**Introduction**

The Luton and Dunstable Hospital Rheumatology Department has submitted a business case requesting the use of certolizumab pegol for the treatment of adults with severe ankylosing spondylitis (AS) who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). The proposed use of certolizumab pegol for this indication is as described for other tumour necrosis factor (TNF) inhibitor treatments in ‘Ankylosing Spondylitis – adalimumab, etanercept and infliximab (NICE technology appraisal guidance 143). The business case also advises (and assumes) that the manufacturer will provide certolizumab as per the agreed confidential patient access scheme (PAS).

Certolizumab pegol is not currently NICE approved for this indication - A multiple technology appraisal evaluating TNF-alpha inhibitors (including CZP) for AS and severe active axial spondyloarthritis (axSpA) without radiographic evidence of AS is currently in development by NICE (expected January 2015).

One small RCT (n=325) demonstrated significantly higher ASAS20 response rates with CZP (200mg or 400mg) at week 12 compared to placebo (57.7% and 63.6% vs 38.3%; p<0.004). These response rates were significantly higher than observed with placebo (38.3%).
rates were maintained through to week 48. Equally improvements were observed from week 1 through to week 48 in BASDAI, BASFI and BASMI scores. Although data from the pivotal trial is positive, the comparator group is placebo and there are no head to head studies with other TNF-inhibitors licensed for AS.

There is no cost-effective data to support its use as a treatment option for AS. Assuming that the manufacturer supplies certolizumab as per the agreed confidential patient access scheme (PAS), certolizumab pegol is less expensive than other TNF inhibitors in the first year.

Certolizumab pegol would present an additional drug for this indication although its place in therapy has not been determined and there is no national guidance or expert consensus to support its use.

| The intervention Mechanism of action | Certolizumab pegol (CZP) is a monoclonal antibody that inhibits the activity of tumour necrosis factor (TNF) alpha. TNF-alpha is an inflammatory cytokine or pro-inflammatory mediator which is involved in the inflammatory processes when present in excessive concentrations. Thus CZP modifies the inflammatory disease process.¹ ² |
| Licensed indication | CZP is indicated for the treatment of severe active ankylosing spondylitis (AS) or severe active axial spondyloarthritis (axSpA) without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI in adults who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs). It is additionally licensed for adults with rheumatoid arthritis and psoriatic arthritis.¹ |
| Usual dosage | The recommended starting dose for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4 followed by a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks. Suitable injection sites include the thigh or abdomen. After proper training in injection technique, patients may self-inject using the pre-filled syringe if their physician determines that it is appropriate and with medical follow-up as necessary.¹ |
| Treatment alternatives/ place in therapy | Conventional therapy includes acute anti-inflammatory treatment with NSAIDs and local corticosteroids, disease-modifying drugs (DMARDs, such as sulfasalazine and methotrexate) and physiotherapy. TNF-inhibitors (adalimumab, CZP, etanercept, golimumab and infliximab) are typically used when the disease has not responded adequately to conventional therapy. NICE technology appraisal 143 recommends adalimumab and etanercept as treatment options for adults with severe active AS only if certain criteria are fulfilled, but it does not recommend infliximab for AS. Golimumab is |
also recommended in NICE technology appraisal 233 as an option for the treatment of severe, active AS in adults only if it is used as described for adalimumab and etanercept in NICE technology appraisal 143.\(^2,3,4\)

**Future alternatives**  
None apparent at present

**National guidance**  
There is no national guidance in place at present for this specific intervention. A multiple technology appraisal evaluating TNF-alpha inhibitors (including CZP) for AS and axSpA without radiographic evidence of AS is currently in development by NICE (expected January 2015).\(^2\) The Scottish Medicines Consortium are also reviewing CZP for the treatment of adult patients with severe active axSpA (expected 12\(^{th}\) May 2014).\(^5\) The British Society for Rheumatology are developing guidelines for AS and biologics (date of issue not stated).\(^6\)

**Evidence for use**  
RAPID-axSpA is a double-blind randomised, placebo-controlled, multicentre trial that evaluated the efficacy and safety of CZP in 325 adult patients with axSpA, including patients with AS (n=178) and nonradiographic axSpA (nr-AxSpA, n=147).\(^7\) All patients had active disease (BASDAI>4, spinal pain >4), an inadequate response or intolerance to NSAIDS, and an increased CRP or evidence of sacroiliitis on MRI. Per protocol, <40% of patients could have a TNF-inhibitor >3 months prior to baseline if they had discontinued because of secondary failure. The trial is ongoing to 204 weeks and is placebo-controlled to 24 weeks, dose-blind to 48 weeks and open-label to 204 weeks.

Patients were randomised 1:1:1 to placebo (n=107), or CZP 400 mg (n=107) at weeks 0, 2 and 4 (loading dose) followed by either CZP 200 mg (n=111) every 2 weeks (Q2W) or CZP 400 mg every 4 weeks (Q4W), administered subcutaneously in a prefilled syringe by unblinded trained site personnel. All patients received injections Q2W, either CZP or placebo, to maintain blinding. The primary endpoint was ASAS20 (Assessment of SpondyloArthritis international Society 20) response at week 12 and these were significantly higher in CZP 200 mg Q2W and CZP 400 mg Q4W arms versus placebo (57.7 and 63.6 vs 38.3, p≤0.004). Improvements in the primary endpoint in CZP-treated patients were observed in both AS (56.9% for CZP 200 mg Q2W and 64.3% for CZP 400 mg Q4W vs 36.8% for placebo; p<0.05) and nr-axSpA patients (58.7% for CZP 200 mg Q2W and 62.7% for CZP 400 mg Q4W vs 40.0% for placebo; p<0.05 and p<0.001, respectively).

There were also significant changes (p<0.001) from baseline at week 24 in the combined CZP arms versus placebo in BASFI (~2.28 vs
−0.40), BASDAI (−3.05 vs −1.05), and BASMI (−0.52 vs −0.07) (all secondary endpoints). Improvements were observed as early as week 1. Similar improvements were reported with CZP versus placebo in both AS and nr-axSpA subpopulations.\(^7\)

Forty-eight week double-blind data for RAPID-axSpA were reported at conference.\(^8\) Patients who were originally randomized to CZP continued on their assigned dose in dose-blind phase; and placebo patients were re-randomized to CZP loading dose followed by CZP 200mg Q2W or CZP 400mg Q4W after week 24, or, for non-responders after week 16 (data for placebo-controlled patients were not reported within the abstract).

Overall, 93% of patients randomised to CZP at baseline completed Wk24 and 88% completed week 48.

Improvements in ASAS20 were observed in CZP-treated patients at week 24 (66.7% for 200 mg and 68.2% for 400 mg) and at week 48 (71.2% for 200 mg and 72.0% for 400 mg). Improvements from baseline were also observed at week 48 for the following outcomes; BASFI (−2.7 for 200mg and −2.4 for 400mg), BASDAI (−3.4 for 200mg and −3.3 for 400mg), and BASMI (−0.7 for 200mg and −0.6 for 400mg).\(^8\)

**Safety**

Adverse data are reported from the RAPID-axSpA trial at week 24.\(^7\) The most common infectious AEs were nasopharyngitis (8.8% CZP vs 6.5% placebo) and upper respiratory tract infection (4.0% CZP vs 2.8% placebo). For non-infectious AEs, headache (6.2% CZP vs 6.5% placebo) and increased blood creatine phosphokinase (5.1% CZP vs 1.9% placebo) were most common. Few serious AEs were reported overall (4.7% CZP vs 4.7% placebo); There were no reported cases of opportunistic infections (including tuberculosis) or malignancies.

At week 48, conference data showed AEs occurred in 248 pts (78.7%; event rate per 100 pt-yrs=419.5) and serious AEs in 25 (7.9%). Serious infections occurred in 10 (3.2%) pts, including suspected tuberculosis in 3 of which 1 was confirmed. No deaths or malignancies were reported.\(^8\)

**Costs for adults**

CZP, net price 200 mg prefilled syringe = £357.50 (UK list price, excl VAT).\(^9\) The business case states that a commercial scheme is already in place locally for rheumatoid arthritis - certolizumab will be provided as per the agreed confidential patient access scheme (PAS). This means that certolizumab pegol costs less than other TNF inhibitors in the first year of treatment and is priced similarly for subsequent years. Confidential information relating to the patient access scheme (PAS) has been removed. **The annual cost using UK list** price will be £10,725 (excl VAT) first year; then £9295 subsequent years.
## Costs of alternatives

<table>
<thead>
<tr>
<th>TNF inhibitor (Subcutaneous, NICE approved)</th>
<th>Dose</th>
<th>Annual cost (excl VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>25 mg twice weekly</td>
<td>£9296</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg every other week</td>
<td>£9156</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50 mg once a month</td>
<td>£9156</td>
</tr>
</tbody>
</table>

## Cost effectiveness (if available)

No cost effectiveness data were identified.

## Potential number of patients in Bedfordshire and Luton

For AS, the prevalence is thought to range from 0.05% to 0.23%. However if we take a midpoint between these two values, say 0.017%, (a prevalence rate quoted by the NICE) for a population of 100,000 this would equate to 17 patients, therefore the annual cost for CZP would be £158,015 (without the PAS discount). Confidential information relating to the patient access scheme (PAS) has been removed.

New criteria for the diagnosis of axSpA have been proposed recently by the Assessment of Spondyloarthritis International Society (ASAS) therefore there are limited epidemiology data for axSpA according to this criteria.

## Affordability considerations

Potential number of patients in Bedfordshire and Luton

Impact per 100,000 population

Affordability considerations

## Number Needed to Treat (NNT) Number Needed to Harm (NNH)

### NNT

For every 5 patients treated with CZP 200mg or 4 patients treated with CZP 400mg, one additional patient would achieve ASAS20 at week 12 (primary endpoint).

Or, for every 3 patients treated with CZP 200mg or CZP 400mg, one additional patient would achieve BASDAI 50 at week 12 (secondary endpoint).

### NNH

For every 7 patients treated with CZP 200mg or 8 patients treated with CZP 400mg, one additional patient would experience an adverse event.

For every 35 patients treated with CZP 200mg or 27 patients treated with CZP 400mg, one additional patient would experience a severe adverse event.

## Ethics

### Equity

See attached assessment against ethical and commissioning principles
| Implementation |  
|----------------|---|
| Patient choice/access considerations | See attached assessment against ethical and commissioning principles |
Decisions from other bodies

Grey literature Comments sought from –

Points for consideration
The license does not specify place in therapy but it is possibly intended as a substitute therapy for the second or third line treatment of active AS, after failure of NSAIDs.

Although data from the pivotal trial is positive, the comparator group is placebo and there are no head to head studies with other TNF-inhibitors licensed for AS.

NICE define as adequate response to treatment as a reduction of the BASDAI score to 50% of the pre-treatment value or by 2 or more units and reduction of the spinal pain VAS by 2cm or more. At week 12, significantly more patients in the CZP groups achieved >50% improvement in BASDAI from baseline (placebo, 13.2%; CZP 200mg, 45.0% and CZP 400mg, 43.9%; p<0.001) [spinal pain VAS were not reported].

There is no cost-effective data to support its use as a treatment option for AS.

Several other TNF-inhibitors (adalimumab, etanercept and golimumab) are already licensed for the treatment of AS and NICE-approved treatment options with the same recommendations for initiation and cessation of therapy. CZP would present an additional drug for this indication although its place in therapy has not been determined and there is no national guidance or expert consensus to support its use.

Limitations of review

CZP is a homecare product that has been used nationally for RA. The SPC does not recommend an optimal duration of therapy. Clinical trial data extends up to 48 months and current NICE guidance recommends that response to treatment should be assessed after 12 weeks and only continued in the presence of an adequate response.
References/ Sources of Review

1. Cimzia™ Summary of Product Characteristics (UCB Pharma). Date of revision: November 2013


5. SMC. Forthcoming Submission: certolizumab pegol (Cimzia). Advice expected May 2014

6. The British Society for Rheumatology. Ankylosing spondylitis and biologics guideline in development (date of issue not stated).


8. Landewe R et al. Effect of certolizumab pegol over 48 weeks in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis. Arthritis and Rheumatism 2013; 65/: S767 (conference abstract)


Appendix 1- Search Strategy

The literature discussed in this review was identified by a rapid search of EMBASE and Medline.

1. EMBASE; exp CERTOLIZUMAB PEGOL/; 2703 results.
2. EMBASE; exp ANKYLOSING SPONDYLITIS/; 18041 results.
3. EMBASE: 1 AND 2; 337 results.
4. EMBASE: *CERTOLIZUMAB PEGOL/; 578 results.
5. EMBASE: *ANKYLOSING SPONDYLITIS/; 11089 results.
6. EMBASE: 4 AND 5; 14 results.
7. EMBASE: 6 [Limit to: Human and English Language]; 13 results.
8. MEDLINE: (CERTOLIZUMAB AND PEGOL).ti,ab; 249 results.
9. MEDLINE: exp SPONDYLITIS, ANKYLOSING/; 11609 results.
10. MEDLINE: 8 AND 9; 4 results.
11. EMBASE,MEDLINE: Duplicate filtered: [6 [Limit to: Human and English Language]], [8 AND 9]; 17 results.
Treatment assessed (April 2014):
Certolizumab pegol (CZP) for the treatment of severe active ankylosing spondylitis (AS) in adults

JPC Recommendation:
- The use of certolizumab pegol for ankylosing spondylitis is supported when it is prescribed, administered and monitored as per NICE TA143 and the manufacturer’s patient access scheme is applied to the drug used for this indication.
- Recommendation to be reviewed when NICE issues its guidance (due January 2015).

1) Clinical Effectiveness
One small RCT (n=325) demonstrated significantly higher ASAS20 response rates with CZP (200mg or 400mg) at week 12 compared to placebo (57.7% and 63.6% vs 38.3%; p<0.004). These response rates were maintained through to week 48. Equally improvements were observed from week 1 through to week 48 in BASDAI, BASFI and BASMI scores.

2) Cost Effectiveness
There is no evidence to support the use of CZP as a cost effective use of NHS resources.

3) Equity
None identified

4) Needs of the community
For AS, the prevalence is thought to range from 0.05% to 0.23%. However if we take a midpoint between these two values, say 0.017%, (a prevalence rate quoted by the NICE) for a population of 100,000 this would equate to 17 patients.

5) Need for healthcare (incorporates patient choice and exceptional need)
Several other TNF-inhibitors are already licensed (and NICE approved) for the treatment of AS. CZP would present an additional drug for this indication although its place in therapy has not been determined.

6) Policy drivers
NICE TA’s for other TNF-inhibitors.

Disinvestment
Not relevant

The JPC agreed the following sections within the CCG Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.