PDL NEW DRUG REVIEW

Proprietary Name: Otezla®
Common Name: apremilast
PDL Category: Biologic Immunomodulators

Comparable Products	Preferred Drug List Status
Enbrel	Preferred with Conditions
Humira	Preferred with Conditions

Summary

Indications and Usage: Treatment of adult patients with active psoriatic arthritis. This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Drug Interactions: Concomitant use of strong CYP450 inducers (such as rifampin) with apremilast may reduce its efficacy. Therefore, the combination of these enzyme inducers (e.g. rifampin, phenobarbital, carbamazepine, and phenytoin) with apremilast is not recommended.

Dosage Forms: Film-coated tablets: 10mg, 20mg, and 30mg

Recommended Dosage: An initial 5-day titration period should initiate therapy (10mg day 1; 10mg BID day 2; 10mg QAM & 20mg QPM day 3; 20mg BID day 4; and 20mg QAM & 30mg QPM day 5). The maintenance dose after the titration period is 30mg PO BID. The titration period is to help reduce the GI symptoms associated with treatment.

Dose adjustments are not required in patients with hepatic impairment. While dose adjustments are not required in those with mild or moderate renal impairment, those with severe renal impairment (Cr Cl <30ml/min) should reduce the dose to 30mg once daily.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug* (*Otezla®*) *minus reported % incidence for placebo.* The most commonly reported adverse events during the 5-day titration period included diarrhea (8.1%), nausea (6%), headache (3%), upper respiratory tract infection (0%), vomiting (0.4%), nasopharyngitis (0%), and upper abdominal pain (0.6%). The most commonly reported adverse events days 6 thru 112 included diarrhea (6.1%), nausea (5.8%), headache (3.7%), upper respiratory tract infection (2.1%), vomiting (2.8%), nasopharyngitis (1%), and upper abdominal pain (1.8%).

There was an increased risk of depression associated with apremilast vs placebo in clinical trials (1% vs 0.8%, respectively). Additionally, 0.3% discontinued treatment during the trials due to depression or depressed mood vs 0% of the placebo group. Serious depression was reported by 0.2% of the apremilast group vs 0% of placebo, with the same rates reporting instances of suicidal ideation and behavior. Therefore, it is recommended to weigh the risks and benefits of use in those with a history of depression and/or suicidal thoughts.

There were reports of weight decrease in clinical trials with apremilast vs placebo (10% vs 3.3%, respectively). As such, it is recommended that weight be monitored regularly during treatment, and if unexplained or clinically significant weight loss occurs, discontinuation of apremilast should be considered.

Contraindications: In those with a known hypersensitivity to apremilast or any component of the compound

Manufacturer: Celegene Corporation

Analysis: Apremilast, the active ingredient of Otezla®, is a phosphodiesterase 4 (PDE4) inhibitor, which is specific for cyclic adenosine monophosphate (cAMP). While the exact mechanism of action of apremilast for the treatment of psoriatic arthritis is not known, inhibition of PDE4 results in increased intracellular cAMP levels.

Three randomized, double-blind, placebo-controlled trials of similar design were undertaken to assess the safety and efficacy of Otezla® for the treatment of patients diagnosed with active psoriatic arthritis for at least 6 months (N=1493). Subjects with previous trials of a biologic, including TNF-blockers, were allowed in the study; however, those with therapeutic failures of >3 agents for psoriatic arthritis (small molecules or biologics) or >1 TNF blocker were excluded. During the trial, stable doses of concomitant oral therapy of methotrexate, sulfasalazine, leflunomide, low dose corticosteroids and/or NSAIDS were allowed. The primary endpoint was the % achieving American College of Rheumatology (ACR) 20 response at week 16. Patients with tender and swollen joint counts who had not improved by ≥20% were considered non-responders.

Results in all 3 studies suggested statistically significant greater improvements in signs/symptoms of psoriatic arthritis (PsA) with Otezla® vs placebo per the ACR 20 response at week 16. The ACR 20 with Otezla® vs placebo was 38% vs 19% ($p<0.05$; **NNT 6**) in Study 1 (PsA-1); 32% vs 19% ($p<0.05$; **NNT 8**) in Study 2 (PsA-2); and 41% vs 18% ($p<0.05$; **NNT 5**) in Study 3 (PsA-3). The ACR 50 at week 16 with Otezla® vs placebo was 16% vs 6% in Study 1; 11% vs 5% in Study 2; and 15% vs 8% in Study 3. These differences were not statistically significant. The ACR 70 at week 16 with Otezla® vs placebo was 4% vs 1% in Study 1; 1% vs 1% in Study 2; and 4% vs 2% in Study 3. These differences were neither clinically or not statistically significant.

Other results from PsA-1 included the mean change in the number of tender joints (-7 vs -2, respectively), the mean change in the number of swollen joints (-5 vs -2, respectively), and the mean change in the patient's assessment of pain (-14 vs -6, respectively). The mean change from baseline for the Health Assessment Questionnaire Disability Index (HAQ-DI) at week 16 was greater with Otezla® vs placebo (-0.244 vs -0.086). The proportion of HAQ-DI responders at week 16 (≥0.3 improvement from baseline) with Otezla® vs placebo was 38% vs 27% (**NNT 10**).

There is no evidence at this time to support that Otezla® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is recommended that Otezla® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Otezla [package insert]. Summit, NJ: Celgene Corporation; 2014.