# London Medicines Evaluation Network Review

## Tocilizumab subcutaneous injection for rheumatoid arthritis

**September 2014**

### Background and licensed indication

Tocilizumab is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass directed against soluble and membrane-bound interleukin 6 receptors. The subcutaneous (SC) injection of tocilizumab was launched in the UK in May 2014. Prior to this, only the intravenous (IV) formulation was available.

Tocilizumab, given by either SC or IV injection, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant of, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

### Dosing

The recommended dose of tocilizumab by **subcutaneous injection is 162mg every week**. Each pre-filled syringe contains 162 mg of tocilizumab in 0.9 ml.

The recommended dose of tocilizumab by **intravenous infusion is 8 mg/kg body weight, given once every four weeks**.

**Switching from IV infusion to SC injection**

Limited information is available regarding switching patients from tocilizumab intravenous infusion to tocilizumab subcutaneous fixed dose formulation. The once-every-week SC dosing interval should be followed. Patients transitioning from the intravenous to the subcutaneous formulation should administer their first subcutaneous dose instead of the next scheduled intravenous dose under the supervision of a qualified healthcare professional.

In clinical practice, the SC formulation could be used in patients already stable on IV tocilizumab therapy and in new patients. The IV formulation may be appropriate in those unable to comply with SC therapy.

### NICE

No NICE guidance for the SC formulation of tocilizumab is in development (June 2014). A **NICE multi-technology appraisal** including tocilizumab is anticipated in February 2016.

NICE approved the use of tocilizumab (IV formulation) in combination with methotrexate in February 2012. Some Trusts may choose to use the SC formulation in place of the IV formulation in patients who meet the NICE criteria for IV tocilizumab:

Tocilizumab in combination with methotrexate is recommended by NICE as an option for the treatment of rheumatoid arthritis in adults if:

- the disease has responded inadequately to DMARDs and it is used as described for TNF inhibitor treatments in *Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130)*, specifically the recommendations on disease activity and choice of treatment or
- the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, and tocilizumab is used as described for TNF inhibitor treatments in *Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (NICE technology appraisal guidance 195)*, specifically the recommendations on disease activity or
- the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab and
- the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.

### Clinical studies

Two phase 3 studies have assessed the efficacy and safety of subcutaneous tocilizumab in patients with moderate to severe RA taking stable doses of DMARDs: BREVACTA (n=656) and SUMMACTA (n=1262). At enrolment, patients included in both studies had inadequate response to one or more DMARD and around 20% had failed an anti-TNF. Neither study evaluated switching from IV to SC tocilizumab.

In BREVACTA, patients were randomised 2:1 to tocilizumab SC 162mg or placebo every 2 weeks, for 24 weeks (double-blind phase). Escape therapy with weekly tocilizumab was available from week 12 for those with less than 20% improvement in tender and swollen joint count. At week 24, those remaining on fortnightly injections were switched to open-label tocilizumab (n=334) for 72 weeks. At 24 weeks, the proportion of patients treated with tocilizumab achieving American College of Rheumatology (ACR) 20 / 50 / 70 responses were 61%, 40% and...
20% respectively, which was sustained to week 48: 62%, 45% and 26% respectively. The Disease Activity Score in 28 joints (DAS28) <2.6 was achieved by 32% and 45% at weeks 24 and 48 respectively.

In the SUMMACTA study, patients were randomised to treatment with either tocilizumab SC 162mg every week plus placebo IV infusion every 4 weeks, or tocilizumab 8mg/kg IV infusion every 4 weeks plus placebo SC every week for 24 weeks (double-blind phase). The primary outcome was the non-inferiority of tocilizumab SC to IV regarding the proportion of patients achieving an ACR20 response at week 24 (per-protocol population, n=1095, non-inferiority margin -12%); non-inferiority was confirmed (see below, table 1).

After week 24, patients were re-randomised to either SC or IV tocilizumab for the 72-week open-label extension period. Results for the intention-to-treat population are below in table 2.

### Table 1: SUMMACTA study, week 24 primary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tocilizumab SC (n=558)</th>
<th>Tocilizumab IV (n=537)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>69.4%</td>
<td>73.4%</td>
<td>-4% (95% CI -9.2 to 1.2)</td>
</tr>
<tr>
<td>ACR50</td>
<td>47%</td>
<td>49%</td>
<td>-1.8% (95% CI -7.5 to 4.0)</td>
</tr>
<tr>
<td>ACR70</td>
<td>24%</td>
<td>28%</td>
<td>-3.8% (95% CI -9.0 to 1.3)</td>
</tr>
</tbody>
</table>

### Table 2: SUMMACTA study, week 97 primary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tocilizumab SC to IV (n=40)</th>
<th>Tocilizumab IV to SC (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>82.5%</td>
<td>88.5%</td>
</tr>
<tr>
<td>ACR50</td>
<td>57.5%</td>
<td>67.3%</td>
</tr>
<tr>
<td>ACR70</td>
<td>37.5%</td>
<td>47.3%</td>
</tr>
</tbody>
</table>

### Safety

In the SUMMACTA study, the safety profile was similar between the two groups with the exception of more injection-site reactions occurring in the SC group vs. the IV group: 10.1% vs. 2.4%. Erythema was most common (4.4% vs. 0.8%), followed by pain (1.9% vs. 0.8%), pruritus (2.2% vs. 0%) and haematoma (0.8% vs. 0.8%). No injection site reaction required dose interruption or withdrawal.

Further details of adverse events can be found on the [Summary of Product Characteristics](#).

### Convenience

Subcutaneous administration may be suitable for:
- Patients who have a preference for SC administration, rather than IV.
- Patients who find it difficult to attend for monthly IV infusion appointments.
- Patients who want to take control of their RA without needing to see a healthcare professional at every treatment dose.

After proper training in injection technique, patients may self-inject with tocilizumab SC injection if their clinician determines that it is appropriate. The total content (0.9 ml) of the pre-filled syringe should be administered as a subcutaneous injection. The recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

### Risk assessment

Guidelines from the British Rheumatology Society on the use of intravenous tocilizumab state a number of safety considerations for patients having tocilizumab therapy. These guidelines do not include subcutaneous administration, but the safety considerations are likely to be similar. The following recommendations come from the [Summary of Product Characteristics](#) for the SC formulation.

1. **Lipid profile:** Increased lipid parameters, including total cholesterol, LDL, HDL and triglycerides have been seen in patients treated with tocilizumab. Assessment of lipid parameters should be carried out every 4-8 weeks following initiation of therapy and patients managed according to local guidelines as necessary.
2. **Neutrophil counts:** Decreases in neutrophil and platelet counts have occurred following tocilizumab treatment. Neutrophils and platelets should be monitored every 4-8 weeks following initiation of therapy and thereafter according to standard clinical practice.
3. **Liver function:** ALT and AST levels should be monitored every 4-8 weeks for the first 6 months of treatment, followed by every 12 weeks thereafter. If ALT or AST levels are >3-5 times the upper limit of normal, tocilizumab therapy should be interrupted.

### Budget impact

There is a [Patient Access Scheme (PAS)](#) in place, agreed by the Department of Health, NICE and the SMC, which ensures that SC tocilizumab is cost-effective to the NHS. The price of tocilizumab SC injection, after the PAS discount, is £716.80 for a monthly pack (4 pre-filled syringes). Tocilizumab will be delivered to RA patients by a homecare provider. A PAS scheme has also been agreed by the Department of Health and NICE for certolizumab, which is funded by the manufacturer for the first 12 weeks of use.
Of the TNF inhibitors approved by NICE for treatment of RA, tocilizumab is priced competitively to subcutaneous adalimumab and etanercept. In year 1 certolizumab is available at a lower acquisition cost compared with tocilizumab due to their respective PAS which are currently in operation.

Drug acquisition costs per 70kg patient over 2 years, including the PAS discounts but excluding VAT are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab SC</td>
<td>162mg/week</td>
<td>£9,318</td>
<td>£9,318</td>
</tr>
<tr>
<td>Etanercept SC</td>
<td>50mg/week</td>
<td>£9,295</td>
<td>£9,295</td>
</tr>
<tr>
<td>Adalimumab SC</td>
<td>40mg/fortnight</td>
<td>£9,156</td>
<td>£9,156</td>
</tr>
<tr>
<td>Certolizumab SC</td>
<td>200mg/fortnight</td>
<td>£6,793</td>
<td>£9,295</td>
</tr>
</tbody>
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Potential acquisition costs per 100,000

<table>
<thead>
<tr>
<th>Population</th>
<th>100,000</th>
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<tbody>
<tr>
<td>Adult population &gt;18yrs</td>
<td>80,000</td>
</tr>
<tr>
<td>RA prevalence in adults (0.86%)</td>
<td>688</td>
</tr>
<tr>
<td>RA adult patients suitable for biologics (0.086%)</td>
<td>69</td>
</tr>
<tr>
<td>RA adults patients on biologic without MTX (32% of all biologic-treated patients)</td>
<td>22</td>
</tr>
</tbody>
</table>

Total yearly cost if all adult patients on biologics without MTX were receiving tocilizumab SC (without PAS discount or VAT) at £11,897 per patient/year £261,140

Funding
CCG-commissioned. PbR-excluded (high-cost drug).

Reference List

(2) UKMI New Drugs Online Database UKMI www.ukmi.nhs.uk/ndd
(8) Burmester GR, Rubbert-Roth A, Cantagrel A et al. The efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). EULAR (European League Against Rheumatism) Annual European Congress of Rheumatology; Paris, France, 11-14 June: 2014

Written by Alexandra Denby, London Medicines Information Service, Northwick Park Hospital, Harrow, HA1 3UJ, alexandra.denby@nhs.net. Roche had the opportunity to carry out a factual check on this review. LMEN would like to thank Scott Mercer, Principal Medical pharmacist from Guys and St Thomas’s Foundation Trust for his comments.