



Northern Treatment
Advisory Group

Certolizumab pegol for the treatment of psoriatic arthritis

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Summary

- Certolizumab pegol (Cimzia[®], UCB Pharma) is a biologic drug which acts as an inhibitor of TNF. It is licensed, in combination with methotrexate, for the treatment of psoriatic arthritis in adults who have had an inadequate response to previous disease-modifying anti-rheumatic drug therapy. It was launched in the UK in March 2014.
- The recommended dose is 200 mg every 2 weeks, which may be switched to 400 mg every 4 weeks once a clinical response has been confirmed. Certolizumab pegol is supplied in a pre-filled syringe for subcutaneous injection. Patients may self-administer following appropriate training.
- Efficacy was assessed in a randomised double-blind phase III RAPID-PsA trial, which lasted 216 weeks. Certolizumab was more effective than placebo for the outcome of American College of Rheumatology 20% improvement in psoriatic arthritis at both 12 weeks (primary clinical outcome) and 24 weeks. Certolizumab was also more likely to produce 50% and 70% improvements in psoriatic arthritis.
- Certolizumab was associated with less radiographic progression of joint damage than placebo, but the clinical importance of the difference observed is not clear.
- Certolizumab was associated with less lost productivity in both paid and household work, and in leisure activities. This effect was more pronounced with the 200 mg every two weeks regimen and with 400 mg every 4 weeks.
- Certolizumab was previously licensed for the treatment of rheumatoid arthritis, and no new safety concerns were highlighted in the psoriatic arthritis population. The most commonly-reported adverse effects were minor infections. Serious adverse events were not common, and no serious event occurred in more than one person.
- There are no direct comparisons with other biologic treatments for psoriatic arthritis. Indirect comparison in a meta-analysis found that certolizumab was associated with a higher risk of serious adverse events and serious infections than other biologic therapies. This finding should be viewed with caution due to the lack of direct comparisons.
- There are limited efficacy and safety data beyond the 24 weeks reported in the published report of RAPID-PsA. The trial is ongoing, and additional safety data covering the whole 216 week trial period are expected to be submitted to the regulator in the second quarter of 2016.
- Certolizumab costs £7,150 per patient in the first year of treatment, and £9,295 per year thereafter. This is similar in cost to the other subcutaneously-administered systemic biologic treatments for psoriatic arthritis: adalimumab, etanercept, golimumab and ustekinumab. Infliximab is also licensed for psoriatic arthritis and may have a lower acquisition cost in some cases, but the cost for intravenous infusion must be considered. **Regional negotiated procurement discounts may be available and CCGs should contact NTAG if more detail is required.**

Introduction and background

Psoriatic arthritis (PsA) is a chronic, inflammatory spondyloarthropathy which affects up to 40% of patients with psoriasis.¹ PsA can occur at any age, but the majority of cases occur in the fourth decade of life, and it affects both genders equally.^{2,3} The prevalence of PsA is estimated to be around 0.3-1% of the population.^{2,4}

Although PsA is generally a chronic and progressive condition, its course may be erratic, with flare-ups and remissions that can result in significant functional, psychological and social morbidity. The skin symptoms of PsA precede the arthritis symptoms in over two thirds of people with the disease. Characteristic skin manifestations include erythematous plaques and scaling which can affect any part of the body, and nail lesions. Articular symptoms range from mild non-destructive synovitis to severe, debilitating, erosive arthropathy.^{1-3,5,6}

Patients with PsA are managed in consultation with specialists in dermatology and rheumatology. The goals of treatment are to relieve pain, reduce inflammation, prevent joint damage, and to improve the signs and symptoms of skin manifestations. Mild PsA can generally be managed with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, with intra-articular corticosteroid injections when necessary. Topical therapies are used for the skin. Disease modifying anti-rheumatic drugs (DMARDs), including methotrexate, sulfasalazine, leflunomide, azathioprine and ciclosporin are used to reduce joint damage and limit disability. After initial treatment with NSAIDs and DMARDs, most people with non-responsive PsA will be treated with a tumour necrosis factor-alpha inhibitor (TNF inhibitor).^{1-3,5,6} The TNF inhibitors adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are licensed for PsA.⁷⁻¹¹ In March 2015, two biosimilar infliximab products (Inflectra®▼ and Remsima®▼) were approved for use in the UK across all current licensed indications, including PsA.^{12,13} A marketing authorisation application for a biosimilar of etanercept has been accepted by the European Medicines Agency.¹⁴ If authorised this is also likely to be available for use in all licensed indications.

It has been shown that up to a third of PSA patients may fail on first-line TNF inhibitor therapy due to primary non-response, secondary loss of efficacy, or adverse events.¹⁵⁻¹⁷ The interleukin 12/23 inhibitor ustekinumab is currently the only recommended treatment options for these patients.¹⁸ However, an increasing number of specialists may consider switching to an alternative TNF inhibitor before ustekinumab.

Certolizumab pegol (Cimzia®[®], UCB Pharma) is a TNF inhibitor which consists of the humanised antigen-binding fragment (Fab) of a mouse antibody, conjugated to polyethylene glycol (PEG). PEGylation improves drug bioavailability and pharmacokinetic profile, and has been shown to increase the circulating half-life of Fab molecules.¹⁹ Certolizumab pegol was licensed for the treatment of PsA in March 2014.²⁰ It is indicated, in combination with methotrexate (MTX), for the treatment of PsA in adults whose disease has not responded adequately to previous DMARD therapy. It may also be given as monotherapy when MTX is not tolerated, or if continued MTX treatment is inappropriate.⁸ It is also licensed for treatment rheumatoid arthritis and axial spondyloarthritis.

This document will review the, efficacy, safety and cost of certolizumab pegol for the treatment of PsA.

Guidance and related advice

There are currently no NICE guidelines specifically on the management of PsA. The TNF inhibitors etanercept, infliximab and adalimumab are recommended by NICE (TA199) for the treatment of active and progressive PsA in adults when the person has peripheral arthritis with three or more tender joints and three or more swollen joints, and the PsA has not responded to adequate trials of at least two standard DMARDs, given on their own or together.²¹ NICE (TA220) recommends golimumab as an option for the treatment of active and progressive PsA in adults only if it is used as described for other TNF inhibitors in TA199, and only if the manufacturer provides the 100 mg dose at the same cost as the 50 mg dose.²² The TNF inhibitor certolizumab pegol was not considered appropriate for a NICE TA and is not currently planned into any other work programme. However, in June 2014, NICE published an evidence summary on certolizumab pegol in which they suggest that the likely place in therapy is an additional treatment option to the currently available TNF inhibitors licensed for PsA.²³ The interleukin inhibitor ustekinumab is recommended by NICE (TA340) as an option, alone or in combination with methotrexate, for treating active PsA in adults only when treatment with TNF inhibitors is contraindicated but would otherwise be considered (as described in TA199 and TA220), or the person has had treatment with one or more TNF- α inhibitors, and only if the manufacturer provides the 90 mg dose at the same cost as the 45 mg dose.¹⁸

NICE advise that biologic therapy should be discontinued in people whose PsA has not shown an adequate response to treatment using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks (24 weeks for ustekinumab), where an adequate response is defined as an improvement in at least two of the four criteria (one of which must be joint tenderness or swelling score), with no worsening in any of the four criteria.^{18,21,22} Patients whose PsARC outcome does not justify continuation of treatment but whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.

Clinical evidence

Certolizumab pegol is being assessed in a single phase III trial, RAPID-PsA. The primary outcomes of the trial were assessed at 12 and 24 weeks and have been fully published. However, the trial was designed to run for 216 weeks in order to collect open-label safety data on long term use of certolizumab. It is expected to be completed in August 2015.

RAPID-PsA enrolled adults with at least a 6 month history of adult-onset PsA, active joint disease, and active psoriatic skin lesions or history of psoriasis. Patients had all failed treatment with at least one previous DMARD, and those with latent or active tuberculosis were excluded unless active treatment was already underway. Other exclusions included clinically significant infection, malignancy, demyelinating disease, diagnosis of other inflammatory arthritis, previous exposure to >2 biologic therapies or >1 TNF inhibitor (for either PsA or psoriasis), or primary failure of previous TNF therapy. Patients with secondary failure to a previous TNF inhibitor were enrolled.²⁴

Concomitant MTX, sulfasalazine or leflunomide were permitted providing the dose was stable and had been initiated ≥ 28 days previously. Oral steroids at a stable dose of ≥ 10 mg/day prednisone or equivalent were permitted. Other DMARDs and intra-articular steroids were not permitted within 28 days prior to the baseline visit. Topical, systemic or photo therapies were not permitted between the baseline visit and week 48.

Patients were randomised to receive double-blind treatment with placebo, certolizumab pegol 200 mg every two weeks (Q2W), or certolizumab pegol 400 mg every four weeks (Q4W), each administered by subcutaneous injection. All patients received loading doses of certolizumab pegol 400 mg (or placebo) at weeks 0, 2 and 4.

Patients in the placebo group who did not achieve at least 10% improvement in swollen and tender joints by week 16 were re-randomised to one of the certolizumab arms in a mandatory escape protocol. At week 24 all remaining placebo-treated patients were re-randomised to receive certolizumab pegol in a dose-blind manner. At week 48 the blinding was removed and all patients continued treatment in an open-label for the remainder of the 216 week trial.

A total of 409 patients were randomised and received at least one dose of study medication, and 368 (90%) completed the first 24 week double-blind phase. Patient characteristics were balanced at baseline; the mean age of participants was 47.6 years, and 55% were female. Between 62-65% of patients were using concomitant MTX at baseline, and approximately 20% had prior experience with a TNF inhibitor. Reasons for discontinuing prior TNF inhibitors included adverse effects, secondary treatment failure, and practical issues such as supply or financial problems.

Disability was measured by mean Health Assessment Questionnaire Disability Index (HAQ-DI) score. The HAQ-DI is a questionnaire designed to assess physical function. It comprises a set of 20 items split into 3 categories, and covers activities such as walking, eating, dressing, personal hygiene and ability to grip. Patients rate each item on a scale from 0 (without any difficulty) to 3 (unable to do). The final score is presented on a scale of 0 to 3 in increments of 0.125, with higher scores indicating higher disability. In the RAPID-PsA trial the baseline score in all groups was 1.3, indicating moderate to severe disability.²⁵

Clinical endpoints

The primary clinical endpoint was American College of Rheumatology 20% response (ACR20) after 12 weeks treatment.²⁴ ACR20 response is defined as at least a 20% improvement in the number of tender and swollen joints, plus at least a 20% improvement in at least three of the five core measures:²⁶

- Pain
- Patient global assessment
- Physician global assessment
- Self-assessed physical disability
- Acute phase reactants (in this case, C-reactive protein, CRP)

Significantly more patients achieved an ACR20 response in both certolizumab pegol groups than with placebo (see table 1). Improvements were noted after 1-2 weeks of treatment, and maintained until week 24. The proportion of responders was higher in

the certolizumab pegol 200 mg Q2W than with 400 mg Q4W, but no statistical analysis of the difference was presented.

Table 1: Proportion achieving clinical efficacy outcomes (RAPID-PsA trial)

Endpoint	Placebo n=136	Certolizumab pegol 200 mg Q2W, n=138			Certolizumab pegol 400 mg Q4W, n=135		
Outcomes at 12 weeks							
ACR20 (primary outcome)	24.3%	58.0%	TD 33.7% (22.8 to 44.6)	p<0.001	51.9%	TD 27.6% (16.5 to 38.7)	p<0.001
ACR50	11.0%	36.2%	nr	p<0.001	32.6%	nr	p<0.001
ACR70	2.9%	24.6%	nr	p<0.001	12.6%	nr	p=0.003
Outcomes at 24 weeks							
ACR20 (key secondary outcome)	23.5%	63.8%	TD 40.2% (29.5 to 51.0)	p<0.001	56.3%	TD 32.8% (21.8 to 43.8)	p<0.001
ACR50	12.5%	44.2%	nr	p<0.001	40.0%	nr	p<0.001
ACR70	4.4%	28.3%	nr	p<0.001	23.7%	nr	p<0.001

TD – treatment difference; nr – not reported.

Key secondary outcomes

Key secondary outcomes were ACR20 response at week 24, change from baseline in HAQ-DI score at week 24, and 75% reduction in psoriasis area and severity index (PASI75) in patients with $\geq 3\%$ body surface area psoriatic skin involvement. ACR20 response at week 24 was similar to the response at week 12 (see table 1 above).

After 24 weeks HAQ-DI scores improved by 0.50 points in the combined certolizumab pegol groups, compared to 0.19 points with placebo ($p<0.001$). A change of 0.35 points in the HAQ-DI is considered clinically important.²⁴ The final mean score in the combined certolizumab groups represents mild to moderate disability, while the placebo group did not improve from the baseline of moderate to severe disability. The EMA reported that the proportion of HAQ-DI responders was higher in both certolizumab pegol groups than with placebo at both 12 and 24 weeks, but did not give a definition of “responder”.

In patients with psoriasis involving ≥ 3 body surface at baseline, PASI75 response at week 24 was more frequent in the certolizumab groups (approximately 60% in both groups) than with placebo (15%). A significant difference in PASI score was seen from week two.

Other outcomes

The response to the Q4W dosing regimen was slightly lower at all time points. The EMA considered that the difference diminished with time, but noted that there was a particularly pronounced difference in the ACR70 outcome at 12 weeks.²⁷ As a result, they recommended that the Q4W regimen should not be used in new patients until a clinical response to Q2W dosing has been confirmed. This switch from Q2W to Q4W dosing was not tested in the pivotal trial.

ACR responses were similar in all groups, irrespective of prior TNF inhibitor exposure. However group sizes were small; only 20-30 patients in each treatment arm had prior TNF inhibitor experience. There were also some differences in baseline characteristics between those with and without prior exposure. For instance TNF inhibitor experienced patients had a slightly longer time since diagnosis (8.2 vs. 10.1 years), were more likely to have ≥ 3 body surface area affected by psoriasis (59.6% vs. 70%) and were less likely to be using concomitant MTX (65% vs. 55%) or other DMARDs (67.8% vs. 57.5%) at baseline.

Response to certolizumab did not appear to be affected by DMARD use, with similar ACR20 responses at week 12 in those with (56.8%) and without (50.0%) concomitant DMARD treatment. Again, group sizes were small.

Radiographic endpoints

The primary radiographic endpoint was change in van der Heijde modified Total Sharp Score (mTSS) after 24 weeks treatment.²⁸ The mTSS quantifies the extent of bone loss and joint space narrowing in the bones of the hands and feet; higher scores represent greater damage. Radiographs were read centrally and independently by two blinded investigators.

There were no significant differences in mTSS scores at baseline, and most patients had no change in score after 24 weeks treatment. The pre-specified analysis used the lowest observed score at baseline and the highest observed score at 24 weeks to impute missing values. This resulted in unrealistic estimation of the true effect. A post-hoc analysis which used the median change from baseline to impute missing values gave more plausible results, and was accepted by the EMA.

The post-hoc analysis found that there was less radiographic progression in both certolizumab groups compared with placebo, although the difference only reached statistical significance in the certolizumab Q2W group (0.01 vs. 0.28 points with placebo, $p=0.004$). There was an increase of 0.11 points in the certolizumab Q4W group ($p=0.07$ vs. placebo). When all certolizumab-treated patients were pooled, progression was significantly less than in the placebo group (0.06 vs. 0.28, $p=0.007$).

The minimum clinically important difference in mTSS scores is not known. In a similar scale used to assess joint damage in rheumatoid arthritis, a change of 6 points has been shown to correlate with an increase in HAQ-DI score of 0.2.²⁹

Quality of life endpoints

The impact of PsA on daily activities and ability to work was assessed during using the work productivity survey (WPS). The WPS is an investigator-administered questionnaire which covers elements such as absenteeism from paid work, days with reduced productivity, impact on household work and effect on social and leisure activities.³⁰

Patients in the certolizumab Q2W group reported fewer work days lost due to arthritis ($p<0.001$), fewer days with $\geq 50\%$ reduction in productivity ($p=0.003$), and less overall interference with work productivity ($p<0.001$) compared with the placebo group. They also reported fewer days where they were unable to do household work, had less than 50% household work productivity, missed social or leisure activities, days where

outside help was required due to arthritis, and less overall interference with household productivity (all $p < 0.01$ vs. placebo).

In the certolizumab Q4W group the only work-related domain which was improved compared to placebo was the overall rate of arthritis interference with productivity ($p = 0.004$). All household domains were improved compared to placebo, except the requirement for outside hired help ($p = 0.58$).

Several quality of life assessments were administered during the RAPID-PsA trial, including the Short Form 36 (SF-36), Psoriatic Arthritis Quality of Life (PsAWOL), Fatigue Assessment Scale (FAS) and patient assessment of pain. All of these measures were significantly improved with certolizumab when compared with placebo, at 4, 12 and 24 weeks.³¹

Safety

The published RAPID-PsA study presented safety data for up to 24 weeks exposure. The manufacturers are expected to submit additional safety data, covering the whole 216 week duration of RAPID-PsA, in the second quarter of 2016. The data available to date are consistent with the expected safety profile for a TNF inhibitor.

Adverse events (AEs) were common in all treatment groups, and most were mild to moderate in severity. No new safety concerns were identified, and AE profile was similar to that established in trials of certolizumab pegol for treatment of rheumatoid arthritis. The most common AEs were minor infections such as nasopharyngitis and upper respiratory tract infection (see table 2 below). No individual serious AEs occurred in more than one person.²⁴

Table 2: Treatment-emergent adverse events in the RAPID-PsA trial (24 weeks)

Adverse effect	Placebo	Certolizumab 200 mg Q2W	Certolizumab 400 mg Q4W
Any treatment-emergent event	92 (67.6%)	94 (68.1%)	96 (71.1%)
Discontinuation due to AE	2 (1.5%)	4 (2.9%)	6 (4.4%)
Serious AEs	6 (4.4%)	8 (5.8%)	13 (9.6%)
Infections	52 (38.2%)	60 (43.5%)	54 (40.0%)
URTI	21 (15.4%)	38 (27.5%)	38 (28.1%)
Serious infections	1 (0.7%)	2 (1.4%)	2 (1.5%)
ALT increased	2 (1.5%)	4 (2.9%)	7 (5.2%)
AST increased	1 (0.7%)	4 (2.9%)	6 (4.4%)
Injection site reactions	3 (2.2%)	6 (4.3%)	13 (9.6%)
Headache	2 (1.5%)	6 (4.3%)	5 (3.7%)
Death	0	1 (0.7%)	1 (0.7%)

URTI – upper respiratory tract infection; ALT – alanine aminotransferase; AST – aspartate aminotransferase

The EMA reported additional safety data in which 70% of participants were exposed for at least 12 months. The overall pattern of AEs was similar to that reported in the published trial.

Hepatic AEs were more common than in rheumatoid arthritis populations assessed previously, and were more common in patients receiving concomitant DMARDs at baseline. Four patients experienced increased alanine aminotransferase (ALT) levels $\geq 3 \times \text{ULN}$. All were in the certolizumab pegol Q4W group, and all had normalised values during unchanged or re-introduced certolizumab treatment.

The certolizumab 400 mg Q4W dosing regimen results in higher maximum plasma drug concentrations, which raises potential concerns regarding safety. However, the EMA reported that the incidences of treatment-emergent AEs, drug-related AEs, severe AEs, serious AEs and discontinuation due to AEs were similar between the two certolizumab groups.

Certolizumab is contraindicated in patients with active tuberculosis or other severe infections, and in patients with moderate to severe heart failure.⁸

There are no direct comparisons of certolizumab with other biologic therapies. A network meta-analysis conducted by the Cochrane Collaboration included an indirect comparison of the biologics. Trials were included if they enrolled adults with any disease treated with abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab.

Certolizumab was the only included biologic with significantly more serious adverse events than the control group (odds ratio 1.57, 95% CI 1.06 to 2.32). This statistical significance was lost when the model was adjusted for dose (OR 1.57, 95% CI 0.96 to 2.57). Certolizumab pegol was also associated with significantly higher risk of serious infections compared with abatacept, adalimumab, etanercept, golimumab and rituximab.³² These findings are derived from indirect comparisons between trials which had important differences; they should be interpreted with caution.

Cost analysis

All biologic agents licensed for treatment of PsA are specified high-cost drugs and are excluded from the national tariff.

NICE guidance recommends that treatment should normally be started with the least expensive drug (taking into account administration costs, required dose and product price per dose), and this may need to be varied for individual patients because of differences in the method of administration and treatment schedules.^{21,22}

Certolizumab pegol is supplied as pre-filled syringes containing 200 mg in 1 mL. The recommended starting dose of is 400 mg administered at weeks 0, 2 and 4. After this loading phase the recommended maintenance dose is 200 mg once every two weeks. An alternative schedule of 400 mg every 4 weeks can be considered, once the clinical response has been confirmed. Clinical response is usually achieved within 12 weeks, at which time response should be reviewed and consideration given to discontinuing treatment in patients who have not shown benefit.⁸

On 1st April 2015, a new Commercial Medicines Unit (CMU) contract started in the NTAG area. Under the CMU contract the price of some products differs substantially from list prices due to locally negotiated procurement discounts (see table 3).³³ In addition, the advent of biosimilars is leading to a shift in the market and manufacturers are bringing in more 'value' added services such as variations of homecare and additional nursing support etc. A new CMU contract which will include the TNF inhibitors is due to start on the 1st of March 2016, so prices may subsequently change.

The costs given below exclude VAT. Depending on whether these drugs are given in hospital or delivered to home will affect whether they are VAT exempt or not.

Table 3. Comparative unit costs of biologics licensed for the treatment of PsA.

Product	Pack size	List price per pack	Comments
Adalimumab PFS 40mg/0.8mL	2	£704.28	Some areas (e.g. London) have a small discount.
Adalimumab pre-filled pen 40mg/0.8mL	2	£704.28	
Certolizumab PFS 200mg	2	£715.00	The manufacturer provides the first 12 weeks of treatment free through a PAS.
Etanercept vials 25mg	4	£357.50	There are some Trust level arrangements and homecare. This price will change if biosimilar etanercept is launched.
Etanercept PFS 25mg/0.5mL	4	£357.50	
Etanercept PFS 50mg/1mL	4	£715.00	
Etanercept pre-filled pen 50 mg/1mL	4	£715.00	
Golimumab PFS 50mg/0.5mL	1	£762.79	100mg dose is provided at the same cost as the 50mg dose through a PAS.
Golimumab pre-filled pen 50 mg/1mL	1	£762.79	
Golimumab pre-filled pen 100 mg/1mL	1	£1,525.94	
Infliximab (Remicade) vials 100mg	1	£419.62	
Infliximab (Inflectra) vials 100mg	1	£377.66	
Infliximab (Remsima) vials 100mg	1	£377.66	
Ustekinumab PFS 45mg/0.5mL	1	£2,147.00	

The estimated average annual treatments costs per PsA patient are shown in table 4. However, the exact cost depends on the duration of treatment, together with the number of patients treated with each product and any differences in dosing, scheduling and administration. The estimated costs given below exclude VAT. Drugs given intravenously are likely to be administered in a hospital setting and therefore VAT will apply.

The annual cost per patients for certolizumab is comparable to the other subcutaneously-administered biologics for PsA. Recently-launched biosimilar preparations of infliximab have a lower acquisition cost than the subcutaneous drugs, but must be administered by intravenous infusion. Patients may self-administer certolizumab following appropriate training in injection technique, with medical follow-up as required.

Table 4. Estimated average annual treatment cost per patient.

Drug	Regimen	First year cost per patient (including administration)	Annual maintenance cost per patient (including administration)
Adalimumab	40 mg every 2 weeks by subcutaneous injection.	£9,156	£9,156
Certolizumab pegol	400 mg in weeks 0, 2 and 4, then 200 mg every 2 weeks, or 400 mg every 4 weeks by subcutaneous injection.*	£7,150	£9,295
Etanercept	25 mg twice weekly or 50 mg once weekly by subcutaneous injection.	£9,295	£9,295
Golimumab	50 mg once monthly, on the same date each month by subcutaneous injection.	£9,156	£9,156
Infliximab Remicade	5 mg/kg in weeks 1, 3 and 7, then every 8 weeks given as an intravenous infusion.**	£13,428 (£17,286)	£10,910 (£14,045)
Inflectra		██████████ ██████████	██████████ ██████████
Remsima		██████████ ██████████	██████████ ██████████
Ustekinumab	45 mg in weeks 1 and 4, then every 12 weeks by subcutaneous injection. Alternatively, 90 mg may be used if body weight >100kg.	£10,735	£9,304

Doses are taken from the relevant summary of product characteristics.^{7-13,34} The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

* Cost of treatment for first year includes the starting dose, and minus the first 12 weeks of treatment cost (£3,575), through the PAS.

** Based on a 70 kg adult, and assumed that vial wastage occurs. It assumes ██████████ for Inflectra® ██████████ and Remsima® ██████████ and the full list price of Remicade® (£419.62). The cost of administration for infliximab is £3,858 in the first year and £3,135 in the subsequent maintenance years. The cost is based on 2015/16 enhanced tariff option. Day case: Inflammatory spine, joint or connective tissue disorders (weighted average of major CC (HD23A), intermediate CC (HD23B) and without CC (HD23C)).³⁵

These data ██████████ are confidential to the NHS and commercially sensitive. Local CCGs should contact NTAG if more detail is required.

Points to consider

Certolizumab pegol was more effective than placebo for the treatment of PsA in a double-blind, randomised clinical trial.²⁴ There are no available data comparing certolizumab pegol with other systemic biologic therapies for the treatment of PsA, and there are limited safety and efficacy data beyond that presented in the 24 week published report. The full 216 week pivotal RAPID-PsA trial is due to be completed in August 2015, with additional data presented to the regulator in the second quarter of 2016.²⁷

The clinical trial program for certolizumab pegol in PsA has not identified any new safety concerns. The most common adverse events were infections. There were few serious adverse events, and none which occurred in more than one patient. An indirect comparison found that certolizumab pegol may be associated with a higher risk of serious adverse events and serious infections than other biologic drugs. There are no available direct comparisons.

Certolizumab is supplied in a pre-filled syringe and is administered as a 200 mg subcutaneous injection once every two weeks. If clinical response is confirmed after 12 weeks, the administration schedule may be altered to 400 mg once every 4 weeks. It should be noted that the 400 mg dose is delivered as two injections of 200 mg each, so this regimen does not reduce the injection burden.

There are several TNF inhibitors licensed for the treatment of PsA. Adalimumab, etanercept and golimumab are administered by subcutaneous injection, while infliximab requires intravenous infusion. NICE recommends selecting the least expensive drug, taking into account administration costs and drug acquisition costs. The interleukin inhibitor ustekinumab is also licensed, but only recommended by NICE if TNF inhibitors are contraindicated or have been used previously.

The cost of certolizumab pegol is similar to the other subcutaneously-administered systemic biologic drugs for PsA. The cost of infliximab varies due to the recent launch of two biosimilar products. Local discounts may mean that the acquisition cost for infliximab is lower than the other drugs in some cases, but the cost of intravenous administration (approx. £3000-4000 per year) must be taken into account.

The SMC has accepted certolizumab pegol for restricted use within NHS Scotland for the treatment of PsA, in line with its licensed indication. Use is restricted to patients whose disease has not responded to adequate trials of at least two standard DMARDs, either individually or in combination. The SMC advice takes into account the benefits of a patient access scheme (PAS), and is contingent on the continuing availability of the scheme or a list price that is equivalent or lower. The PAS takes the form of a simple discount, which reduces the list price of certolizumab pegol.³⁶

The AWMSG has accepted certolizumab pegol for use within NHS Wales for the treatment of PsA, in line with its licensed indication. This advice applies only when the approved Wales PAS is utilised.³⁷

Author's declaration: The author has no relevant interests to declare.

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