Brand Name: Otezla

Generic Name: apremilast

Manufacturer[1]: Celgene Corp.

Drug Class[2]: Phosphodiesterase-4 Enzyme Inhibitor

Uses:

Labeled Uses[2]: Treatment of adult patients with active psoriatic arthritis (PsA).
Unlabeled Uses[2]: none

Mechanism of Action[2,3,4]

Apremilast is an inhibitor of phosphodiesterase 4 (PDE4) and specific for cyclic adenosine monophosphate (cAMP). This action results in increased intracellular cAMP levels and regulation of several inflammatory mediators, including: decreased expression of nitric oxide synthase, TNF-a, and interleukin (IL)-23, and increased IL-10.

Pharmacokinetics[2]:

Absorption:

T_{max}	2.5 hours
V_d	87 L
$t_{½}$	6-9 hours
Clearance	10L/hr
Protein binding	68%
Bioavailability	73%

Metabolism: Apremilast is primarily metabolized by CYP3A4 in the liver with minor involvement of CYP1A2 and CYP2A6, and P-glycoprotein. An inactive metabolite (M12) is produced.

Elimination: Apremilast is mostly eliminated in the urine (58%) with 3% being unchanged and excretion in feces accounts for 39% with 7% being unchanged.

Efficacy:

Kavanaugh, A, Mease, P., Gomez-Reino, J, Adebajo, A., Wollenhaupt, J., Gladman, D. et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. Published online first: 2014;0:1-7.

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

Description of Study: *Methods*: Patients older than 18 years of age and had a diagnosis of active PsA were enrolled in the study. Prior tumor necrosis factor blocker efficacy failures were limited to less than 10% of patients enrolled. Therapy with methotrexate, leflunomide or sulfasalazine must have lasted for at least 16 weeks and be a stable dose for at least 4 weeks before screening. Corticosteriods and NSAIDs were permitted in stable doses. Patients were excluded if they failed more than three agents for PsA or more than one tumor necrosis factor blocker, or they had a history of current inflammatory rheumatic or autoimmune joint disease other than PsA, erythrodermic, guttate or generalized pustular psoriasis, were functional class IV, had used phototherapy or DMARDs other than those listed above within 4 weeks of randomization, had used biologics within 12 weeks of randomization or alefacept or ustekinumab within 24 weeks of randomization; or had prior treatment with apremilast. Topical therapy for psoriasis within 2 weeks of randomization was not permitted. Patients with active tuberculosis or a history of incompletely treated tuberculosis could not participate. Patients were randomized into 3 groups (placebo, apremilast 20mg BID, or apremilast 30mg BID. Safety was assessed at weeks 4, 16, and 24 and efficacy was measured at 16 and 24 weeks. Patients who had not improved by 20% from baseline were considered non-responders and entered a rescue protocol. The placebo group was re-randomized into one of the treatment groups but others continued on first assigned dose. All patients eventually entered a 28 week active treatment phase. *Outcome Results:* The primary efficacy endpoint was the proportion of patients meeting 20% improvement from baseline in modified ACR response criteria at week 16. The secondary endpoint was change from baseline in Health Assessment Questionnaire-Disability Index at week 16. At week 16, 31.3% of patients ($p=0.014$) on 20 mg BID achieved an ACR20 response vs. placebo 19.4%. A dose-related effect was observed in those receiving 30mg; they achieved higher ACR20 rates, but statistical comparison was not conducted. Adverse effects occurring in $\geq$5% of any treatment group included diarrhea, nausea, headache, and upper respiratory infection. AEs were comparable across groups (placebo 4.8%, 20 mg 6%, 30mg 7.1%).

Limitations: This study was limited in duration. There was an extensive list of exclusion criteria for this study which limits the extrapolation of results. There were 107/165 in the placebo group that entered the escape protocol, 78/163 in 20 mg group, and 58/161in 30 mg group also were not responsive and entered the escape protocol at week 16 which was not displayed appropriately in the text of the study. Two authors received research grants from the manufacturer/research company. One author has received consulting fees from the manufacturer/research company. Four authors are employees of the drug manufacturer/research company. The study was also funded by the manufacturer.

Conclusion: This study shows that apremilast improves symptoms of PsA based on ACR20 response rates compared to placebo in patients with active PsA that have tried other traditional therapies.

C. Birbara, F. J. Blanco, J. J. Crowley, C. Hu, R. Stevens, C. J. Edwards. Efficacy of Apremilast, An Oral Phosphodiesterase 4 Inhibitor, On Physical Function And Pain in Patients With Psoriatic Arthritis, Including Current Skin Involvement: Results of a Phase 3, Randomized, Controlled Trial. Ann Rheum Dis. 2013;72:678.

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

Description of Study: *Methods*: Patients with active psoriatic arthritis and 1 or more ≥2 cm psoriatic lesions at baseline regardless of prior DMARD or biologic usage were enrolled in the study. 505 patients were randomized to placebo, apremilast 20mg BID group, or apremilast 30 mg BID. 27.9% had prior biologic use and 8.7% were considered biologic failures. 60.6% were taking DMARDs at baseline. Patients in placebo group not achieving response by week 16 were randomized into one of the treatment groups. *Outcome Results:* At week 16 efficacy was measured. 29.4%; p=0.02 of patients receiving apremilast 20 mg BID, and 42.8%; p=<0.0001 of patients receiving apremilast 30 mg achieved the primary endpoint of an ACR20 vs. 18.9% patients receiving placebo. At week 24 secondary outcomes were measured. Physical function, fatigue, and pain had all improved significantly. There was a dose related effect observed and those taking apremilast 30 mg achieved better outcomes. The most common adverse effects were diarrhea, nausea, headache, and upper respiratory infection. The majority (>93%) were mild or moderate and discontinuation rates were low (6-8%).

Limitations: This study is only available as a detailed abstract, therefore the ability to analyze the study is limited. Power was not reported for this study. Two of the authors are employed by the manufacturing company which could promote bias toward the treatment. One author is a consultant for the research company. The study was also funded by the manufacturer.

Conclusion: The results of the study showed that apremilast 30 mg increases ACR20 greater than other study groups. This data is clinically meaningful for patients with active psoriatic arthritis regardless of previous therapy trials or concurrent therapy. Adverse effects were minimal and acceptable for the study.

Strand, V., Fiorentino, D., Hu C., Day, R., Stevens R., and Papp, K. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized controlled study. Health and Quality of Life Outcomes 2013, 11:82.

Study Design: Multicenter, double blind, randomized, placebo-controlled study

Description of Study: *Methods*: Men and women greater than 18 years of age with stable, chronic, moderate to severe plaque psoriasis and were candidates for phototherapy or systemic therapy were enrolled. 352 patients were randomized to receive apremilast 10 mg, 20 mg, or 30 mg BID or placebo for 16 weeks. At week 16, placebo patients were randomized to receive either 20 mg or 30 mg. During the trial concomitant phototherapy and use of systemic, biologic, or topical agents were prohibited. Changes from baseline to

week 16 and improvements ≥ minimum clinically important differences (MCID) were used for patient reported outcomes. These included DLQI, pruritus VAS scores, and short form health survey. *Outcome Results*: DLQI scores were significantly lower in 20 mg ($p<0.0001$) and 30 mg ($p=0.005$) groups, but not with 10 mg ($p=.132$). 25% of placebo, 33.7% 10 mg group, 49.4% 20 mg group, and 44.3% 30 mg group reported improvements ≥ MCID. Pruritis VAS scores improved greater in 20 and 30 mg groups than the placebo or 10 mg group. Baseline short form health survey scores were 0.5 standard deviations lower than the US normative scores of 50. After week 16 scores approached the US normative values in those receiving treatment compared to placebo. Most frequently reported adverse effects were headache, nausea, vomiting, nasopharyngitis, and upper respiratory tract infection.

Limitations: This study cannot be extrapolated to patients with other forms of psoriasis. The study duration was limited to 16 weeks and further durations could be useful. Since data is patient reported there could be other factors affecting results. The study was supported by the drug manufacturer including editorial support and funding for the manuscript. There was also an author employed by the manufacturer.

Conclusion: In addition to efficacy of therapy the impact on patients' quality of life is important for clinical use of medications. This study shows that apremilast 20 mg and 30 mg BID significantly improve measures of health related quality of life in patients with chronic, moderate to severe plaque psoriasis. The benefits of therapy outweigh the risks with apremilast treatment.

Contraindications[4]

Hypersensitivity to apremilast or any component of the product.

Precautions[2,3,4]:

Neuropsychiatric effects: Depression, suicidal ideation and other neuropsychiatric effects have been reported with use of this medication. Patients with a history of these effects should use caution. Patients should report worsening psychiatric symptoms and consider risk/benefits of therapy. Possible discontinuation of therapy may be necessary.

Weight loss: Use of this medication may cause weight loss and regular monitoring should occur. May consider discontinuing therapy if unexplained or significant weight loss occurs.

Renal impairment: Use caution in patients with CrCl <30, increased exposure can occur. Reduce dose in these patients.

Drug-drug interactions: Administering this medication simultaneously with strong CYP450 inducers in not recommended. Dose or frequency may need adjustment.

Adverse Effects[2,3,4]:

Occurring in ≥1-10% of patients

Endocrine and metabolic:

Weight loss (5- 10% of body weight in 10% of patients)

Gastrointestinal

Diarrhea (8% -9%)
Nausea (7% to 9%)
Vomiting (< 3%)
Upper abdominal pain (< 2%)

Central nervous system

Headache (5% to 6%)

Respiratory

Upper respiratory tract infection (4%)
Nasopharyngtis (3%)

Occurring in 1% of patients or less

Psychiatric

Depression, suicidal behavior, suicidal thoughts (1%)

Drug Interactions[2,3,4]

Bosentan: Serum concentration of CYP3A4 substrates may be decreased. Monitor therapy.

CYP3A4 inducers: Serum concentrations of apremilast may be decreased. Avoid combination with phenytoin, carbamazepine, primidone, phenobarbital, rifampin, mitotane, rigabutin, fosphenytoin, St John's Wort, rifapentine, enzalutamide, dabrafenib, deferasirox, siltuximab, and tocilizumab.

Dosing/Administration[2,3,4]

Adult Dosing

Psoriatic arthritis, active: Initial dose: 10 mg in the morning titrated as follows to a 30 mg twice daily maintenance dose.
Dosage titration: Titrate over 5 days as follows: Day 2: 10 mg twice daily; Day 3 10 mg in the morning and 20 mg in the evening; Day 4: 20 mg twice daily; Day 5: 20 mg in the morning and 30 mg in the evening. Maintenance dose: 30 mg twice daily starting on day 6. Do not crush, split, or chew.

Pediatrics (<18 years of age)

Safety and efficacy not established in patients under 18 years of age

Renal impairment

CrCL < 30ml/min: initiate with 10 mg orally in the morning for 3 days, 20 mg orally once daily in the morning on days 4 and 5, and then start maintenance dose of 30 mg orally in the morning on day 6 and each day thereafter.

Hepatic impairment

No dosage adjustment necessary.

Use in special circumstances[2]:

Pregnancy/lactation: FDA pregnancy category C. Use only if benefit justifies the risk to the fetus. Use with caution in breast-feeding women. Unknown if apremilast is excreted into breast milk.

Conclusion:

Apremilast has proven efficacy for patients with psoriatic arthritis and has shown improvement in patients with plaque psoriasis. Studies have shown that apremilast is generally well tolerated and most side effects are of moderate intensity when they do occur. Apremilast has been shown to improve outcomes in patients who have taken or are taking other medications for PsA. The precautionary profiles of apremilast may limit its use in specific populations. At this point apremilast might not be a first line choice of therapy due to high cost and since it is being dispensed only in specialty pharmacies. Currently, it offers another choice with a unique mechanism of action for PsA in patientswho have failed trials of other medications that may be less expensive and more easily accessible.

References:

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5. Kavanaugh, A, Mease, P., Gomez-Reino, J, Adebajo, A., Wollenhaupt, J., Gladman, D. et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. Published online first: 2014;0:1-7.
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7. Strand, V., Fiorentino, D., Hu C., Day, R., Stevens R., and Papp, K. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized controlled study. Health and Quality of Life Outcomes 2013, 11:82.

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