Otezla (apremilast)

STRENGTH	DOSAGE FORM	ROUTE	GPID
30 mg	Tablet	Oral	36172
Titration pack containing: 10 mg, 20 mg, 30 mg tablets	Tablet	Oral	36173

MANUFACTURER

Celgene Corporation

INDICATION(S)

For the treatment of adult patients with active psoriatic arthritis.

DRUG CLASS

INFLAMMATORY DISEASE; PHOSPHODIESTERASE 4 (PDE4) INHIBITOR

PLACE IN THERAPY

Otezla is the only FDA-approved oral treatment for psoriatic arthritis (PsA), a chronic inflammatory condition associated with psoriasis. Up to 30% of psoriasis patients will develop PsA which is characterized by pain stiffness, swelling and tenderness of the joints, inflammation of specific ligaments and tendons, and a decrease in physical functioning. Non-steroidal anti- inflammatory drugs (NSAIDs) and oral disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), are used off-label as early pharmacological therapies for PsA treatment. Currently approved treatments for PsA include corticosteroids, tumor necrosis factor (TNF) blockers (Cimzia, Enbrel, Humira, Remicade, and Simponi), and an interleukin-12/interleukin-23 inhibitor (Stelara). Otezla works differently from current agents, through intracellular inhibition of phosphodiesterase 4 (PDE4).

The American Academy of Dermatology (AAD) PsA treatment guidelines recommend therapy with NSAIDs in mild disease. Failure of NSAID treatment defines moderate disease in which an oral DMARD or TNF inhibitor is recommended. Failure of monotherapy with either of these agents defines severe disease in which combination therapy with oral DMARD and TNF inhibitor is then recommended.

Clinical trials demonstrated effectiveness of Otezla in both DMARD-naïve patients and those experienced or concurrently on DMARD therapy, suggesting that it could be used before DMARDs or in patients who do not respond adequately, or experience side effects to treatment with oral and/or biologic DMARDs. With few adverse effects compared to oral and biologic DMARDs, over time, it may develop a niche for use in early treatment.

EFFICACY

Apremilast was evaluated for the treatment of PsA in four clinical trials termed the PALACE series. PALACE 1, 2, and 3 were structured in a similar manner, with only few differences in inclusion criteria and stratification in the PALACE 3 trial. In PALACE 1, 2, and 3, 1493 adult patients with active PsA (≥ 3

swollen and ≥ 3 tender joints) despite prior or current treatment with DMARD therapy were randomized in a 1:1:1 manner to placebo, apremilast 20 mg twice daily or apremilast 30 mg twice daily. The primary study endpoint of these trials was attainment of an American College of Rheumatology 20% improvement (ACR20) response at 16 weeks. Patients in the placebo group who were non-responders at week 16 were re-randomized to one of the two treatment groups. At week 24, those still receiving placebo were re-randomized to a treatment group and all patients were followed for 52 weeks.

Concomitant use of stable doses of MTX (≤25 mg/week), sulfasalazine (SSZ) (≤2 g/day), leflunomide (LEF) (≤ 20 mg/day), low dose oral corticosteroids (equivalent to ≤ to 10 mg of prednisone/day) and/or NSAIDs was permitted during the trial period. Patients who were therapeutic failures of more than 3 agents for PsA (small molecule or biologics) or more than 1 biologic TNF inhibitor were excluded. Previous treatment with biologics, including TNF-inhibitors, was allowed (up to 10% could be TNF-inhibitor failures). Treatment assignments were stratified based on oral DMARD use at baseline in all three trials with the additional stratification of body surface area (BSA)> 3% with psoriasis in PALACE-3. Furthermore, PALACE-3 had the additional inclusion criteria of having one psoriatic skin lesion of at least 2 cm in diameter.

Patients received concomitant therapy with at least one DMARD (65%), MTX (55%), SSZ (9%) and LEF (7%), low dose oral corticosteroids (14%) and NSAIDs (71%). Prior treatment with oral DMARDs alone was reported in 76% of patient and biologic DMARDs reported in 22% of patients, including 9% who had failed prior biologic DMARD treatment.

PALACE 4 evaluated the safety and efficacy of apremilast 20 mg twice daily and 30 mg twice daily in over 500 DMARD naïve patients with active PsA. Exclusion criteria included patients with prior treatment with conventional DMARDs or biologics. Concurrent treatment with stable doses of oral corticosteroids (≤ 10 mg/day prednisone equivalent), NSAIDs, and narcotic analgesics was permitted. Trial structure was similar to PALACE 1, 2, and 3 with the same primary endpoint of ACR 20 response at week 16. ACR 20 responses for all PALACE trials are listed in the table below.

ACR 20 Response at Week 16			
Study	**Placebo**	**Apremilast 30 mg BID**	**P-Value**
PALACE-1[a]	19%	38%	P<0.001
PALACE-2[a]	19%	32%	P<0.01
PALACE-3[a]	18%	41%	P<0.001
PALACE-4	16%	31%	P<0.001
[a]Concomitant use of stable doses of oral DMARDs was permitted in placebo and treatment groups			

SAFETY

The most common adverse effects (≥ 5%) associated with Otezla are diarrhea, nausea and headache. The majority of adverse reactions occurred within the first two weeks of treatment and tended to resolve over time with continued dosing. The proportion of patients who discontinued treatment due to

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any adverse reaction was 4.6% for patients taking Otezla 30mg twice daily and 1.2% for placebo-treated patients.

Use of Otezla with strong cytochrome P450 enzyme inducers (e.g. rifampin) is not recommended as it may result in a loss of efficacy of Otezla. Otezla was reported to have weight decrease of 5-10% of body weight, thus patients should have their weight monitored regularly. Patients taking Otezla should also be monitored for the emergence or worsening of depression, suicidal thoughts or other mood changes and these symptoms should be reported immediately. Otezla is pregnancy category C.

DOSAGE

Otezla can be administered without regard to meals. Do not crush, split or chew the tablets.
It is recommended that a dose titration is performed when initiating Otezla therapy in order to reduce gastrointestinal side effects. Following a 5-day titration, the recommended maintenance dose is 30 mg twice daily beginning on day 6. The dose titration schedule is listed in the table below.

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & Thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Renal dose adjustments:

- Reduce dose to 30 mg daily if CrCl <30 ml/min
- Titrate using only the AM doses from the schedule listed in the table above

COST

Drug	Cost/unit	Cost per 28 days
Otezla (apremilast) 30 mg tablet, 27 tablet starter pack; 5 day titration followed by 30 mg twice daily	AWP=$37.50	1st 2 weeks:$1013 $2100 maintenance
Humira (adalimumab) 40 mg syringe or pen; 40 mg SC every other week	AWP=$1501.50	$3003
Cimzia (certolizumab pegol) 400 mg/2ml syringe; 200 mg every other week or 400 mg every 4 weeks SC, initially 400 mg at weeks 0, 2 and 4	AWP=$3323	1st month: $9968 $3323 maintenance
Simponi (golimumab) 50 mg/0.5 ml syringe or pen; 50 mg SC once monthly	AWP=$3253	$3253
Remicade (infliximab) 100 mg vial; 5 mg/kg IV every 8 weeks; initially 5 mg/kg given IV at weeks 0, 4, and 6.	AWP=$1061.80	1st 6 weeks: $10618* $3185 (per 56 days)*
Enbrel (etanercept) 50 mg pen or syringe; 50 mg SC every week	AWP=$773.40	$3093
Stelara (ustekinumab) 45 mg syringe;	AWP=$8848.30	1st month: $17696.6 $8848 (per 84 days)

*Based on a 70 kg individual

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FORMULARY PLACEMENT RECOMMENDATIONS

Based on initial clinical assessment, consider NOT ADDING Otezla to formulary to the formulary pending complete review by the appropriate oversight committee for the plan.

REFERENCES

- Otezla (apremilast) [Prescribing Information]. Summit, NJ: Celgene Corporation; March 2014
- National Psoriasis Foundation. Psoriatic Arthritis. http://www.psoriasis.org/psoriatic-arthritis. (accessed 2014 April 3)
- Gottlieb A, Korman NJ et al. Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis. *J Am Acad Dermatol.* 2008;58:851-64