

# Certolizumab Pegol (CIMZIA) in Psoriatic Arthritis

## National Drug Monograph

April 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

### FDA Approval Information

#### Description/Mechanism of Action

Certolizumab pegol is a PEGylated recombinant, humanized Fc-free antibody Fab' fragment that is specific for human tumor necrosis factor alpha (TNF $\alpha$ ). Lacking an Fc region, certolizumab does not activate antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity, unlike whole antibodies and etanercept.

FDA-approved indications at the time of this monograph review are

- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- Treatment of adults with moderately to severely active rheumatoid arthritis.
- Treatment of adult patients with active psoriatic arthritis.
- Treatment of adults with active ankylosing spondylitis.

#### Indication(s) Under Review in This Document

Treatment of adult patients with active psoriatic arthritis

#### Dosage Form(s) Under Review

For Injection: 200 mg lyophilized powder for reconstitution in a single-use vial, with 1 ml of Sterile Water for Injection

Injection: 200 mg/ml solution in a single-use prefilled syringe

#### REMS

REMS  No REMS  Postmarketing Requirements

See Other Considerations for additional REMS information

#### Pregnancy Rating

Category B

### Executive Summary

#### Efficacy

- The FDA approval of certolizumab for PsA was largely based on results of RA Prevention of structural Damage (RAPID)-PsA, a multicenter, double-blind, placebo-controlled, phase III randomized clinical trial.
- The week-12 clinical response (20% or greater improvement in the American College of Rheumatology score, **ACR20**, the primary efficacy measure) was 58.0%, 51.9% and 24.3% in the CER200, CER400 and placebo groups, respectively (p < 0.001), showing superiority of CER200 and CER400 over placebo.
- Similar to other TNFIs, certolizumab has been shown to be efficacious in terms of all the major outcomes in the treatment of PsA.
- Older TNFIs (pooled, adalimumab, etanercept, golimumab and infliximab) seem to be about twice as likely as certolizumab to achieve ACR20 response at weeks 12–24.

#### Safety

- The safety profile of certolizumab is generally similar to that for other TNFIs.
- Certolizumab carries a boxed warning for serious infections and malignancy.
- Activated partial thromboplastin time (aPTT) may be falsely increased by certolizumab.

#### Other Considerations

- Larger and longer-term studies are needed to adequately assess the risks of chronic certolizumab therapy.

#### Projected Place in

- Studies directly comparing certolizumab with other agents are lacking.

<b>Therapy</b>	<ul style="list-style-type: none"> <li>Although it differs structurally and mechanistically from the TNF-inhibiting whole monoclonal antibodies and the fusion protein etanercept, certolizumab does not seem to provide any clear clinical advantages over the older TNFIs.</li> </ul>
----------------	---

**Background**

**Purpose for Review**

To review the comparative safety and efficacy of certolizumab in psoriatic arthritis (PsA) to inform an update to the VA PBM-MAP-VPE [Criteria for Use of Biologics in Psoriasis and Psoriatic Arthritis](#).  
Previously reviewed for rheumatoid arthritis and Crohn’s disease (2010).

- Issues to be determined:
- ✓ Does certolizumab offer efficacy advantages over available alternatives?
  - ✓ Does certolizumab offer safety advantages over available alternatives?
  - ✓ Does certolizumab provide advantages in subgroups of patients?

**Other Therapeutic Options**

Other therapeutic options including biologic DMARDs (bDMARDs) at approximately the same line of therapy as certolizumab are shown in the tables below.

Formulary Alternatives	Other Considerations	Clinical Guidance
None		
Nonformulary Alternatives	Other Considerations	Clinical Guidance
<i>Tumor Necrosis Factor Inhibitors</i>	Effectiveness is established in PsA.	<a href="#">PBM Criteria for Use</a> in psoriasis and PsA are available.
Adalimumab	Administered subcutaneously except	
Etanercept	infliximab is given	
Golimumab	intravenously.	
Infliximab		
<i>Phosphodiesterase-4 Inhibitor</i>	Orally administered. Disease-modifying capability is uncertain.	Place in therapy is unclear. <a href="#">PBM Criteria for Use</a> in psoriasis and PsA are available.
Apremilast		
<i>Anti-IL-12/23 Monoclonal Antibody</i>	Administered subcutaneously. Every-12-week maintenance dosing. Inhibits radiographic progression. Lacks cytopenias and TNFI-related complications and contraindications.	
Ustekinumab		
<i>Anti-IL-17A Monoclonal Antibody</i>	Approved for PsA in 1/2016. Administered subcutaneously. Inhibits radiographic progression. <sup>34</sup>	
Secukinumab		

**Efficacy (FDA Approved Indications)**

**Literature Search Summary**

A literature search was performed on PubMed/Medline (1966 to 2 March 2016) using the search terms *certolizumab*, *CIMZIA*, “*Arthritis, Psoriatic*” and *RAPID-PsA*. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer’s AMCP dossier were searched for relevant clinical trials. No FDA Medical Review(s) for the psoriatic arthritis indication was found.

## Review of Efficacy

### Major Efficacy-Safety Trial: RAPID-PsA

The FDA approval of certolizumab for PsA was largely based on results of RA Prevention of structural Damage (RAPID)-PsA, a multicenter, double-blind, placebo-controlled, phase III randomized clinical trial (RCT) involving 409 adult patients with a CASPAR diagnosis of PsA for at least 6 months and active joint disease.<sup>1</sup> Study patients had to have failed  $\geq 1$  disease-modifying antirheumatic drug (DMARD). Prior treatment with up to two biologics or up to one TNFI was allowed. During the 24-week double-blind phase of the trial, patients were randomized to either subcutaneously administered placebo (N = 136) or certolizumab 200 mg every 2 weeks (CER200, N = 138) or certolizumab 400 mg every 4 weeks (CER400, N = 135). Both certolizumab groups initiated therapy with a loading dose consisting of 400 mg at weeks 0, 2 and 4. At week 16, 59 patients not meeting predefined minimal response at weeks 14 and 16 were allowed to escape from the placebo arm to blinded, randomized active treatment with either CER200 or CER400 (following loading doses at weeks 16, 18 and 20). The study continued as a blinded dose-controlled study with randomization of the remaining placebo-treated patients at week 24 to either CER200 or CER400 (including loading doses) and continued to week 48. Thereafter, the trial was open-label with all patients continuing their same dose of CER to week 216. Unlike with other TNFI trials, randomization included stratification by prior TNFI exposure, allowing prospective subgroup comparisons, although patients who had primary TNFI failure were excluded from the trial.

Continuation of existing csDMARD therapy with methotrexate, sulfasalazine or leflunomide at stable doses was allowed, as was treatment with stable doses of oral glucocorticoids (up to 10 mg/day prednisone equivalent). The study population had a mean age of about 48 years, 55.2% of patients were male, 98% were white, 64.3% had enthesitis, 26.4% had confirmed dactylitis and 61.6% had at least 3% body surface area skin involvement. Of the total 273 certolizumab-treated patients, 54 (19.8%) had received prior TNFI therapy. Discontinuations of prior TNF inhibitor were due to clinical events (secondary failure, adverse reactions), and nonclinical reasons (such as financial and supply problems).

- The week-12 clinical response (20% or greater improvement in the American College of Rheumatology score, **ACR20**, the primary efficacy measure) was 58.0%, 51.9% and 24.3% in the CER200, CER400 and placebo groups, respectively ( $p < 0.001$ ), showing superiority of CER200 and CER400 over placebo (Table 1).<sup>1</sup> Corresponding NNTs were 3 and 4 for CER200 and CER400, respectively.

**Table 1 Response Rates in RAPID-PsA Trial**

Response Measure	CER200 N = 138		CER400 N = 135		PBO N = 136	
	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24
ACR20, %	58.0	63.8	51.9	56.3	24.3	23.5
ACR50, %	36.2	44.2	32.6	40.0	11.0	12.5
ACR70, %	24.6	28.3	12.3	23.7	2.9	4.4

P-values  $\leq 0.016$  for all comparisons vs. placebo

- Statistically and clinically significant treatment differences in ACR20 response were seen as early as week 1 and continued to week 24 (60%)<sup>1,2</sup> and week 96 (64%),<sup>2</sup> and were similar in patients with or without prior TNFI exposure.<sup>1,2</sup> Treatment differences were also seen in ACR50 and ACR70 responder rates from week 4 to 24.<sup>1</sup>
- Based on week 24 results, certolizumab (combined groups) was also efficacious relative to placebo in terms of **physical function (HAQ-DI -0.50 vs. -0.19;  $p < 0.001$ )**. CER200 and CER400 were superior to placebo also in terms of **psoriasis area and severity index (PASI75) response (62.2%, 60.5% versus 15.1%, respectively;  $p < 0.001$ )**, **psoriatic arthritis response criteria (PsARC) (78.3%, 77.0% versus 33.1%;  $p < 0.001$ )**, and **minimal disease activity (MDA) response (33.3%, 34.1% versus 5.9%; post hoc analysis,  $p < 0.001$ )**.<sup>1</sup>
- The presence or absence of concomitant DMARD therapy did not seem to affect ACR20 or PsARC response to treatment at Week 12 or 24.<sup>1</sup> ACR20 responses at Weeks 12 and 24 showed superiority of CER200 and CER400 over placebo regardless of prior TNFI exposure.
- Effects on ACR20 response, mean HAQ-DI scores and PASI scores persisted to Week 96 (poster presentations).<sup>3,4,5</sup> Over 40% of patients with baseline psoriasis affecting  $\geq 3\%$  body surface area achieved **complete clearance** at Week 24, and PASI scores of 0 were achieved at Week 96 by 53.5% (lower extremities) to 78.7% (head) of patients, depending on the body part affected.<sup>3</sup>

- In 262 patients (64.3%) with **enthesitis** at baseline, the mean change from baseline to week 24 in the Leeds Enthesitis Index (LEI; range 0–6) was –2.0 on CER200 ( $p < 0.001$ ) and –1.8 on CER400 ( $p = 0.003$ ) versus –1.1 on placebo.<sup>1</sup> Poster presentations reported longer-term results. Mean LEI scores gradually improved from Week 24 to Week 96 regardless of prior TNFI exposure, with about 71% of 172 certolizumab-treated patients who had baseline involvement achieving an LEI of 0 (zero) at Week 96.<sup>5,6</sup>
- In 108 patients (26.4%) with baseline **dactylitis**, the mean change from baseline to week 24 in the Leeds Dactylitis Index (LDI) was –40.7 on CER200 ( $p = 0.002$ ) and –53.5 ( $p < 0.001$ ) on CER400 versus –22.0 on placebo.<sup>1</sup> Mean LDI scores improved from Week 24 (7.34 and 0.82 in patients with and without prior TNFI exposure, respectively) to scores of 0.0 in both subgroups at Week 96 (results presented as poster presentations).<sup>5,6</sup> Of certolizumab-treated patients with baseline dactylitis and prior TNFI exposure ( $n = 17$ ), the percentage of patients who had an LDI score of 0 was 81.3% at Week 24 and 81.8% at Week 96.<sup>6</sup> For certolizumab-treated patients without prior TNFI exposure ( $n = 56$ ), the corresponding percentages were 71.4% and 91.3%.
- Of the 299 patients (73.3%) with baseline **nail disease**, the mean change from baseline to week 24 in the Modified Nail Psoriasis Severity Index (mNAPSI; range 0–13) was –1.6 on CER200 ( $P = 0.003$ ) and –2.0 on CER 400 ( $p < 0.001$ ) versus –1.1 on placebo.<sup>1</sup> Mean mNAPSI scores improved from Week 24 to Week 96 regardless of prior TNFI exposure (poster presentations).<sup>6,5</sup> Of 38 patients with baseline nail disease and prior TNFI exposure, 38.0% and 65.1% had mNAPSI scores of 0 (zero) at Week 24 and Week 96, respectively.<sup>6</sup> Of 159 patients without prior TNFI exposure, 40.5% and 65.1% had mNAPSI scores of 0 at Week 24 and Week 96, respectively.<sup>6</sup>
- Analyses of kinetics curves suggested no clinically important differences between CER200 and CER400, although the study was not designed to evaluate equivalence between the two dosing regimens.<sup>1</sup>
- Assessment of **radiographic progression** was affected by the imputation method used to account for missing values.<sup>7</sup> Using the prespecified imputation method, the authors found an unrealistic measure of progression in all treatment arms based on van der Heijde modified Total Sharp Scores (mTSSs). Four of five treatment differences in post hoc imputation analyses reached nominal  $p$ -values  $< 0.05$ , suggesting that certolizumab (combined dosage groups) may be efficacious relative to placebo in inhibiting radiographic progression. CER200 was significantly better than placebo, whereas CER400 was no better than placebo in inhibiting radiographic progression as measured by mean mTSS at Week 24. More CER200 patients (83.3%) and CER400 patients (76.3%) than placebo patients (34.6%;  $p < 0.001$ ) achieved nonprogression, predefined as a change in mTSS of  $\leq 0$  from baseline to week 24. Significant treatment differences were also seen when analyses used a post hoc nonprogression definition of  $\leq 0.5$  mTSS change from baseline. Patients with high mTSS ( $> 6$ ) and C-reactive protein levels ( $> 15$  mg/dl) at baseline seemed to achieve greater inhibition of radiologic progression than those with lower values.
- Certolizumab was significantly better than placebo ( $p < 0.05$ ) in improving **SF-36, Psoriatic Arthritis Quality of Life (PsAQOL), Fatigue Assessment Scale, pain visual analog scale (VAS), and Dermatology Life Quality Index (DLQI)** scores, regardless of prior TNFI exposure.<sup>8</sup> There was poor correlation between patient-reported outcomes (PROs) and clinical outcomes with certolizumab in PsA. According to the authors, other TNFI studies have shown moderate correlations between PROs and clinical outcomes.
- Significant improvements in **job and household productivity** as well as engagement in **social activities** occurred in certolizumab-treated patients relative to placebo patients.<sup>9</sup> The beneficial effects on work productivity persisted to Week 96 (poster presentation).<sup>10</sup>

#### *Certolizumab Versus Other Agents in PsA*

Similar to other TNFIs, certolizumab has been shown to be efficacious in terms of all the major outcomes in the treatment of PsA.<sup>11,12</sup> A meta-analysis of 12 placebo-controlled RCTs indirectly compared bDMARDs and small-molecule agents in patients with active PsA who had experienced an inadequate response or intolerance to csDMARDs or NSAIDs ( $N = 1989$  active treatment,  $N = 1175$  placebo;  $K = 1$ ,  $N = 409$  for certolizumab).<sup>13</sup>

- Older TNFIs (pooled, adalimumab, etanercept, golimumab and infliximab) seemed to be about twice as likely as certolizumab to achieve ACR20 response at weeks 12–24 (Table 2).

**Table 2 Indirect Comparisons by ACR20 Response Rate**

Indirect Treatment Comparison	RR	95% CI	P-value
Older TNFIs / Certolizumab	2.20	1.48–3.26	< 0.001
Certolizumab / Apremilast 20 mg	1.53	0.88–1.53	NSD
Certolizumab / Apremilast 30 mg	1.10	0.66–1.82	NSD
Certolizumab / Ustekinumab 45 mg	1.08	0.71–1.64	NSD
Certolizumab / Ustekinumab 90 mg	0.95	0.63–1.44	NSD
Certolizumab / Secukinumab 75 mg	0.86	0.42–1.79	NSD
Certolizumab / Secukinumab 150 mg	0.50	0.25–1.00	0.05
Certolizumab / Secukinumab 300 mg	0.55	0.28–1.09	0.08

Source: Ref 13

- Individual TNFIs were also more likely to achieve ACR20 response than certolizumab with the exception of adalimumab, which showed no significant difference in indirect comparisons (RR 1.7, 95% CI 0.94–3.09; NSD).
- Certolizumab was about half as likely to achieve ACR20 response as secukinumab (150 and 300 mg); however, the difference did not reach the level of statistical significance.
- Overall, results of all included studies showed moderate heterogeneity. It is uncertain whether the study populations for certolizumab and the older TNFIs were comparable.

*Comparative Summary of Pharmacologic Treatments for Specific Conditions in PsA*

Work groups of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have performed a series of systematic reviews of the literature to update treatment guidelines for PsA. For each of the specific conditions, two or more TNFIs showed efficacy and may be used as alternative therapies. The systematic review of treatments for psoriasis in PsA<sup>14</sup> was largely based on the approved indications for agents and is not summarized here.

Peripheral Arthritis<sup>15</sup>

- In a systematic review of RCTs and observational studies, indirect comparisons of treatments relative to placebo suggested that certolizumab, abatacept, adalimumab, etanercept, golimumab and infliximab had comparable NNTs for ACR20 at 24 weeks (Table 3).

**Table 3 Number Needed to Treat for ACR20**

Time Point, wk	Intervention, mean dose, mg	ACR20 NNT	
12	ADA 40 qowk	5	
12	APR 20 bid	4	
12	APR 40 qd	5	Source: Ref 15
12	UST 90 qwk	4	ABT, Abatacept;
16	INF 5 / kg	2	ADA, Adalimumab;
24	ABT 10 mg/kg	4	APR, Apremilast;
24	ADA 40 qowk	3	CER, Certolizumab;
24	CER 200 q2wk	3	ETA, Etanercept;
24	ETA 25 biwk	3	GOL, Golimumab;
24	GOL 50 qmo	3	INF, Infliximab;
24	INF 5 / kg	3	UST, Ustekinumab

Dactylitis<sup>16</sup>

- According to a systematic review of 29 open-label observational studies or RCTs that evaluated treatments for PsA and reported dactylitis as an outcome measure (N = 6589), certolizumab is one of only three or four agents shown to be efficacious for dactylitis.
- When calculable, the effect size relative to placebo for mean change in dactylitis score from baseline was 0.50 (moderate) at 24 weeks with certolizumab (1 RCT), 0.41 (moderate) at 16 weeks with infliximab (1 RCT) and 0.29 (small) at 24 weeks with ustekinumab (2 RCTs),.

- Golimumab also showed efficacy in two Phase II trials. Open-label observational studies have suggested potential benefit with adalimumab, but 3 RCTs failed to show efficacy with this agent. Etanercept improved dactylitis from baseline but needs to be evaluated in controlled trials. Apremilast produced no significant benefit in RCTs. (Apremilast was associated with 100% median reduction in dactylitis counts only after 52 weeks of therapy in a study without a placebo control.<sup>17</sup>) The effects of anakinra on dactylitis remain unclear.

#### Enthesitis<sup>18</sup>

- High-quality data from RCTs showed that the TNFIs certolizumab, golimumab and infliximab and the non-TNFIs apremilast (30 mg twice daily) and ustekinumab significantly improve enthesitis. Adalimumab showed no significant differences from placebo in exploratory analyses (with inadequate sample size) of two RCTs and has not been adequately studied. With etanercept, 70% and 80% of patients experienced improvements in enthesitis scores from baseline to 12 and 24 weeks, respectively; however, the study had no placebo control.
- Effect sizes, based on different enthesitis measures, were moderate for golimumab at 14–24 weeks and certolizumab at 24 weeks, and small for ustekinumab and apremilast at 24 weeks. NNTs for infliximab were 5.9 to 8.3 over 14 to 24 weeks, reflecting small effect sizes. Only the certolizumab trial used an enthesitis measure (the Leeds Enthesitis Index, LEI) that has been validated in PsA.
- Based on the TNFI data and the central involvement of TNF in the pathophysiology of enthesial inflammation, the authors concluded that TNFIs *as a class* are effective for enthesitis.
- Sulfasalazine was ineffective and glucocorticoid injections were associated with worse outcomes.

#### Psoriatic Nail<sup>19</sup>

- Adalimumab, certolizumab, etanercept, golimumab, infliximab and ustekinumab have the best evidence of efficacy for psoriatic nail from RCTs involving patients with psoriasis and observational studies involving patients with psoriasis or psoriatic arthritis.
- Of the topical therapies, calcipotriol with or without betamethasone dipropionate has limited evidence showing modest efficacy in mild cases of psoriatic nail (< 2 nails) when treatment is given for ≥ 12 weeks. Tacrolimus and tazarotene have also been shown to have modest efficacy, whereas 5-fluorouracil was ineffective.
- Of the conventional synthetic therapies, methotrexate showed no benefit over placebo in one RCT and was inferior to briakinumab (investigational IL 12/23 inhibitor) in another RCT. Cyclosporine was not significantly different from methotrexate. The systematic review found no placebo-controlled trials evaluating cyclosporine.

#### Axial Disease<sup>20</sup>

- No treatments for axial disease in PsA have been specifically studied. Treatments effective for ankylosing spondylitis have been assumed to be effective for axial PsA.
- High-quality data from ankylosing spondylitis, psoriasis and PsA trials have shown that adalimumab, certolizumab, etanercept, golimumab and infliximab significantly improve disease activity, range of motion, physical function, and quality of life as well as inhibit radiologic progression.
- Ustekinumab has been shown to significantly improve axial disease activity (BASDAI) responder rates, physical function, and quality of life – physical function, and significantly inhibit radiologic progression in PSUMMIT 1 and 2.<sup>21,21</sup> Spinal mobility (Bath Ankylosing Spondylitis Metrology Index, BASMI) was not assessed.

To summarize, in inconclusive indirect comparisons certolizumab shows efficacy similar to that of other TNFIs for the treatment of peripheral arthritis, dactylitis, enthesitis, nail psoriasis and axial disease. Certolizumab has also been shown to be efficacious for psoriatic skin manifestations associated with PsA but lacks an FDA-approved indication for plaque psoriasis at the time of this monograph review.

#### Potential Off-Label Use

- Plaque psoriasis – A Phase II placebo-controlled RCT showed that certolizumab significantly improved psoriasis outcome measures in the treatment of 176 patients with moderate to severe plaque psoriasis.<sup>22</sup> Several ongoing studies listed at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) are evaluating the efficacy and safety of certolizumab in plaque psoriasis.
- Ulcerative colitis – No published studies were found. An open-label observational study evaluated certolizumab in 10 patients with ulcerative colitis (abstract).<sup>23</sup>

- Axial spondyloarthritis (AxSpA) – An ongoing Phase III, double-blind, placebo-controlled trial evaluated certolizumab in 325 patients with adult-onset active AxSpA.<sup>24</sup> Data from 178 of these patients supported FDA approval of certolizumab for the treatment of adults with active ankylosing spondylitis.

**Safety**

The safety profile of certolizumab is generally similar to that for other TNFIs. For more detailed information, refer to the prescribing information.

<b>Boxed Warning</b>	<p><b>SERIOUS INFECTIONS AND MALIGNANCY</b></p> <ul style="list-style-type: none"> <li>• Increased risk of serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.</li> <li>• Certolizumab should be discontinued if a patient develops a serious infection or sepsis.</li> <li>• Perform test for latent TB; if positive, start treatment for TB prior to starting certolizumab.</li> <li>• Monitor all patients for active TB during treatment, even if initial latent TB test is negative.</li> <li>• Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which certolizumab is a member.</li> </ul>
<b>Contraindications</b>	<ul style="list-style-type: none"> <li>• None</li> </ul>
<b>Warnings / Precautions</b>	<ul style="list-style-type: none"> <li>• Serious infections including tuberculosis – do not start certolizumab during an active infection; stop certolizumab if infection becomes serious.</li> <li>• Invasive fungal infections – consider empiric antifungal therapy for patients living in endemic areas who develop systemic illness during therapy.</li> <li>• Lymphoma and other malignancies</li> <li>• Heart failure</li> <li>• Anaphylaxis or serious allergic reactions</li> <li>• Hepatitis B virus reactivation – test for HBV infection before starting certolizumab; monitor HBV carriers and if reactivation occurs stop certolizumab and begin antiviral therapy.</li> <li>• Demyelinating disease</li> <li>• Cytopenias, pancytopenia – educate patients; consider stopping certolizumab</li> <li>• Lupus-like syndrome – stop certolizumab if syndrome develops.</li> <li>• Immunizations – avoid live or live attenuated vaccines</li> <li>• Immunosuppression</li> </ul>
<b>Adverse Reactions</b>	
<b>Common Adverse Reactions</b>	Upper respiratory tract infection, headache, hypertension, nasopharyngitis, back pain, pyrexia, pharyngitis, rash, acute bronchitis, fatigue
<b>Deaths / Serious Adverse Reactions</b>	No deaths were deemed to be related to certolizumab. SAEs: 6%, 10% and 4% for CER200, CER400 and placebo in RAPID-PsA. <sup>24</sup> Most Serious Adverse Reactions – serious infections, malignancies, heart failure
<b>Discontinuations Due to Adverse Reactions</b>	2.9%, 5.2% and 1.5% for CER200, CER400 and placebo in RAPID-PsA.

**Drug Interactions**

**Drug-Drug Interactions**

- Anakinra, Abatacept, Rituximab, Natalizumab – concurrent use not recommended
- Live Vaccines – avoid concurrent use

**Drug-Food Interactions**

- None

**Drug-Lab Interactions**

- Activated Partial Thromboplastin Time (aPTT) – may be falsely increased by certolizumab

**Risk Evaluation**

As of 1 March 2016

**Sentinel Event Advisories**

- None
- Sources: ISMP, FDA, TJC

**Look-alike / Sound-alike Error Potential**

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Certolizumab Pegol 200mg syringe	None	None	None	Cetuximab Ceritinib*
CIMZIA	CYRAMZA*	None	None	CINRYZE CYMBALTA*

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List). \* Indicates new LASA names since last review in 2010.

**Other Considerations**

**Comparative Risks of Infection and Malignancy Among TNFIs**

- In one systematic review of 20 RCTs (N = 6810), there was no increased risk of overall infection, serious infection or cancer with short-term TNFI use for psoriasis or PsA.<sup>25</sup> Confidence intervals for odds ratios of infection overlapped among the different TNFIs (adalimumab, certolizumab, etanercept, golimumab and infliximab), although there was only one unpublished study and wider confidence intervals for certolizumab. Larger and longer-term studies are needed to adequately assess the risks of chronic certolizumab therapy.

**Dosing and Administration**

- The recommended dose for adult patients with psoriatic arthritis is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at week 2 and 4, followed by 200 mg every other week.
- For maintenance dosing, 400 mg every 4 weeks can be considered.

**Special Populations (Adults)**

**Elderly**

- Clinical trials did not provide sufficient data.
- Other reported clinical experience have not identified differences in response between elderly and young patients.
- Population pharmacokinetic studies showed no age-related difference in drug concentration.
- Use caution.

**Pregnancy**

- Category B – no adequate and well-controlled studies in pregnant women.
- Data from 10 pregnant women suggested low placental transfer of certolizumab.
- An observational evaluation of 372 cases with known pregnancy outcomes after exposure to certolizumab (identified in the UCB

	Pharma safety database) suggested that maternal exposure to certolizumab seems to lack harmful effects on pregnancy outcomes. <sup>26</sup>
<b>Lactation</b>	• Whether certolizumab is excreted into human milk is unknown.
<b>Renal Impairment</b>	• No data
<b>Hepatic Impairment</b>	• No data
<b>Pharmacogenetics/genomics</b>	• Polymorphisms of –308 G/A and –238 G/A on TNF gene promoter region – controversial role in predicting response to TNFI therapy in rheumatoid arthritis. <sup>27</sup>

### Projected Place in Therapy

- PsA is a chronic, progressive, inflammatory, oligoarticular, autoimmune spondyloarthropathy that affects approximately 1% of adults in the US.<sup>28</sup> In addition to peripheral and axial synovitis, manifestations of PsA may include enthesitis, dactylitis, anterior uveitis, iritis and skin and nail involvement. Inflammatory bowel disease–like gastrointestinal symptoms may also occur. Patients with the comorbidity of PsA and psoriasis are more likely to report that the condition affects their job and that they are unemployed, relative to those with psoriasis alone.<sup>29</sup>
- The optimal treatment approach to PsA was evaluated in the Tight Control of Psoriatic Arthritis (TICOPA) study. It showed that tight control aimed at achieving minimal disease activity (i.e., treat to target) produced better joint and skin outcomes but a higher risk of adverse effects than standard therapy.<sup>30</sup>
- The selection of therapy for PsA should take into consideration the predominant features of the disease and response to prior therapies.
  - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA; 2015) *strongly recommends* TNFIs for (1) peripheral arthritis in patients naïve to csDMARDs, inadequate responders to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and inadequate responders to biologic therapy (e.g., other TNFI, IL-12/23 inhibitor, IL-17 inhibitor); (2) axial PsA in patients naïve to biologics; and (3) patients with enthesitis, dactylitis (specifically, infliximab, adalimumab, golimumab and certolizumab), plaque psoriasis, or nail psoriasis.<sup>31</sup> The csDMARDs may be used first in many cases; however, in patients with poor prognostic factors (e.g., increased levels of inflammatory markers, high active joint counts), early escalation of therapy should be considered. The guidance *conditionally recommends* (1) TNFIs for axial PsA in inadequate responders to biologic therapy and (2) etanercept for dactylitis. CsDMARDs such as methotrexate, sulfasalazine and leflunomide are *strongly recommended* for peripheral arthritis in csDMARD-naïve patients and for plaque psoriasis. GRAPPA 2015 *strongly recommends* the use of nonsteroidal antiinflammatory drugs (NSAIDs) for axial PsA in biologic-naïve patients and *conditionally recommends* NSAIDs for other predominant symptoms including peripheral arthritis in csDMARD-naïve patients, inadequate responders to csDMARDs, or biologic inadequate responders.
  - The European League Against Rheumatism (EULAR) Recommendations for the Management of Psoriatic Arthritis with Pharmacologic Therapies, 2015 Update suggests that TNFIs would usually be the first bDMARDs of choice.<sup>32</sup>
  - UpToDate suggests the use of TNFIs for inadequate responders to 3 months of therapy with one csDMARD, typically methotrexate (two csDMARDs if leflunomide is required by the funding agency), and the csDMARD may be discontinued in TNFI responders.<sup>33</sup> Patients who do not respond to two different TNFIs or who have contraindications to TNFIs may receive a trial of ustekinumab or secukinumab.
- Studies directly comparing certolizumab with other agents are lacking. The quality of evidence is moderate (based on a single well-designed trial) for the efficacy and short-term safety of certolizumab. Results of the long-term (up to 4.5 years) phase of the RAPID-PsA trial have been only partially published to date.
- In summary, certolizumab was the fifth TNFI marketed in the US. Although it differs structurally and mechanistically from the TNF-inhibiting whole monoclonal antibodies and the fusion protein etanercept, certolizumab is similar in efficacy and safety and does not seem to provide any clear clinical advantages relative to the older TNFIs. Certolizumab is offered at a competitive VA drug acquisition price.

## References

- <sup>1</sup> Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis*. 2014 Jan;73(1):48-55
- <sup>2</sup> Mease P, Deodhar A, Fleischmann R, Wollenhaupt J, Gladman D, Leszczyński P, Vitek P, Turkiewicz A, Khraishi M, FitzGerald O, Landewé R, de Longueville M, Hoepken B, Peterson L, van der Heijde D. Effect of certolizumab pegol over 96 weeks in patients with psoriatic arthritis with and without prior antitumour necrosis factor exposure. *RMD Open*. 2015 Jun 25;1(1):e000119
- <sup>3</sup> Gottlieb AB, Hoepken B, Peterson L, Taylor P. Associations between Skin Outcomes by Body Area Affected and Health-related Quality of Life in Patients with Psoriatic Arthritis Treated with Certolizumab. Poster presented at the American College of Rheumatology Annual Meeting 2015, San Francisco, CA.
- <sup>4</sup> Khraishi M, Hoepken B, Davies O, Arledge T, Peterson L, Mease PJ. Sustained improvements in Skin Outcomes Following Certolizumab Pegol Treatment of Psoriatic Arthritis Patients with Prior Anti-TNF Exposure or Severe Skin Involvement at Baseline. Poster presented at the EULAR Congress, Rome, Italy, 10–13 June 2015.
- <sup>5</sup> FitzGerald O, Fleischmann R, Hoepken B, Peterson L, Gladman D. Improvements in Extra-articular Manifestations of Psoriatic Arthritis over 96 Weeks of Certolizumab Pegol Treatment. Poster presented at the EULAR Congress, Rome, Italy, 10–13 June 2015.
- <sup>6</sup> Gladman D, Gottlieb AB, Hoepken B, Peterson L, FitzGerald O. Long-term Improvements with Certolizumab Pegol in Joints and Extra-articular Manifestations of Psoriatic Arthritis in Patients with and without Prior Anti-TNF Exposure. Poster presented at the American College of Rheumatology Annual Meeting 2015, San Francisco, CA.
- <sup>7</sup> van der Heijde D, Fleischmann R, Wollenhaupt J, Deodhar A, Kielar D, Woltering F, Stach C, Hoepken B, Arledge T, Mease PJ. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. *Ann Rheum Dis*. 2014 Jan;73(1):233-7
- <sup>8</sup> Gladman D, Fleischmann R, Coteur G, Woltering F, Mease PJ. Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. *Arthritis Care Res (Hoboken)*. 2014 Jul;66(7):1085-92
- <sup>9</sup> Kavanaugh A, Gladman D, van der Heijde D, Purcaru O, Mease P. Improvements in productivity at paid work and within the household, and increased participation in daily activities after 24 weeks of certolizumab pegol treatment of patients with psoriatic arthritis: results of a phase 3 double-blind randomised placebo-controlled study. *Ann Rheum Dis*. 2015 Jan;74(1):44-51
- <sup>10</sup> Kavanaugh A, Gladman D, van der Heijde D, Purcaru O, Mease PJ. Sustained Improvements in Workplace and Household Productivity and Social Participation with Certolizumab Pegol over 96 Weeks in Patients with Psoriatic Arthritis. Poster presented at the American College of Rheumatology Annual Meeting 2014, Boston, MA, 14–19 November 2014.
- <sup>11</sup> Elyoussfi S, Thomas BJ, Ciurtin C. Tailored treatment options for patients with psoriatic arthritis and psoriasis: review of established and new biologic and small molecule therapies. *Rheumatol Int*. 2016 Feb 18. [Epub ahead of print]
- <sup>12</sup> Ramiro S, Smolen JS, Landewé R, van der Heijde D, Dougados M, Emery P, de Wit M, Cutolo M, Oliver S, Gossec L. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis*. 2016 Mar;75(3):490-8
- <sup>13</sup> Ungprasert P, Thongprayoon C, Davis JM 3rd. Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: A meta-analysis. *Semin Arthritis Rheum*. 2016 Feb;45(4):428-38
- <sup>14</sup> Boehncke W-H, Alvarez Martinez D, Solomon JA, Gottlieb AB. Safety and efficacy of therapies for skin symptoms of psoriasis in patients with psoriatic arthritis: A systematic review. *J Rheumatol* 2014;41:2301-5.
- <sup>15</sup> Acosta Felquer ML, Coates LC, Soriano ER, Ranza R, Espinoza LR, Helliwell PS, FitzGerald O, McHugh N, Roussou E, Mease PJ. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. *J Rheumatol*. 2014 Nov;41(11):2277-85
- <sup>16</sup> Rose S, Toloza S, Bautista-Molano W, Helliwell PS; GRAPPA Dactylitis Study Group. Comprehensive treatment of dactylitis in psoriatic arthritis. *J Rheumatol*. 2014 Nov;41(11):2295-300
- <sup>17</sup> Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, Hochfeld M, Teng LL, Schett G, Lespessailles E, Hall S. Longterm (52-week) Results of a Phase III Randomized, Controlled Trial of

- 
- Apremilast in Patients with Psoriatic Arthritis. *J Rheumatol*. 2015 Jan 15 pii: jrheum.140647. [Epub ahead of print] PubMed PMID: 25593233
- 18 Orbai AM, Weitz J, Siegel EL, Siebert S, Savage LJ, Aydin SZ, Luime JJ, Elkayam O, Neerinckx B, Urbancek S, de Vlam K, Ritchlin CT; GRAPPA Enthesitis Working Group. Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. *J Rheumatol*. 2014 Nov;41(11):2290-4
- 19 Armstrong AW, Tuong W, Love TJ, Carneiro S, Grynspan R, Lee SS, Kavanaugh A. Treatments for nail psoriasis: a systematic review by the GRAPPA Nail Psoriasis Work Group. *J Rheumatol*. 2014 Nov;41(11):2306-14
- 20 Nash P, Lubrano E, Cauli A, Taylor WJ, Olivieri I, Gladman DD. Updated guidelines for the management of axial disease in psoriatic arthritis. *J Rheumatol*. 2014 Nov;41(11):2286-9
- 21 Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, Wang Y, Shen YK, Doyle MK, Mendelsohn AM, Gottlieb AB; PSUMMIT 2 Study Group. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis*. 2014 Jun;73(6):990-9
- 22 Reich K, Ortonne JP, Gottlieb AB et al. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: results of a phase II randomised, placebo-controlled trial with a re-treatment extension. *Br J Dermatol*. 2012;167:180-190.
- 23 Lee SD, Osterman MT, Parrott SC, Wheat CL. Assessment of the efficacy and safety of certolizumab pegol for the treatment of moderate to severe ulcerative colitis [Abstract]. Presented at: Digestive Disease Week (DDW) 2012, May 19-22, 2012. 326. San Diego, CA.
- 24 AMCP Dossier for CIMZIA (Certolizumab Pegol). UCB, Inc., Smyrna, GA, 2013.
- 25 Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. *J Am Acad Dermatol*. 2011 Jun;64(6):1035-50
- 26 Clowse MEB, Wolf DC, Förger F, Cush JJ, Golembesky A, et al. Pregnancy Outcome in Subjects Exposed to Certolizumab Pegol. *J Rheumatol* 2015;42:2270–2278.
- 27 Cuchacovich M, Bueno D, Carvajal R, Bravo N, Aguillón JC, Catalán D, Soto L. Clinical parameters and biomarkers for anti-TNF treatment prognosis in rheumatoid arthritis patients. *Clin Rheumatol*. 2014 Dec;33(12):1707-14
- 28 Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005;64(2 Suppl): ii14-17
- 29 Ciocon DH, Horn EJ, Kimball AB. Quality of life and treatment satisfaction among patients with psoriasis and psoriatic arthritis and patients with psoriasis only : results of the 2005 Spring US National Psoriasis Foundation Survey. *Am J Clin Dermatol*. 2008;9(2):111-7
- 30 Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, Meads DM, Emery P, Conaghan PG, Helliwell PS. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet*. 2015 Dec 19;386(10012):2489-98
- 31 Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta Felquer M, et al. Group for research and assessment of psoriasis and psoriatic arthritis: Treatment recommendations for psoriatic arthritis 2015. *Arthritis Rheumatol*. 2016 Jan 8. doi:10.1002/art.39573. [Epub ahead of print]
- 32 Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis*. 2015 Dec 7. pii: annrheumdis-2015-208337. doi:10.1136/annrheumdis-2015-208337. [Epub ahead of print]
- 33 Gladman DD and Richlin C. Treatment of psoriatic arthritis. In: UpToDate, Sieper J, Romain PL (Eds), UpToDate, Waltham, MA. (Accessed on 3 February 2016.)
- 

Prepared April 2016. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager – Formulary, Pharmacy Benefits Management Services (10P4P)

---

**Appendix A: GRADEing the Evidence**

<b>Quality of Evidence</b>	<b>Description</b>
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.