

Abbreviations used in appendix tables:

ACR: American College of Rheumatology
ACR20: American College of Rheumatology 20 Response
AEs: adverse events
APR: apremilast
BID: twice daily dosing
BL: baseline
BSA: body surface area
CASPAR: Classification Criteria for Psoriatic Arthritis
CRP: C-reactive protein
Cs: Corticosteroids
csDMARDs: conventional synthetic disease-modifying antirheumatic drugs
DB: double blind
DLQI: Dermatology Life Quality Index
DR: dose-ranging
FACIT-F: Functional Assessment of Chronic Illness Therapy for Fatigue
Global VAS: global disease activity by visual analog scale
HAQ-DI: Health Assessment Questionnaire-Disability Index
MCID: minimum clinically important difference
MTX: methotrexate
NSAIDs: non-steroidal anti-inflammatory drugs
NSDs: no significant differences
OR: Odds Ratio
PASI: Psoriasis area and severity index
PASI-75: Psoriatic Area and Severity Index, 50% reduction
Pruritus VAS: pruritus visual analog scale
Pain VAS: patient-reported pain by visual analog scale
PASI-50: Psoriatic Area and Severity Index, 50% reduction
PASI-75: Psoriatic Area and Severity Index, 50% reduction
PBO: placebo
PC: placebo controlled
POM: primary outcome
PsA: psoriatic arthritis
PsARC: Psoriatic Arthritis Response Criteria
QD: once daily dosing
RCT: randomized controlled trial
SAEs: serious adverse event
SF-36 MCS: Short-Form 36 Health Survey Mental Component Summary Scores
SF-36 PCS: Short-Form 36 Health Survey Physical Component Summary Scores
SF-36: Short-Form 36 Health Survey
SOM: Secondary outcome measures
TNFI: tumor necrosis factor inhibitor
WDAEs: any adverse event leading to withdrawal

Table 8 Summary of Apremilast Studies in Psoriatic Arthritis

Reference	Design, Study Population	Findings
Schett G et al.[15]	24-wk, Phase II, PC, DB, RCT comparing APR 20 mg BID (N=69) vs. APR 40 mg QD (N=67) vs. PBO (N=68). Patients were randomized to a 12-week phase of placebo, apremilast 20 mg BID, or apremilast 40mg once a day. Patients receiving placebo were re-randomized at the end of 12 weeks to receive apremilast and those originally started on APR continued same therapy for another 12 weeks. Following treatment, there was a 4-week observational phase after treatment cessation. 204 adults with symptomatic PsA (according to the Moll and Wright criteria) for ≥6 months before screening, and discontinued immunosuppressants other than MTX for an adequate washout period. Patients were also required to have active PsA, defined as ≥3 swollen joints and ≥3 tender joints, at the time of screening and baseline, and to have tested negative for serum rheumatoid factor. 52% male, 97% white, 44% taking MTX at baseline, mean duration of PsA 7.8 years, mostly polyarticular disease. Limitations: No radiographic measures were evaluated. Moll and Wright criteria discriminate poorly between PsA and RA.	Apremilast was superior to PBO in terms of: POM: Proportion of patients achieving ACR20 criteria at the end of 12 weeks of treatment: APR 20mg BID: 43.5%, (p<0.001), APR 40mg QD: 35.8%, p=0.002, PBO: 11.8%. Median time to respond among responders: 4 wk. Patients that received PBO for the first 12 weeks were then re-randomized to APR treatment for the next 12 weeks (treatment-extension phase) and the proportion of patients achieving ACR20: PBO/APR 20mg BID: 40.0%, PBO/APR 40mg QD: 45.0% SOM at 12 weeks for APR 20mg BID, APR 40mg QD, and PBO: ACR50: 17.4%(p=0.012), 13.4% (p=0.056), 2.9% ARC70: No significant differences seen between APR and PBO PsARC: 52.5% (<0.001), 50.7% (P=0.001), 22.1% Overall, APR was not associated with a reduction in CRP levels. Post hoc analyses suggested a potential differential treatment effect in patients with CRP >8 mg/l. No significant difference in ACR20 for patients receiving (n = 60 on APR) vs. not receiving concomitant MTX Results for those randomized to APR at week 12 showed results consistent with those originally randomized to APR. Safety of APR 20mg BID vs APR 40mg QD, vs PBO at 12 weeks: Diarrhea 20.3%, 26.9%, 8.8%, Headache 18.8%, 22.4%, 16.2% Nausea 17.4%, 22.4%, 17.6% Fatigue 7.2%, 16.4%, 8.8% Nasopharyngitis 11.6%, 11.9%, 17.6% Overall, well tolerated, no life-threatening or disabling adverse events, and no deaths.
Strand V, Schett et al.[14]	See Schett, et al. (2012). Reports health-related quality of life measures.	Apremilast was superior to PBO in terms of: Mean change in Global VAS: APR20 BID : -10.3 (p<0.05), APR40 QD: -10.4 (p<0.05), PBO: 1.0 (MCID=10.0) Mean change in Pain VAS: -11.2 (p<0.05) vs. -11.5 (p<0.05) vs. -1.3 (MCID=10.0) Mean change in FACIT-F: 4.1 (p<0.05) vs. 4.3 (p<0.05) vs. 0.5 (MCID=4.0) Mean change in SF-36 MCS: 3.4 (p<0.05) vs. 1.1 vs. -0.8 (MCID=2.5) Mean change in SF-36 PCS: 2.4 (p<0.05) vs. 2.1 vs. 0.8 (MCID=2.5) Safety was not assessed, but 80.9% of the total patients completed 12 weeks of treatment.

Reference	Design, Study Population	Findings
Kavanaugh A et al. (2014)[13] PALACE 1	24-wk Phase 3 PC DB RCT comparing APR 20 mg BID(N=168) vs. APR 30 mg BID (N=168) vs. PBO (N=168) 504 adults with active PsA (CASPAR dx), prior TNFI failures limited to10% of pts; stable on conventional synthetic DMARDs (csDMARDs), corticosteroids (CSs), and/or NSAIDs Selected exclusion criteria: failure of more than three agents for psoriatic arthritis (DMARDs or biologics) or more than one TNF blocker, ACR Classification of Functional Status in Rheumatoid Arthritis functional class IV 49% male, 90% white, 65% taking DMARDs at baseline NSDs in baseline characteristics except: APR20 group had higher baseline CS usage rates compared to APR30 and PBO (14.9% vs. 9.5% vs. 7.1%)	Apremilast was superior to PBO in terms of: POM: Achieved ACR20 at wk 16: 31.3% (p=0.0140) vs. 39.8% (p=0.0001) vs. 19.4%. SOM: Mean change from baseline in HAQ-DI at wk 16: -0.20 (p=0.0252) vs. -.025 (p=0.0015) vs. -0.9 (MCID= -0.22) Mean change in swollen joint count: -4.1 (p=0.0023) vs. -5.1 (p<0.0001) vs. 1.4 Mean change in tender joint count: -5.0 (p=0.0035) vs. -7.8 (p<0.0001) vs. -0.91 Safety: Deaths: 1 (0.2%) on APR20 (multiorgan failure due to pre-existing vit B12 deficiency). Investigator considered death unrelated to APR. SAEs: 4.8% vs. 5.4% vs. 4.2% Severe AEs: 4.8% vs. 6.5% vs. 3.6% WDAEs: 6.0% vs. 7.1% vs. 4.8% AEs: 60.1% vs. 61.3% vs. 48.2% AEs in ³10% of any tx group: Diarrhea: 11.3% vs. 19.0% vs. 2.4% Nausea: 9.5% vs. 18.5% vs. 6.5% Headache: 10.1% vs.10.7% vs. 4.8%
Cutolo M. et al.[16] PALACE 2 [abstract]	52-wk PC DB RCT comparing APR 20 mg BID (N=163) vs. APR 30 mg BID (N=162) vs. PBO (N=159) Patients were randomized to PBO, APR 20mg BID, or APR 30mg BID stratified by baseline DMARD use. At week 16, patients on PBO with <20% reduction from baseline in swollen and tender joint counts qualified for protocol-defined early escape and thus re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At week 24, all remaining PBO patients were re-randomized to APR20 or APR30 through week 52. Patients taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or a combination). 484 adults with diagnosis of PsA by any criteria for ≥6 months, meet CASPAR criteria at time of screening, have failed treatment with DMARDs, and active psoriatic arthritis defined as ≥3 swollen joints and ≥3 tender joints. Stable doses of NSAIDS, narcotics, and low dose oral corticosteroids allowed. Selected exclusion criteria: failure of more than three agents for psoriatic arthritis (DMARDs or biologics) or more than one TNF blocker, ACR Classification of Functional Status in Rheumatoid Arthritis functional class IV 43% male, age 50.9 ± 11.32, mean duration of PsA in years 7.47 ± 8.163. No baseline patient characteristics reported.	Apremilast was superior to PBO in terms of: POM: Proportion of patients achieving ACR20 criteria at the end of 16 weeks of treatment: APR 20mg BID: 38.4%, (p=0.0002), APR 30mg BID: 34.4%, (p=0.0024), PBO: 19.5%. Patients receiving a full 52 weeks of APR 20mg BID and APR 30mg BID achieved ACR20 rates of 52.9% and 52.6% respectively. SOM: Patients that received a full 52 weeks of APR 20mg BID or APR 30mg BID also showed: ACR20: 52.9%, 52.6% HAQ-DI mean change from BL of -0.192 (0.573) and -0.330 (0.509) respectively, no MCID reported Patients with BL BSA ≥3%, PASI-50 was achieved by 49.2% and 58.9% respectively, PASI-75 achieved by 27.1% and 39.3% SF-36 Physical Functioning domain score mean change from BL of 5.05 (7.96) and 6.35 (8.67) Note: No radiographic measures were evaluated Results for those randomized to APR at weeks 16 or 24 showed results consistent with those originally randomized to APR. Safety of APR 20mg BID vs APR 30mg BID, vs PBO at 24 weeks: Any severe adverse event: 4.7%, 5.1%, 1.89% Diarrhea: 14.81%, 11.11%, 5.03% Nausea: 16.05%, 8.55%, 1.89% Headache: 11.11%, 5.56%, 4.40% Upper respiratory tract infection: 6.79%, 11.11%, 3.77% Nasopharyngitis: 4.94%, 6.84%, 3.77% Hypertension: 3.09%, 4.27%, 4.40% APR had an acceptable safety profile and was generally well-tolerated up to 52 weeks.

Reference	Design, Study Population	Findings
Edwards CJ et al.[17] PALACE 3 [abstract]	52-wk PC DB RCT comparing APR 20 mg BID (N=169) vs. APR 30 mg BID (N=167) vs. PBO (N=169) Patients were randomized to PBO, APR 20mg BID, or APR 30mg BID stratified by baseline DMARD use and BSA ≥3%. At week 16, patients on PBO with <20% reduction from baseline in swollen and tender joint counts qualified for protocol-defined early escape and thus re-randomized to APR20 or APR30 and those on APR remained on the initial APR dose. At week 24, all remaining PBO patients were re-randomized to APR20 or APR30 through week 52. Patients taking concurrent DMARDs were allowed to continue stable doses (MTX, sulfasalazine, leflunomide, or a combination). 505 adults with diagnosis of PsA by any criteria for ≥6 months, meet CASPAR criteria at time of screening, have failed treatment with DMARDs, and active psoriatic arthritis defined as ≥3 swollen joints and ≥3 tender joints. Stable doses of NSAIDS, narcotics, and low dose oral corticosteroids allowed. Selected exclusion criteria: failure of more than three agents for psoriatic arthritis (DMARDs or biologics) or more than one TNF blocker, ACR Classification of Functional Status in Rheumatoid Arthritis functional class IV 47% male, age 49.7 ± 11.69, mean duration of PsA in years 7.33 ± 7.284. No further baseline patient characteristics reported.	Apremilast was superior to PBO in terms of: POM: Proportion of patients achieving ACR20 criteria at the end of 16 weeks of treatment: APR 20mg BID: 29.4%, (p=0.0235), APR 30mg BID: 42.8%, (p<0.0001), PBO: 18.9%. Patients receiving a full 52 weeks of APR 20mg BID and APR 30mg BID achieved ACR20 rates of 56.0% and 63.0% respectively. SOM: Patients that received a full 52 weeks of APR 20mg BID or APR 30mg BID also showed: HAQ-DI mean change from BL of -0.332 (0.505) and -0.350 (505) MCID of 0.13 and 0.30 respectively Patients with BL BSA ≥3%, PASI-75 was achieved by 28.6% and 39.1% respectively, PASI-75 achieved by 49.2% and 54.7% Results for those randomized to APR at weeks 16 or 24 showed results consistent with those originally randomized to APR. Note: No radiographic measures were evaluated Safety of APR 20mg BID vs APR 30mg BID, vs PBO at 24 weeks: Any severe adverse event: 5.4% (APR20), 4.1% (APR30) Diarrhea: 15.29%, 15.57%, 1.79% Nausea: 11.18%, 13.77%, 5.36% Vomiting: 2.94%, 4.79%, 0.60% Headache: 9.41%, 11.98%, 4.76% Upper respiratory tract infection: 6.47 %, 7.19%, 1.79% Nasopharyngitis: 4.12 %, 2.40%, 1.19% APR had an acceptable safety profile and was generally well-tolerated up to 52 weeks.

Table 9 Summary of Apremilast Studies in Plaque Psoriasis

Reference	Design, Study Population	Findings
Papp, Cather, et al.[18]	24-wk, Phase 2b, PC, DR, RCT comparing APR 10 mg BID (N=89) vs. APR 20 mg BID (N=87) vs. APR 30 mg BID (N=88) vs. PBO (N=88). Patients were randomized to a 16-week phase of placebo, APR 10 mg BID, APR 20 mg BID, or APR 30 mg BID. Patients receiving placebo were re-randomized at the end of 16 weeks to receive APR10, APR20, or APR40 and those originally started on APR continued same therapy for another 8 weeks. 352 adults with moderate to severe plaque psoriasis (PASI ≥12; BSA ≥10%) for 6 months or longer. Patients had to discontinue immunosuppressants, TNFI, and phototherapy for an adequate washout period 63% male, 93% white, mean duration of plaque psoriasis for 19 years, mean baseline PASI score was 18.5 and mean baseline BSA was 22%	Apremilast was superior to PBO in terms of: POM: Proportion of patients achieving PASI-75 at week 16: APR20 BID 29% (OR 6.69; 95% CI 2.43-18.5; p,0.0001), APR30 BID 41% (OR 11.5; 4.24-31.16; p<0.0001) compared with PBO 6% Safety of APR 10 mg BID vs APR 20mg BID vs APR 30mg BID, vs PBO at 16 weeks: Diarrhea: 7% vs 7% vs 14% vs 5% Nausea: 11% vs 15% vs 18% vs 8% Vomiting: 0 vs 3% vs 5% vs 1% Headache: 6% vs 9% vs 10% vs 6% Upper respiratory tract infection: 10% vs 14% vs 16% vs 6% Nasopharyngitis: 10% vs 8% vs 6% vs 8% SAEs: 0% vs 3% vs 2% vs 2% WDAEs: 2% vs 9% vs 11% vs 6% APR had an acceptable safety profile and was generally well-tolerated
Strand V, Fiorentino et al.[19]	Health-related quality of life and other Patient-reported Outcomes for the study by Papp, Cather, et al (2012)	Apremilast was superior to PBO in terms of: Mean percent change in DLQI: APR20: -5.9 (p<0.001), APR30: -4.4 (p=0.005) PBO: -1.9 (MCID=5.0) Mean percent change in pruritus VAS: -35.5 (p=0.005) vs -43.7 (p<0.05) vs. -6.1 (MCID=10.0) Mean change in SF-36 MCS: APR 10: 2.8 (p=0.008) vs. APR 20: 3.3 (p=0.007) vs. APR30: 3.0 (p=0.005) vs. PBO -0.5 (MCID=2.5)

Reference	Design, Study Population	Findings
Papp, Kaufmann, et al. (2013)	12-wk, Phase 2, MC, PC, DB, parallel-group, dose-comparison, RCT comparing APR 20 mg QD (N=87) vs. APR 20 mg BID (N=85) vs. PBO (N=87). 259 adults with moderate to severe plaque psoriasis (PASI ≥12; BSA ≥10%) for 6 months or longer. Patients had to discontinue immunosuppressants, TNFI, and phototherapy for an adequate washout period 63% male, 97% white, mean duration of moderate to severe psoriasis for 19.1 years, mean baseline PASI score was 19.5 and mean baseline BSA was 29.6%	Apremilast was superior to PBO in terms of: POM: Proportion of patients achieving PASI-75 at week 12: APR20 BID: 24.4% (p=0.023) vs. PBO : 10.3% SOM:APR 20 mg QD vs APR 20 mg BID vs PBO at 12 weeks Mean percent reduction in PASI: 30.3% (P0.021) vs. 52.1% (P<0.001) vs. 17.4% Mean reduction in BSA involvement: 15.2% (P=0.104) vs. 30.8% (P<0.001) vs. 3.2% Mean reduction in sPGA: 0.8 (P=0.755) vs. 1.3 (P<0.001) vs. 0.7 Safety of APR 20 mg QD vs APR 20 mg BID vs PBO at 12 weeks: Diarrhea: 10.3% vs 5.9% vs 2.3% Nausea: 3.4% vs 5.9% vs 0% Vomiting: 2.3% vs 2.4% vs 0% Headache: 18.4% vs 12.9% vs 10.3% Upper respiratory tract infection: Nasopharyngitis: 13.8% vs 14.1% vs 13.8% Upper abdominal pain: 2.3% vs 1.2% vs 1.1% SAEs: 1.1% vs 1.1% vs 4.6% WDAEs: 8%% vs 3.5% vs 8% APR had an acceptable safety profile and was generally well-tolerated