Otezla (Apremilast), an Oral PDE-4 Inhibitor, Receives FDA Approval for the Treatment of Patients with Active Psoriatic Arthritis and Plaque Psoriasis

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Psoriatic arthritis and psoriasis, often referred to as psoriatic diseases, are autoimmune diseases characterized by chronic inflammation, tissue and organ involvement, and the accelerated growth cycle of skin cells. Both psoriatic arthritis and psoriasis impose a substantial physical, emotional, and economic burden on the millions of individuals in the United States who are affected by these conditions.

Psoriatic Arthritis

Psoriatic arthritis, a progressive, potentially debilitating type of arthritic inflammation, affects approximately 7 million people in the United States.[1,2] The symptoms of psoriatic arthritis, like the symptoms of psoriasis, may flare and subside, varying from person to person.[3] In some cases, the arthritis precedes skin disorders. Psoriatic arthritis can affect any joint in the body; it may affect 1 or more joints (eg, 1 or both knees), and it may affect fingers and toes.[3] Some patients also develop dactylitis, a condition in which the fingers and toes swell profusely or enthesitis, which is characterized by inflammation of sites at which tendons and ligaments attach to the bone.[3] Many patients with psoriatic arthritis are affected by the joint disease and the psoriasis that often accompanies it.[4]

The chronic pain, fatigue, limitations in physical function, and work disability associated with psoriatic arthritis can have a profound effect on the patient's health-related quality of life.[5] Furthermore, the risk for cardiovascular disease and other comorbidities is greater in patients with psoriatic arthritis and other inflammatory diseases than in individuals without these diseases.[2,4] Psoriatic arthritis can also have a substantial impact on a patient's psychological well-being, because of the itching, pain, and potential for social rejection encountered by many patients.[2,4]

Psoriatic arthritis imposes a considerable economic burden on patients and society. Based on a 2010 review of the literature, in the United States, direct annual medical costs associated with psoriatic arthritis total nearly $1.9 billion.[4] In this review of 49 studies, patients with psoriatic arthritis had a lower health-related quality of life compared with the general population.[4] Moreover, the direct and indirect costs associated with psoriatic arthritis, including lost productivity and disability, increase with worsening disease activity (ie, joint involvement and psoriatic skin lesions) and worsening physical function.[4]

Evidence shows that persistent inflammation associated with psoriatic arthritis causes joint damage over time. Consequently, early diagnosis of psoriatic arthritis is essential, because early detection and treatment may prevent further damage to the joints.[3]

The therapeutic goals for patients with psoriatic arthritis are to alleviate symptoms, control inflammation in affected joints, and prevent joint pain and disability.[6] Treatment depends on the severity of the disease, the number of joints involved, and the associated skin symptoms.[1]

During the early stages of psoriatic arthritis, nonsteroidal anti-inflammatory drugs (NSAIDs) and cortisone may be used to manage mild inflammation. For patients with erosive disease or for those in whom NSAIDs fail to work, the disease-modifying antirheumatic drugs (DMARDs), including methotrexate, sulfasalazine, leflunomide, and a number of biologic agents may be used to slow the progression of psoriatic arthritis and spare the joints and other tissues from permanent damage.[1,6]

Until recently, the US Food and Drug Administration (FDA)-approved treatments for psoriatic arthritis included corticosteroids, several tumor necrosis factor blockers (adalimumab, certolizumab, etanercept, golimumab, infliximab), and an interleukin-12/interleukin-23 inhibitor (ustekinumab).[7]

Plaque Psoriasis

Psoriasis is a chronic, relapsing disease that is characterized by thick patches of inflamed, scaly skin resulting from excessive proliferation of skin cells.[8] Affecting an estimated 7.5 million Americans, psoriasis is the most prevalent autoimmune disease in the United States. In many cases, psoriasis can be disfiguring and disabling.[8] Psoriasis is categorized as moderate when it involves 3% to 10% of the body and severe when it involves more than 10% of the body.[9]

Plaque psoriasis is the most common form of psoriasis and is characterized by raised, red patches covered with a silvery white buildup of dead skin cells or scale. These plaques typically appear on the scalp, knees, elbows, and lower back. They are often painful, and they can crack and bleed.[10]

Patients with psoriasis have a higher risk for developing psoriatic arthritis, eye disorders, obesity, type 2 diabetes, and hypertension compared with individuals without psoriasis.[11] An estimated 15% to 30% of patients with psoriasis will develop psoriatic arthritis.[1,3] In addition, patients with psoriasis have a higher risk for cardiovascular disease, Parkinson's disease, kidney disease, and other autoimmune diseases compared with individuals without psoriasis.[11]

Psoriasis can have a dramatic impact on patients' quality of life and self-esteem, and can lead to depression, social isolation, and work-related problems.[11] Furthermore, psoriasis imposes a considerable financial burden on patients and on the US healthcare system as a whole. In 2008, the total annual US costs attributed to psoriasis reached $11.25 billion.[8]

The therapeutic goals for psoriasis include (1) slowing the speed of skin growth to reduce inflammation and plaque formation, and (2) smoothing the skin.[11] Topical treatments for psoriasis include topical corticosteroids, vitamin D analogues, anthralin, topical retinoids, calcineurin inhibitors, salicylic acid, and coal tar. Phototherapy with artificial ultraviolet A or ultraviolet B light is sometimes used alone or in combination with other medications. Oral or injectable therapies include methotrexate, retinoids, cyclosporine, and the biologic immunomodulator agents, including several tumor necrosis factor-alpha inhibitors (eg, adalimumab, etanercept, infliximab) and the interleukin-12/interleukin-23 inhibitor (ie, ustekinumab).[11,12]

Oral Therapy for Psoriatic Arthritis and Plaque Psoriasis

On March 21, 2014, the FDA approved apremilast (Otezla; Celgene) for the treatment of adults with active psoriatic arthritis.[7] Apremilast, an oral inhibitor of phosphodiesterase (PDE)-4, is the first oral therapy to receive FDA approval for the treatment of adults with active psoriatic arthritis.[7,13]

According to Curtis Rosebraugh, MD, MPH, Director of the Office of Drug Evaluation II at the FDA Center for Drug Evaluation and Research, "Relief of pain and inflammation and improving physical function are important treatment goals for patients with active psoriatic arthritis. Otezla provides a new treatment option for patients suffering from this disease."[7]

On September 23, 2014, apremilast received a new indication by the FDA for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Apremilast is the first and the only PDE-4 agent approved for the treatment of patients with plaque psoriasis.[14]

M. Shane Chapman, MD, Section Chief of Dermatology at Dartmouth-Hitchcock Medical Center, stated, "OTEZLA offers an important new treatment option for patients whose symptoms are not adequately improving with their current treatments. In clinical trials, OTEZLA reduced redness, thickness, and scaliness of plaques in patients with moderate or severe plaque psoriasis." Dr Chapman further commented, "Because the product labeling does not require routine laboratory monitoring, oral OTEZLA may be a welcome new option for patients and physicians looking for a different treatment experience."[14]

Mechanism of Action

Apremilast is a small-molecule inhibitor of PDE-4 specific for cyclic adenosine monophosphate (cAMP). Inhibition of PDE-4 results in increased intracellular cAMP levels. The specific mechanism by which apremilast exerts its therapeutic effect in patients with psoriatic arthritis and psoriasis is not well-defined.[13]

Dosing and Administration

To reduce the risk of gastrointestinal symptoms, it is recommended that apremilast be titrated to the recommended dose of 30 mg twice daily, to be taken orally starting on day 6. The recommended initial dosage titration of apremilast from day 1 to day 5 (for both psoriatic arthritis and psoriasis) is shown in **Table 1**.[13] Coadministration of apremilast with food does not alter the extent of absorption of this drug.[13]

The recommended dose for patients with severe renal impairment is 30 mg once daily. For initial dose titration in these patients, titration should follow the morning schedule in Table 1; the afternoon doses should be skipped.[13]

Table 1 Apremilast Dosage Titration Schedule for Patients with Psoriatic Arthritis and Psoriasis

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 and beyond	
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

Source: Otezla (apremilast) tablets prescribing information; September 2014.

Table 2 Apremilast versus Placebo: Patients with Psoriatic Arthritis and ACR Response at Week 16 in 3 Clinical Trials

Patients achieving ACR response at week 16	PALACE-1 study		PALACE-2 study		PALACE-3 study	
	Placebo ± DMARDs (N = 168)	Apremilast[a] ± DMARDs (N = 168)	Placebo ± DMARDs (N = 159)	Apremilast[a] ± DMARDs (N = 162)	Placebo ± DMARDs (N = 169)	Apremilast[a] ± DMARDs (N = 167)
ACR20, %	19	38[b]	19	32[b]	18	41[b]
ACR50, %	6	16	5	11	8	15
ACR70, %	1	4	1	1	2	4

[a]Apremilast 30 mg twice daily.
[b]Significantly different from placebo (P <.05).
ACR indicates American College of Rheumatology; DMARD, disease-modifying antirheumatic drug.
Sources: Otezla (apremilast) tablets prescribing information; September 2014; Kavanaugh A, et al. *Ann Rheum Dis*. 2014;73:1020-1026; Husni ME. June 14, 2014.

Apremilast is available in 10-mg, 20-mg, and 30-mg tablets.[13]

Clinical Trials

Psoriatic Arthritis

The safety and efficacy of apremilast for the treatment of patients with psoriatic arthritis were demonstrated in 3 multicenter, randomized, double-blind, placebo-controlled clinical trials of similar design.[13] In these studies (ie, PALACE-1, PALACE-2, and PALACE-3), a total of 1493 adult patients with active psoriatic arthritis (≥3 swollen joints and ≥3 tender joints) despite previous or current treatment with DMARD therapy were randomized to receive placebo, apremilast 20 mg twice daily, or apremilast 30 mg twice daily.[13,15,16]

Enrolled patients had a diagnosis of psoriatic arthritis for at least 6 months. The primary end point was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at week 16.[13] An ACR20 is defined as a 20% improvement in tender and swollen joint counts and a 20% improvement in 3 of the 5 remaining ACR core set measures (ie, patient and physician global assessments, pain, disability, others).[17] An ACR50 represents a 50% improvement in both measures; an ACR70, a 70% improvement in both measures.[17]

In these studies, placebo-controlled efficacy data were also collected and analyzed through week 24.[13] If patients' tender and swollen joint counts had not improved by at least 20%, they were considered nonresponders at week 16. Placebo nonresponders were rerandomized 1:1 in a blinded fashion to either apremilast 20 mg twice daily or 30 mg twice daily, after titration. Patients receiving apremilast continued their initial treatment. At week 24, all remaining patients receiving placebo were rerandomized to either 20 mg twice daily or to 30 mg twice daily.[13]

Patients enrolled across the 3 clinical studies had a median duration of psoriatic arthritis disease of 5 years, with a variety of psoriatic arthritis subtypes, including symmetric polyarthritis (62%), asymmetric oligoarthritis (27%), distal interphalangeal joint arthritis (6%), arthritis mutilans (3%), and predominant spondylitis (2.1%).[13]

Patients received concomitant therapy with at least 1 DMARD (65%), methotrexate (55%), sulfasalazine (9%), leflunomide (7%), low-dose oral corticosteroids (14%), and NSAIDs (71%). Previous treatment with small-molecule DMARDs was reported in only 76% of patients, and previous treatment with biologic DMARDs was reported in 22% of patients, including 9% who failed previous biologic DMARD treatment.[13]

The proportion of patients who achieved a clinical response (ie, ACR20, ACR50, or ACR70 responses) in the PALACE 1, PALACE 2, and PALACE 3 studies are shown in **Table 2**.[13] Patients receiving apremilast with or without DMARDs showed a greater improvement in signs and symptoms of psoriatic arthritis compared with placebo with or without DMARDs as demonstrated by the proportion of patients who achieved an ACR20 response at week 16.[13]

Apremilast 30 mg twice daily also demonstrated improvement for each ACR component versus placebo at week 16 in the PALACE-1 study, as shown in **Table 3**.[15] These results from the PALACE-1 trial were consistent with those observed in the PALACE-2 and PALACE-3 trials.[13]

In the PALACE-1 study, apremilast 30 mg twice daily also showed a greater improvement in mean change from baseline for the health assessment questionnaire disability index (HAQ-DI) score at week 16 compared with the placebo group. The proportions of HAQ-DI responders (≥0.3 improvement from baseline) at week 16 were 38% for the apremilast (30 mg twice daily) group compared with 27% for the placebo group. Consistent results were observed in studies PALACE-2 and PALACE-3.[13,15]

Treatment with apremilast demonstrated improvement in dactylitis and enthesitis in patients with preexisting dactylitis or enthesitis.[13]

Table 3 Patients with Psoriatic Arthritis: Mean Change in ACR Components with Apremilast, at Week 16 of the PALACE-1 Study

ACR component	Placebo (N = 168)	Apremilast 30 mg twice daily (N = 168)
Number of tender joints[a]		
Sample size, N	166	164
Baseline[a]	23	23
Mean change at week 16[b]	–2	–7
Number of swollen joints[c]		
Sample size, N	166	164
Baseline[c]	13	13
Mean change at week 16[b]	–2	–5
Patient's assessment of pain (VAS)[d]		
Sample size, N	165	159
Baseline[d]	61	58
Mean change at week 16[b]	–6	–14
Patient's global assessment of disease activity (VAS)[d]		
Sample size, N	165	159
Baseline[d]	59	56
Mean change at week 16[b]	–3	–10
Physician's global assessment of disease activity[d]		
Sample size, N	158	159
Baseline[d]	55	56
Mean change at week 16[b]	–8	–19
HAQ-DI score[e]		
Sample size, N	165	159
Baseline[e]	1.2	1.2
Mean change at week 16[b]	–0.09	–0.2
C-reactive protein[f]		
Sample size, N	166	167
Baseline[f]	1.1	0.8
Mean change at week 16[a]	0.1	–0.1

[a]Scale, 0-78.
[b]Mean changes from baseline are least square means from analyses of covariance.
[c]Scale, 0-76.
[d]0 = best; 100 = worst.
[e]0 = best; 3 = worst; the HAQ-DI measures the subject's ability to perform daily activities.
[f]Reference range, 0-0.5 mg/dL.
ACR indicates American College of Rheumatology; HAQ-DI, health assessment questionnaire disability index; VAS, visual analog scale.
Sources: Otezla (apremilast) tablets prescribing information; September 2014; Kavanaugh A, et al. *Ann Rheum Dis*. 2014;73:1020-1026.

Psoriasis

The safety and efficacy of apremilast for the treatment of patients with plaque psoriasis were evaluated in 2 multicenter, randomized, double-blind, placebo-controlled clinical trials—ESTEEM-1 and ESTEEM-2.[18,19] These studies included a total of 1257 patients aged ≥18 years with moderate to severe plaque psoriasis, as determined by body surface area involvement of ≥10%; static Physicians' Global Assessment (sPGA) score of ≥3 (moderate or severe disease); Psoriasis Area and Severity Index (PASI) score ≥12; and candidates for phototherapy or systemic therapy. Patients were allowed to use low-potency topical corticosteroids on the face, axilla, and groin; patients with scalp psoriasis were allowed to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions.[13]

In both studies, patients were randomized in a 2:1 ratio to apremilast 30 mg twice daily or to placebo for 16 weeks. Both studies assessed the proportion of patients who achieved PASI-75 at week 16 and those who achieved an sPGA score of clear (0) or almost clear (1) at week 16.[13]

Across both studies, the patients' median was 46 years (range, 18-83 years).[13] The mean baseline body surface area involvement was 25.19% (median, 21.0%), the mean baseline PASI score was 19.07 (median, 16.80), and the proportions of patients with sPGA score of 3 (moderate) and 4 (severe) at baseline were 70.0% and 29.8%, respectively. A total of 18% of patients had a history of psoriatic arthritis. Approximately 30% of all patients had received previous phototherapy, and 54% of patients had received previous conventional systemic and/or biologic therapy for the treatment of psoriasis (ie, 37% received previous conventional systemic therapy, and 30% received previous biologic therapy). Approximately 33% of patients had not received previous phototherapy, conventional systemic or biologic therapy.[13]

The proportion of patients who achieved PASI-75 responses and sPGA score of clear or almost clear are presented in **Table 4**.[13]

ESTEEM-1 clinical trial. A total of 844 patients were enrolled in the ESTEEM-1 clinical trial.[18] At 16 weeks, significantly more patients who received apremilast achieved a PASI-75 compared with placebo (33.1% vs 5.3%, respectively; P <.001).[18] Furthermore, significantly more patients who received apremilast (21.7%) achieved an sPGA score of clear or almost clear compared with placebo (3.9%).[13]

ESTEEM-2 clinical trial. A total of 411 patients were enrolled in the ESTEEM-2 clinical trial.[19] At week 16, significantly more patients who received apremilast achieved a PASI-75 compared with placebo (28.8% vs

Table 4 Apremilast versus Placebo: Clinical Response in Patients with Plaque Psoriasis at Week 16 in the ESTEEM-1 and ESTEEM-2 Clinical Trials

	ESTEEM-1		ESTEEM-2	
Clinical response	Placebo, N (%) (N = 282)	Apremilast 30 mg twice daily, N (%) (N = 562)	Placebo, N (%) (N = 137)	Apremilast 30 mg twice daily, N (%) (N = 274)
PASI -75	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
sPGA of clear or almost clear	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)

PASI indicates Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment.
Sources: Otezla (apremilast) tablets prescribing information; September 2014; Papp K, et al. *J Am Acad Dermatol.* 2014;70 (5 suppl 1). Abstract P8359; Paul C, et al. *J Am Acad Dermatol.* 2014;70(5 suppl 1). Abstract P8412.

5.8%, respectively; P <.001).[19] In addition, significantly more patients who received apremilast achieved an sPGA of clear or almost clear compared with placebo (20.4% vs 4.4%, respectively; P <.001).[19]

The median time to loss of PASI-75 response among the patients who were rerandomized to placebo at week 32 during the randomized treatment withdrawal phase was 5.1 weeks.[13]

Safety

In the psoriatic arthritis clinical trials, the most common adverse reactions associated with apremilast and occurring in ≥5% of patients were nausea (8.9%), diarrhea (7.7%), and headache (5.9%). In addition, upper respiratory tract infections were reported in 3.9% of patients and vomiting in 3.2%.[13]

The most common reasons leading to treatment discontinuation with apremilast among patients with psoriatic arthritis were diarrhea (1.8%), nausea (1.8%), and headache (1.2%).[13] In clinical trials, the proportion of patients with psoriatic arthritis who discontinued treatment because of any adverse reaction was 4.6% for patients taking apremilast 30 mg twice daily and 1.2% for patients who received a placebo.[13]

In the plaque psoriasis clinical trials, the most common adverse reactions associated with apremilast (occurring in ≥5% of patients) were diarrhea (17%), nausea (17%), upper respiratory tract infection (9%), tension headache (8%), and headache (6%).[13] The most frequently reported reasons for the discontinuation of apremilast were nausea (1.6%), diarrhea (1.0%), and headache (0.8%).[13]

Contraindications

Apremilast is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation.[13]

Drug Interactions

Use of apremilast with strong cytochrome P450 enzyme inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended, because it may result in a loss of efficacy of apremilast.[13]

Warnings and Precautions

Depression. Patients should be advised of the potential emergence or worsening of depression, suicidal thoughts, or other mood changes. The risks and benefits of treatment with apremilast should be weighed carefully in patients with a history of depression and/or suicidal thoughts or behavior.[13]

Weight loss. The patient's weight should be monitored regularly. If unexplained or clinically significant weight loss occurs, discontinuation of apremilast should be considered.[13]

Use in Specific Populations

Pregnancy. Adequate and well-controlled studies with apremilast have not been conducted in pregnant women. Apremilast should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.[13]

Nursing mothers. It is not known whether apremilast or its metabolites are present in human milk. However, because many drugs are present in human milk, use caution when apremilast is administered to a nursing woman.[13]

Pediatric use. The safety and efficacy of apremilast in patients aged <18 years have not been established.[13]

Geriatric use. In the psoriatic arthritis clinical trials and in the plaque psoriases clinical trials, no overall differences were observed between older patients (aged ≥65 years) and younger patients.[13]

Severe renal impairment. Increased systemic exposure of apremilast has been observed in patients with severe renal impairment; the dose of apremilast should be reduced to 30 mg once daily in patients with severe renal impairment.[13]

Hepatic impairment. No dose adjustment is necessary in patients with hepatic impairment.[13]

Conclusion

The FDA approval of apremilast marks the availability of the first oral option for the treatment of patients with active psoriatic arthritis and the first PDE-4 inhibitor for the treatment of patients with moderate to severe plaque psoriasis. The option of an oral therapy adds convenience for patients and can also be important for patients who are unable or unwilling to use other treatment options.

The safety and efficacy of apremilast for the treatment of patients with psoriatic arthritis were demonstrated in 3 randomized, double-blind, placebo-controlled clinical trials. In all 3 studies, significantly more patients who received apremilast achieved an ACR20 response at week 16 compared with those receiving a placebo. Treatment with apremilast 30 mg twice daily also resulted in improvement for each ACR component, including tender joints, swollen joints, and physical function.

The FDA approval of apremilast marks the availability of the first oral option for the treatment of patients with active psoriatic arthritis and the first PDE-4 inhibitor for the treatment of patients with moderate to severe plaque psoriasis.

Patients with plaque psoriasis who received apremilast showed significant and clinically meaningful improvements in PASI scores at week 16. In addition, these studies demonstrated clinical improvement, as measured by sPGA scores of clear to almost clear. ■

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