Formulary Drug Reviews

Apremilast

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Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with *The Formulary Monograph Service*. Through the cooperation of *The Formulary*, *Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, call *The Formulary* at 800-322-4349. The September 2014 monograph topics are tedizolid phosphate, ceritinib, omega-3-carboxylic acids, umecclidinium bromide inhalation powder, and siltuximab. The DUE/MUE is on avoidance of insulin use errors.

Generic Name:	Apremilast
Proprietary Name:	Otezla (Celgene Corporation)
Approval Rating:	1S
Therapeutic Class:	Anti-inflammatories
Similar Drugs:	Roflumilast
Sound- or Look-Alike Names:	Apresoline, cilomilast, roflumilast

INDICATIONS

Apremilast is indicated for the treatment of active psoriatic arthritis in adults.¹

CLINICAL PHARMACOLOGY

Phosphodiesterase 4 (PDE4) is an intracellular enzyme that is predominantly expressed in cells of the

immune system. PDE4 hydrolyses cyclic adenosine monophosphate (cAMP) into AMP, leading to production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-2, IL-8, IL-12, IL-23, and interferon-gamma, as well as suppression of anti-inflammatory cytokines, such as IL-10.²⁻⁸ Inhibition of PDE4 causes accumulation of intracellular cAMP, which activates protein kinase A and other effectors involved with the regulation of pro-inflammatory cytokines, neutrophil degranulation, and chemotaxis and adhesion to endothelial cells.^{1,2,8}

Apremilast is a novel, orally available small molecule that inhibits the activity of PDE4, subsequently inhibiting the production of TNF-alpha, IL-2, IL-8, IL-12, IL-23, CXCL9, CXCL10, CCL4, interferon-gamma, and leukotriene B4 and increasing the production of IL-10.^{1-5,8-10} The specific mechanism(s) by which apremilast exerts its therapeutic action in psoriatic arthritis patients is not well defined.¹ Apremilast also suppresses arthritis in rodents and reduces the severity of psoriasiform features in mice with psoriatic xenografts.^{3,6,11}

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PHARMACOKINETICS

Following oral administration on an empty stomach, the peak plasma concentration ($C_{\max}$) of apremilast is reached at a median of approximately 2.5 hours, and the absolute bioavailability is approximately 73%. Coadministration of apremilast with food does not alter the extent of absorption.^{1,3,9,12}

Apremilast has a mean apparent volume of distribution of 87 L, and plasma protein binding is approximately 68%.¹

Apremilast is extensively metabolized with up to 23 metabolites identified in plasma, urine, and feces. Apremilast is metabolized by cytochrome oxidative metabolism, followed by glucuronidation and non-cytochrome-mediated hydrolysis. In vitro, apremilast is primarily metabolized by cytochrome 450 (CYP-450) 3A4, with minor contributions from CYP1A2 and CYP2A6. Following oral administration, the main components in plasma are unchanged apremilast (45%) and the inactive metabolite O-desmethyl apremilast glucuronide (39%).^{1,9} The minor metabolites M7 and M17 retained activity similar to apremilast but are present in concentrations of less than 2% of apremilast concentrations.⁹ Other major metabolites (M14 and M16) are at least 50-fold less active in their ability to inhibit PDE4 and TNF-alpha than apremilast.⁹

In healthy patients, apremilast plasma clearance is about 10 L/h, and the terminal elimination half-life is 6 to 9 hours.^{1,7,9,12} The half-life of apremilast metabolites is 11 to 16 hours.⁹ Following oral administration of radiolabeled apremilast, about 58% and 39% of the radioactivity and about 3% and 7% of unchanged radioactive apremilast is recovered in urine and feces, respectively.^{1,9}

The pharmacokinetics of apremilast are not affected by moderate or severe hepatic impairment. In patients with severe renal impairment given a single dose of apremilast 30 mg, the area under the curve (AUC) and $C_{\max}$ of apremilast increased by approximately 88% and 42%, respectively.¹ Elderly patients (65 to 85 years of age) have a 13% higher AUC and 6% higher $C_{\max}$ compared with younger patients (18 to 55 years of age).¹ Women have a higher AUC (31% increase compared with men) and a higher $C_{\max}$ (8% higher than men).¹

COMPARATIVE EFFICACY

Indication: Plaque Psoriasis

Guidelines

Guideline: Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis: Section 6;

Guidelines of Care for the Treatment of Psoriasis and Psoriatic Arthritis: Case-Based Presentations and Evidence-Based Conclusions

Reference: Menter A, et al, 2011¹³

Comments: For the treatment of mild psoriasis (involvement of less than 5% body surface area [BSA]), the use of topical corticosteroids first line as monotherapy or in conjunction with topical nonsteroidal agents, such as vitamin D analogues, retinoids, topical calcineurin inhibitors, or topical tacrolimus, is recommended. Targeted phototherapies are recommended for the treatment of moderate to severe psoriasis (involvement of more than 5% BSA) not adequately controlled by topical agents. The guideline also recommends the use of adalimumab, alefacept, cyclosporine, etanercept, infliximab, methotrexate, or ustekinumab as monotherapy or in combination. Apremilast is not addressed in the current guideline.

Studies

Drug: Apremilast vs Placebo

Reference: Reich K, et al, 2013 (ESTEEM 1)^{14,15}

Study Design: Phase 3, randomized, double-blind, placebo-controlled, multicenter study

Study Funding: Celgene Corporation

Patients: 844 patients with moderate to severe psoriasis, defined as psoriasis area and severity index (PASI) of at least 12, BSA involvement of at least 10%, and static physician's global assessment (sPGA) of at least 3. Mean age was 46 years, mean duration of psoriasis was 19.4 years, mean PASI score was 19, BSA involvement was more than 20% in 49.2% of patients, 28.7% had prior biologic exposure, and 6.6% were biologic failures.

Intervention: Patients were randomized 2:1 to apremilast 30 mg twice daily or placebo through week 16. From week 17 to 32, all patients were treated with apremilast 30 mg, followed by a randomized withdrawal phase through week 52.

Results:

Primary Endpoint(s)

- Proportion of patients achieving a reduction of 75% or greater from baseline PASI (PASI-75) at week 16 was 33.1% for apremilast and 5.3% for placebo ($P < .001$). The number needed to treat (NNT) for achievement of a PASI-75 at week 16 is 3.6.

Secondary Endpoint(s)

- Proportion of patients achieving a PASI-50 at week 16 was 58.7% for apremilast and 17%

for placebo ($P < .001$). The NNT for achievement of a PASI-50 at week 16 is 2.4.

- The mean change from baseline in PASI score was -52.1% for apremilast and -16.7% for placebo ($P < .001$).

Comments: Treatment groups were similar regarding baseline demographic and disease characteristics. Adverse events for the apremilast and placebo treatment groups occurring at a rate of at least 5% were diarrhea (18.8% vs 7.1%, respectively), nausea (15.7% vs 6.7%, respectively), upper respiratory tract infection (10.2% vs 7.4%, respectively), nasopharyngitis (7.3% vs 8.2%, respectively), tension headache (7.3% vs 4.3%, respectively), and headache (5.5% vs 4.6%, respectively). Discontinuation of drug therapy occurred in 3% to 5% of patients because of adverse events.

Limitations: Results of this study are only available as a meeting abstract. The ethnicity of the enrolled patients was not provided in this abstract.

Reference: Papp K, et al, 2012⁴

Study Design: Randomized, double-blind, international, multicenter, parallel-group, dose-comparison study

Study Funding: Celgene Corporation

Patients: 260 patients (mean age, 46.1 years; 62.9% men; 96.9% White) with at least a 6-month history of moderate to severe plaque psoriasis, PASI score of at least 10, and BSA involvement of at least 10%, and were candidates for phototherapy or systemic therapy. Subjects who failed to respond to cyclosporine, alefacept, etanercept, efalizumab, infliximab, or adalimumab were excluded.

Intervention: Apremilast 20 mg once daily ($n = 87$), apremilast 20 mg twice daily ($n = 85$), or placebo ($n = 87$) for 12 weeks followed by an optional 4-week, treatment-free, observational follow-up phase. Capsules were taken in the morning before meals and in the evening.

Results:

Primary Endpoint(s)

- Proportion achieving a PASI-75 at week 12 versus placebo: apremilast twice daily, 24.4% ($P = .023$); apremilast once daily, 10.3%; and placebo, 10.3%. The NNT for achievement of a PASI-75 with apremilast twice daily compared with placebo at week 12 is 7.1.

Secondary Endpoint(s)

- Proportion of subjects achieving PASI-50: apremilast twice daily, 57% ($P < .001$); apre-

milast once daily, 27.6%; and placebo, 23%. The NNT for achievement of a PASI-50 with apremilast twice daily compared with placebo at week 12 is 3.

- Proportion of subjects achieving PASI-90: apremilast twice daily, 14%; placebo, 5.7%.
- Mean percent change from baseline PASI: apremilast twice daily, 52.1% ($P < .001$); apremilast once daily, 30.3% ($P = .021$); and placebo, 17.4%.
- Mean percent change from baseline in percent of BSA involvement: apremilast twice daily, -30.8% ($P < .001$); apremilast once daily, -15.2% ; and placebo, -3.2% .
- Mean change from baseline in overall Static Physician's Global Assessment: apremilast twice daily, -1.3 ($P < .001$); apremilast once daily, -0.8 ; and placebo, -0.7% .
- Relapse (defined as a 50% loss of maximal PASI score in subjects who achieved PASI-50 or greater) during the observation follow-up phase: apremilast twice daily, 26.4%; apremilast once daily, 24.2%; and placebo, 21.7%.

Comments: The phase 2 trial set and met a 90% power. The mean number of days the subjects took the study medication was 76.6 in the placebo group, 75.7 in the apremilast once-daily group, and 79.9 in the apremilast twice-daily group. Discontinuation due to adverse events was similar between groups, although fewer patients discontinued apremilast twice daily (twice daily, 3.5%; once daily, 8%; placebo, 8%).

Limitations: No study sites were in the United States; studies were conducted in Canada, the Czech Republic, and Germany.

Reference: Papp K, et al, 2012³

Study Design: Randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-ranging study

Study Funding: Celgene Corporation

Patients: 352 patients (mean age, 44.3 years; 63% men; 93% White) with at least a 6-month history of moderate to severe plaque psoriasis, a PASI score of at least 12, and BSA involvement of at least 10% who were candidates for phototherapy or systemic therapy. Mean PASI score was 18.5 and mean affected BSA was 22%.

Intervention: Patients were randomized to receive oral apremilast 10 mg twice daily ($n = 89$),

apremilast 20 mg twice daily ($n = 87$), apremilast 30 mg twice daily ($n = 88$), or placebo ($n = 88$) for 16 weeks. At week 16, placebo patients were randomized to apremilast 20 or 30 mg twice daily for the remaining 6 weeks of the study. Additionally, investigators and patients were made aware that treatment was active, but the dose was concealed.

Results:

Primary Endpoint(s)

- Achievement of PASI-75: apremilast 10 mg, 11%; apremilast 20 mg, 29% ($P < .001$); apremilast 30 mg, 41% ($P < .001$); and placebo, 6%. The NNT for achievement of PASI-75 at week 16 was 4.4 with apremilast 20 mg and 2.9 with apremilast 30 mg.
- Proportion achieving a PASI-75 at week 16 versus placebo: apremilast 10 mg (odds ratio [OR], 2.1; 95% confidence interval [CI], 0.69 to 6.42); apremilast 20 mg (OR, 6.69; 95% CI, 2.43 to 18.5; $P < .001$); and apremilast 30 mg (OR, 11.5; 95% CI, 4.24 to 31.16; $P < .001$) versus placebo.

Secondary Endpoint(s)

- Proportion of patients achieving PASI-50 at week 16: apremilast 10 mg, 38.2% ($P = .06$); apremilast 20 mg, 47.1% ($P = .002$); apremilast 30 mg, 60.2% ($P < .001$); and placebo, 25%. The NNT for achievement of PASI-50 at week 16 was 4.5 with apremilast 20 mg and 2.9 with apremilast 30 mg.
- Proportion of patients achieving PASI-75 at week 16: apremilast 10 mg, 11.2% ($P = .19$); apremilast 20 mg, 28.7% ($P < .001$); apremilast 30 mg, 40.9% ($P < .001$); and placebo, 5.7%. The NNT for achievement of PASI-75 at week 16 was 4.4 with apremilast 20 mg and 2.9 with apremilast 30 mg.
- Proportion of patients achieving PASI-90 at week 16: apremilast 10 mg, 4.5% ($P = .18$); apremilast 20 mg, 9.2% ($P = .016$); apremilast 30 mg, 11.4% ($P = .005$); and placebo, 1.1%. The NNT for achievement of PASI-90 at week 16 was 12.4 with apremilast 20 mg and 9.7 with apremilast 30 mg.
- Median days to PASI-50 or PASI-75 (weeks 0 through 16):
 - PASI-50: apremilast 10 mg, 41 days (95% CI, 29 to 44 days); apremilast 20 mg, 42 days (95% CI, 34 to 44 days); apremilast 30 mg, 30 days (29 to 43 days); and placebo, 45.5 days (95% CI, 40 to 85 days).

- PASI-75: apremilast 10 mg, 70 days (95% CI, 45 to 85 days); apremilast 20 mg, 83 days (95% CI, 57 to 85 days); apremilast 30 mg, 44 days (43 to 81 days); and placebo, 57 days (95% CI, 43 to 111 days).

- Percentage change from baseline in affected BSA at week 16: apremilast 10 mg, -28.5% ($P = .002$); apremilast 20 mg, -38.4% ($P < .001$); apremilast 30 mg, -49.4% ($P < .001$); and placebo, -8.4%.

- Change from baseline in Dermatology Life Quality Index at week 16: apremilast 10 mg, -3.2; apremilast 20 mg, -5.9 ($P < .001$); apremilast 30 mg, -4.4 ($P = .005$); and placebo, -1.9.

Comments: Phase 2b study conducted at 35 sites in the United States and Canada. PASI-100 by week 16 was achieved by 3 patients assigned to apremilast 20 mg and 2 patients assigned to apremilast 30 mg; however, these results were not statistically significant. Adverse events leading to study discontinuation were similar among groups and occurred in 6% of the placebo group, 2% of the apremilast 10 mg group, 9% of the apremilast 20 mg group, and 11% of the apremilast 30 mg group.

Limitations: Not a diverse population; study population was mainly obese White men.

Indication: Psoriatic Arthritis

Guidelines

Guideline: Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis: Section 6; Guidelines of Care for the Treatment of Psoriasis and Psoriatic Arthritis: Case-Based Presentations and Evidence-Based Conclusions

Reference: Menter A, et al, 2011¹³

Comments: For the treatment of mild psoriatic arthritis in adult patients, the guidelines suggest initiation of nonsteroidal anti-inflammatory drugs (NSAIDs). If there is no response after 2 to 3 months of therapy with NSAIDs, treatment with methotrexate should be considered. The guidelines suggest initiating methotrexate with appropriate dose escalation for adult patients with moderate to severe psoriatic arthritis. If there is minimal improvement after 12 to 16 weeks in signs and symptoms of psoriatic arthritis, it is appropriate to either add or switch to any TNF-alpha inhibitor (eg, adalimumab, etanercept, golimumab, infliximab). Ustekinumab with methotrexate is recommended

second line. NSAIDs and low-dosage prednisone (10 mg/day) can be used as adjunctive therapy. Apremilast is not addressed in the current guideline.

Studies

Drug: Apremilast vs Placebo

Reference: Schett G, et al, 2013 (PALACE 1, PALACE 2, PALACE 3)^{1,16-23}

Study Design: Three identical, phase 3, randomized, double-blind, multicenter, placebo-controlled studies

Study Funding: Celgene Corporation

Patients: 1,493 patients with active psoriatic arthritis (at least 3 swollen joints and at least 3 tender joints) despite prior or current treatment with disease-modifying antirheumatic drug (DMARD) therapy and a diagnosis of psoriatic arthritis for at least 6 months. Previous treatment with a biologic agent, including TNF-blockers, was allowed (up to 10% of patients could be TNF-blocker therapeutic failures). Patients with subtypes of psoriatic arthritis were enrolled, including symmetric polyarthritis (62%), asymmetric oligoarthritis (27%), distal interphalangeal joint arthritis (6%), arthritis mutilans (3%), and predominant spondylitis (2.1%). The median duration of psoriatic arthritis disease was 5 years. Patients receiving stable doses of methotrexate (up to 25 mg/week), sulfasalazine (up to 2 g/day), leflunomide (up to 20 mg/day), low-dose oral corticosteroids (up to 10 mg prednisone equivalents), and/or NSAIDs were allowed to continue throughout the study. Patients received concomitant therapy with at least 1 DMARD (65%), methotrexate (55%), sulfasalazine (9%), leflunomide (7%), low-dose oral corticosteroids (14%), and NSAIDs (71%). Prior treatment with small-molecule DMARDs only was reported in 76% of patients, and prior treatment with biologic DMARDs was reported in 22% of patients, including 9% who had failed prior biologic DMARD treatment. Patients who had failed to respond to more than 3 DMARD agents (small-molecule or biologic) or more than 1 biologic TNF-blocker were excluded.

Intervention: Across the 3 studies, patients were randomized 1:1:1 to receive apremilast 20 mg twice daily ($n = 500$), apremilast 30 mg twice daily ($n = 497$), or placebo ($n = 496$). Patients were titrated over the first 5 days and treated for

24 weeks. At week 16, patients with less than 20% in swollen and tender joint counts qualified for protocol-defined early escape; patients receiving placebo re-randomized to apremilast 20 or 30 mg; and those on apremilast remained on the initial apremilast dose. At week 24, all placebo patients were re-randomized to apremilast 20 or 30 mg through week 52. Prior background therapy with stable doses of methotrexate, sulfasalazine, leflunomide, low-dose oral corticosteroids, and/or NSAIDs was allowed.

Results:

Primary Endpoint(s)

- Proportion of patients achieving an American College of Rheumatology 20% improvement criteria (ACR20) by week 16¹:
 - PALACE 1: 38% for apremilast 30 mg ($n = 168$) and 19% for placebo ($n = 168$) ($P < .05$); NNT = 5.3.
 - PALACE 2: 32% for apremilast 30 mg ($n = 162$) and 19% for placebo ($n = 159$) ($P < .05$); NNT = 7.7.
 - PALACE 3: 41% for apremilast 30 mg ($n = 167$) and 18% for placebo ($n = 169$) ($P < .05$); NNT = 4.4.

Secondary Endpoint(s)

- Proportion of patients achieving an ACR50 by week 16¹:
 - PALACE 1: 16% for apremilast 30 mg ($n = 168$) and 6% for placebo ($n = 168$).
 - PALACE 2: 11% for apremilast 30 mg ($n = 162$) and 5% for placebo ($n = 159$).
 - PALACE 3: 15% for apremilast 30 mg ($n = 167$) and 8% for placebo ($n = 169$).
- Proportion of patients achieving an ACR70 by week 16¹:
 - PALACE 1: 4% for apremilast 30 mg ($n = 168$) and 1% for placebo ($n = 168$).
 - PALACE 2: 1% for apremilast 30 mg ($n = 162$) and 1% for placebo ($n = 159$).
 - PALACE 3: 4% for apremilast 30 mg ($n = 167$) and 2% for placebo ($n = 169$).
- Change from baseline in swollen joint count (SJC) at week 16¹⁷:
 - PALACE 1: -16.7% for placebo, -39.3% ($P = .0035$) for apremilast 20 mg, and -50% ($P < .001$) for apremilast 30 mg.
 - PALACE 2: -33.3% for placebo, -50% ($P = .0029$) for apremilast 20 mg, and -53.9% ($P < .001$) for apremilast 30 mg.

- PALACE 3: -20% for placebo, -36.4% ($P = .03$) for apremilast 20 mg, and -50% ($P = .001$) for apremilast 30 mg.
- Change from baseline in tender joint count (TJC) at week 16¹⁷:
 - PALACE 1: -7% for placebo, -23.3% ($P < .001$) for apremilast 20 mg, and -42.9% ($P < .001$) for apremilast 30 mg.
 - PALACE 2: -8.7% for placebo, -36.2% ($P < .001$) for apremilast 20 mg, and -33.3% ($P = .002$) for apremilast 30 mg.
 - PALACE 3: -8.6% for placebo, -30% ($P < .001$) for apremilast 20 mg, and -43.7% ($P < .001$) for apremilast 30 mg.

Other Endpoint(s)

- The proportion of patients achieving a minimum clinically important difference (MCID) in the Health Assessment Questionnaire Disability Index (HAQ-DI) score of at least 0.3 for patients receiving apremilast 30 mg was 44.7%, 47%, and 52% for PALACE 1, PALACE 2, and PALACE 3, respectively.¹⁶
- The proportion of patients achieving a MCID in Short Form 36 (SF-36) physical functioning score of at least 2.5 for patients receiving apremilast 30 mg was 60%, 53.9%, and 58.3% for PALACE 1, PALACE 2, and PALACE 3, respectively.¹⁶

Comments: Patients were stratified by DMARD use and BSA involvement of 3% or more. In patients receiving apremilast for 52 weeks, sustained improvements in SJC/TJC were observed at week 52 with SJC improvements up to -87.5% and TJC improvements up to -70%. Mean changes from baseline exceeded MCID of 2.5 in patients treated with apremilast for 52 weeks was maintained between weeks 24 and 52. Most common adverse events in apremilast-treated patients were diarrhea (14.3%), nausea (12.6%), headache (10.1%), upper respiratory tract infection (10.3%), and nasopharyngitis (7.4%). Diarrhea, nausea, and headache appeared to increase in a dose-dependent manner. Apremilast was not associated with any changes in laboratory values (eg, ALT, AST, creatinine, glucose, cholesterol).²⁰ Discontinuations due to adverse events were 7.5% for apremilast 20 mg and 8.3% for apremilast 30 mg and occurred primarily in the first 24 weeks.

Limitations: Results of studies are only available as meeting abstracts and as pooled data in the product information, with the exception of PALACE 1.

Reference: Wells AF, et al, 2013 (PALACE 4)²⁴

Study Design: Phase 3, randomized, double-blind, multicenter, placebo-controlled study

Study Funding: Celgene Corporation

Patients: 527 patients with psoriatic arthritis and who were DMARD-naïve. Patients had a mean diagnosis of psoriatic arthritis for 3.41 years; mean age was 49.4 years and 47.4% were male; mean duration of psoriasis was 15.8 years, mean SJC of 11.2, mean TJC of 20.1, and mean HAQ-DI of 1.068; 73.1% were using NSAIDs at baseline.

Intervention: Patients were randomized 1:1:1 to receive apremilast 20 mg twice daily, apremilast 30 mg twice daily, or placebo. Patients were titrated over the first 5 days and treated for 52 weeks. At week 16, patients with a less than 20% SJC or TJC qualified for protocol-defined early escape, patients receiving placebo re-randomized to apremilast 20 or 30 mg, and those on apremilast remained on the initial apremilast dose. At week 24, all remaining placebo patients were re-randomized to apremilast 20 or 30 mg through week 52.

Results:

Primary Endpoint(s)

- Proportion of per-protocol patients ($n = 501$) achieving an ACR20 by week 16 was 16.9% for placebo, 29.2% for apremilast 20 mg ($P = .008$), and 32.3% for apremilast 30 mg ($P = .001$).

Secondary Endpoint(s)

- Proportion of patients achieving an ACR20 by week 52 was 53% for apremilast 20 mg and 59% for apremilast 30 mg.
- Proportion of patients achieving an ACR50 by week 52 was 27% for apremilast 20 mg and 32% for apremilast 30 mg.
- Proportion of patients achieving an ACR70 by week 52 was 14% for apremilast 20 mg and 18% for apremilast 30 mg.

Other Endpoint(s)

- Change of SJC from baseline by week 52 was -89% for apremilast 20 mg and -100% for apremilast 30 mg.
- Change of TJC from baseline by week 52 was -67% for apremilast 20 mg and -67% for apremilast 30 mg.
- Change of HAQ-DI from baseline by week 52 was -0.319% for apremilast 20 mg and -0.392% for apremilast 30 mg.

Comments: Patient population naïve to DMARD treatment. Adverse reactions occurring in at least

5% of patients treated with apremilast include nausea, diarrhea, headache, and upper respiratory tract infection. No gastrointestinal (GI) adverse events occurred up to week 52, and discontinuation related to these adverse events was 2% or less.

Limitations: Results of this study are only available as a meeting abstract. Primary result reported from per-protocol population only.

Reference: Schett G, et al, 2012⁸

Study Design: Randomized, double-blind, multicenter, placebo-controlled study

Study Funding: Celgene Corporation

Patients: 204 patients (approximately 50 years of age; 52% men; 96% White) with at least a 6-month history of psoriatic arthritis (according to the Moll and Wright criteria). Patients also discontinued treatment with immunosuppressants other than methotrexate for an adequate washout period prior to randomization. Patients were permitted a stable dose of oral corticosteroids (prednisone dose or equivalent of 10 mg or less per day) and NSAIDs if received for at least 28 days and 14 days prior to enrollment, respectively.

Intervention: Patients were randomized 1:1:1 to receive apremilast 20 mg twice per day ($n = 69$), apremilast 40 mg once per day ($n = 67$), or placebo ($n = 68$) for 12 weeks followed by an optional 4-week, treatment-free, observational follow-up phase or a 12-week treatment-extension phase. Patients were stratified during the randomization process based on baseline methotrexate use. Patients who had been receiving methotrexate prior to the study had to have been using the drug for at least 24 weeks and been on a stable dose for at least 8 weeks before screening and throughout the study. At the end of week 12, patients receiving placebo were eligible to be entered into the treatment-extension phase and were re-randomized to apremilast 20 mg twice daily or apremilast 40 mg once daily. Patients originally randomized to receive apremilast were continued on the same dose if they continued in the treatment-extension phase. A one-time 20 mg dose reduction was permitted for patients experiencing intolerable adverse events. Other drugs allowed during the study included acetaminophen, loratadine, pseudoephedrine, guaifenesin, calcium, and contraceptives (women only).

Results:

Primary Endpoint(s)

- Proportion of patients achieving an ACR20 by week 12: apremilast 20 mg twice daily, 43.5% ($P < .001$); apremilast 40 mg once daily, 35.8% ($P = .002$); and placebo, 11.8%. The NNT for achievement of ACR20 at week 12 was 3.2 with apremilast 20 mg twice daily and 4.2 with apremilast 40 mg once daily.

Secondary Endpoint(s)

- Improvement from baseline by week 12:
 - Psoriatic arthritis response criteria: apremilast 20 mg twice daily, 52.5% ($P < .001$); apremilast 40 mg once daily, 50.7% ($P < .001$); and placebo, 22.1%.
- Response rate by week 12:
 - ACR50: apremilast 20 mg twice daily, 17.4% ($P = .012$); apremilast 40 mg once daily, 13.4% ($P = .056$); and placebo, 2.9%. The NNT for achievement of ACR50 at week 12 was 6.9 with apremilast 20 mg twice daily.
 - ACR70: apremilast 20 mg twice daily, 5.8%; apremilast 40 mg once daily, 7.5%; and placebo, 1.5%.
- Time to ACR20: mean time to response was 4 weeks.
- Withdrawals due to lack of efficacy: apremilast 20 mg twice daily, 3 patients; apremilast 40 mg once daily, 2 patients; and placebo, 6 patients.
- Dose reductions or treatment interruptions: apremilast 20 mg twice daily, 9 patients; apremilast 40 mg once daily, 12 patients; and placebo, 6 patients.

Comments: Phase 2 clinical trial. Power set at 80% and achieved. Randomization was stratified by baseline methotrexate use; 44% of the patients were receiving methotrexate (range, 1.5 to 30 mg weekly) at baseline. The ACR20 response rate at the end of the extension phase was 42.5% in the apremilast 20 mg twice-daily group, 43.5% in the apremilast 40 mg once-daily group, 40% in the placebo/apremilast 20 mg twice-daily group, and 45% in the placebo/apremilast 40 mg once-daily group. The subgroup analysis based on baseline methotrexate found no difference in the response rates; 46.7% achieved an ACR20 in the concomitant methotrexate group who received apremilast 20 mg twice daily versus 41% in those who did not receive methotrexate, and the ACR20 response rates in the apremilast 40 mg once-daily group were 36.7% and

35.1%, respectively. The most frequently reported adverse reactions were nausea, vomiting, and diarrhea and occurred most commonly with apremilast 40 mg once daily. The dropout rate by week 12 was 10% in the 40 mg group, 20% in the 20 mg group, and 26% in the placebo group.

Limitations: Not a diverse population (mainly White men). No study sites were in the United States; studies were conducted in Canada, Belgium, Germany, the Netherlands, and the United Kingdom. The initial protocol did not include the treatment-extension phase; therefore, some patients completed the 12-week trial before this option was available.

Indication: Ankylosing Spondylitis

Studies

Drug: Apremilast vs Placebo

Reference: Pathan E, et al, 2012²

Study Design: Randomized, double-blind, single-center, placebo-controlled study

Study Funding: Celgene Corporation

Patients: 38 patients (approximately 42 years of age; ratio of men:women = 8:1; mean disease duration, 20 years) with ankylosing spondylitis for at least 2 years and back pain and stiffness noted with a score of at least 1 on questions 2 and 5 of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Intervention: Apremilast 30 mg twice daily or placebo for 12 weeks.

Results:

Primary Endpoint(s)

- Mean change in BASDAI score at week 12: -1.59 and -0.77 for apremilast and placebo, respectively.

Secondary Endpoint(s)

- Mean change in Bath Ankylosing Spondylitis Functional Index score at week 12: -1.74 and -0.28 for apremilast and placebo, respectively.
- Mean change in Bath Ankylosing Spondylitis Metrology Index score at week 12: -0.51 and -0.21 for apremilast and placebo, respectively.

Comments: Phase 2 pilot study. Power was estimated at 80% based on prior anti-TNF studies. The majority of patients were taking a stable dose of NSAIDs during the study. All parameters showed numerical differences, but none of them were statistically different.

Limitations: Study likely underpowered to detect a significance of apremilast for treatment of

ankylosing spondylitis. Small sample size with a short duration of treatment; may need a larger and longer trial to detect any beneficial effects.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Apremilast is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation.¹

Warnings and Precautions

Treatment with apremilast is associated with an increase in depression or depressed mood. During weeks 0 to 16 of the 3 placebo-controlled clinical trials, 1% (10 of 998) of patients treated with apremilast reported depression or depressed mood compared with 0.8% (4 of 495) treated with placebo, resulting in 0.3% (4 of 1,441) of apremilast patients discontinuing treatment. Depression was reported as serious in 0.2% (3 of 1,441) of apremilast patients, and suicidal ideation and behavior occurred in 0.2% (3 of 1,441) of apremilast patients. No placebo-treated patients discontinued therapy due to depression or experienced serious depression or suicidal ideation and behavior; however, 2 placebo-treated patients committed suicide compared with 0 apremilast patients. The risks and benefits of treatment with apremilast should be considered in patients with a history of depression and/or suicidal thoughts or behavior.¹

During controlled clinical trials, a 5% to 10% decrease in body weight occurred in 10% of patients treated with apremilast 30 mg twice daily and 3.3% with placebo. Unexplained or clinically significant weight loss should be evaluated, and discontinuation of apremilast should be considered.¹

Coadministration of rifampin, a strong CYP-450 enzyme inducer, resulted in a reduction of systemic apremilast exposure, which may result in a loss of apremilast efficacy. The use of CYP-450 enzyme inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin) with apremilast is not recommended.¹

Apremilast pharmacokinetics were not characterized in patients with mild (creatinine clearance [CrCl] of 60 to 89 mL/min) or moderate (CrCl of 30 to 59 mL/min) renal impairment. In patients with severe renal impairment (CrCl less than 30 mL/min), the apremilast dose should be reduced.¹

Apremilast pharmacokinetics were characterized in patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment. No dose adjustment is necessary.¹

In clinical studies of apremilast, no overall differences were observed in the safety profile of elderly patients (65 years and older) and younger adult patients (younger than 65 years).¹

The safety and effectiveness of apremilast in pediatric patients younger than 18 years have not been established.¹

Apremilast is Pregnancy Category C. Apremilast has not been adequately studied in pregnant women. In animal embryo-fetal development studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in no adverse effect at an exposure of 1.4-times the maximal recommended human dose (MRHD) and increases in abortion/embryo-fetal death at 2.1 times the MRHD. In mice, there were no apremilast-induced malformations up to exposures 4 times the MRHD.¹ There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to apremilast during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972.¹

Apremilast was detected in milk of lactating mice. It is not known whether apremilast or its metabolites are present in human milk. Use caution when administering apremilast to a breast-feeding woman.¹

ADVERSE REACTIONS

The most common (at least 5%) adverse reactions associated with apremilast are diarrhea, nausea, and headache. The most common adverse reactions leading to discontinuation of apremilast were nausea (1.8%), diarrhea (1.8%), and headache (1.2%).¹ The most common adverse reactions are displayed in Table 1.

DRUG INTERACTIONS

Apremilast exposure is decreased when coadministered with strong CYP-450 inducers (eg, rifampin, phenobarbital, carbamazepine, phenytoin) and may result in loss of apremilast efficacy. The use of CYP-450 enzyme inducers with apremilast is not recommended.¹

RECOMMENDED MONITORING

Patients, their caregivers, and families should be advised to monitor for emergent or worsening depression or for suicidal thoughts or other mood changes and, if such changes occur, to contact their health care provider.¹

Apremilast-treated patients should have their body weight assessed regularly. Evaluate unexplained or clinically significant weight loss and consider apremilast discontinuation.¹

DOSING

To treat psoriatic arthritis, apremilast should be titrated over 5 days to reduce GI symptoms as follows: apremilast 10 mg in the morning on day 1; apremilast 10 mg in the morning and apremilast 10 mg in the evening on day 2; apremilast 10 mg in the morning and apremilast 20 mg in the evening on day 3; apremilast 20 mg in the morning and apremilast 20 mg in the evening on day 4; and apremilast 20 mg in the morning and apremilast 30 mg in the evening on day 5. Following the 5-day titration, the recommended maintenance dosage is apremilast 30 mg twice daily starting on day 6.¹

Apremilast can be administered without regard to meals; however, tablets should not be crushed, split, or chewed.¹

Table 1. Adverse reactions reported in $\geq 2\%$ of patients administered apremilast 30 mg twice daily and $\geq 1\%$ greater than observed in placebo for up to 112 days¹

Adverse reactions	Days 1 to 5 Placebo (<i>n</i> = 495) vs apremilast (<i>n</i> = 497)	Days 6 to 112 Placebo (<i>n</i> = 490) vs apremilast (<i>n</i> = 493)
Diarrhea	1.2% vs 9.3%	1.6% vs 7.7%
Nausea	1.4% vs 7.4%	3.1% vs 8.9%
Headache	1.8% vs 4.8%	2.2% vs 5.9%
Upper respiratory tract infection	0.6% vs 0.6%	1.8% vs 3.9%
Vomiting	0.4% vs 0.8%	0.4% vs 3.2%
Nasopharyngitis	0.2% vs 0.2%	1.6% vs 2.6%
Abdominal pain, upper	0% vs 0.6%	0.2% vs 2%

In patients with severe renal impairment (CrCl less than 30 mL/min), apremilast should be reduced to 30 mg once daily. For initial dosage titration, apremilast titration is recommended using only the morning scheduled dose and then skipping the evening doses.¹

PRODUCT AVAILABILITY

Apremilast was approved for marketing in the United States on March 21, 2014.²⁵ Apremilast is available as 10, 20, and 30 mg film-coated tablets. Apremilast is supplied in a 2-week starter pack containing a 13-tablet blister titration pack containing 10, 20, and 30 mg tablets with 14 additional 30 mg tablets; a 28-count carton with 2 blister cards containing fourteen 30 mg tablets; and 60-count bottles of 30 mg tablets. Apremilast tablets should be stored below 30°C (86°F).¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMs is required for apremilast.²⁵

CONCLUSION

Apremilast is the second oral selective PDE4 inhibitor on the market. The first PDE4 inhibitor, roflumilast, was approved to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Apremilast was studied for very different therapeutic indications, including the treatment of ankylosing spondylitis, plaque psoriasis (moderate to severe), cutaneous sarcoidosis, and psoriatic arthritis. The results from the phase 2, placebo-controlled trials show that apremilast appears to be safe and effective in the treatment of plaque psoriasis and psoriatic arthritis. Unfortunately, all the phase 3 trials are placebo-controlled trials with no active comparative group.

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