

tocilizumab, 162mg, solution for injection in pre-filled syringe (RoActemra®) SMC No. (982/14)

Roche Products Ltd.

04 July 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tocilizumab (RoActemra®) is accepted for restricted use within NHS Scotland.

Indication under review: In combination with methotrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to 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. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

SMC restriction: tocilizumab is restricted to use in accordance with current eligibility and continuation rules for biologic therapies in rheumatoid arthritis.

A phase III, randomised, double-blind, parallel-group study in adult patients with rheumatoid arthritis demonstrated that subcutaneous tocilizumab was non-inferior to tocilizumab intravenous infusion for the primary outcome of proportion of patients who achieved an American College of Rheumatology 20% response.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of subcutaneous tocilizumab. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

In combination with methotrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to 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. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Dosing Information

The recommended dose is 162mg subcutaneously once every week.¹

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA.

Limited information is available regarding switching patients from tocilizumab intravenous formulation to tocilizumab subcutaneous fixed-dose formulation. The once weekly dosing interval should be followed.¹

Patients transitioning from intravenous to subcutaneous formulations should administer their first subcutaneous dose instead of the next scheduled intravenous dose under the supervision of a qualified healthcare professional.¹

Product availability date

19 May 2014

Summary of evidence on comparative efficacy

Tocilizumab is a humanised anti-interleukin-6 (IL-6) receptor antibody that blocks the action of IL-6, one of a number of pro-inflammatory cytokines (that also includes IL-1 and tumour necrosis factor alpha [TNFα]) considered to play a central role in maintaining inflammation in rheumatoid arthritis. Tocilizumab intravenous infusion has a marketing authorisation for moderate to severe active rheumatoid arthritis (RA) in adults, active systemic juvenile idiopathic arthritis in children aged ≥2 years, and juvenile idiopathic polyarthritis in children aged ≥2 years. A new subcutaneous formulation of tocilizumab (tocilizumab SC) has now been licensed for treatment of moderate to severe rheumatoid arthritis in adults.

A randomised, double-blind, parallel-group, non-inferiority study (SUMMACTA²) compared the safety and efficacy of tocilizumab SC with intravenous tocilizumab (tocilizumab IV) in combination with traditional disease-modifying antirheumatic drugs (DMARDs) in patients with moderate to severe RA. Eligible patients were aged ≥18 years with a diagnosis of RA according to the American College of Rheumatology (revised 1987) criteria of at least 6 months duration, and with the following major criteria: swollen joint count ≥4 (66-joint count) and tender joint

count ≥ 4 (68-joint count) at screening and baseline; C-reactive protein (CRP) $\geq 10\text{mg/L}$ and/or erythrocyte sedimentation rate (ESR) $\geq 28\text{mm/h}$ at screening. Patients must have received one or more traditional DMARDs at a stable dose for 8 weeks or longer before baseline, and were required to have had an inadequate response to DMARDs (up to 20% of patients were allowed to have failed one or more TNF inhibitor). Patients were randomised equally to receive tocilizumab SC 162mg weekly plus IV placebo every 4 weeks ($n=631$); or tocilizumab 8mg/kg IV every 4 weeks plus SC placebo weekly ($n=631$) for 24 weeks. Patients were stratified by geographical region and body weight category ($<60\text{kg}$, $\geq 60\text{kg}$ to $<100\text{kg}$ or $\geq 100\text{kg}$). The primary outcome was the proportion of patients who achieved an American College of Rheumatology 20% (ACR20) response at week 24, assessed in the per protocol population ($n=558$ for tocilizumab SC; $n=537$ for tocilizumab IV). The proportion of patients who achieved an ACR20 response at week 24 was 69% for tocilizumab SC and 73% for tocilizumab IV. The difference between the groups was -4.0% (95% CI: -9.2 to 1.2). Since the lower bound of the 95% CI was greater than the pre-specified margin of -12%, non-inferiority was demonstrated. Secondary outcomes included the proportion of patients who achieved an ACR50 and ACR70 response, remission based on the disease activity score using 28 joints (disease activity score [DAS28] < 2.6) and a decrease from baseline of 0.3 or greater in the health assessment questionnaire-disability index (HAQ-DI) at week 24. The results for all secondary outcomes were similar between the two treatment groups.² The proportion of patients who achieved ACR20/50/70 responses were similar in both groups across all body weight categories.²

Patients who completed 24 weeks of double-blind treatment could enter a 72-week open-label phase of the SUMMACTA study. Patients who initially received tocilizumab SC were re-randomised 11:1 to receive tocilizumab SC or tocilizumab IV, and patients who initially received tocilizumab IV were re-randomised 2:1 to receive tocilizumab IV or tocilizumab SC. An interim analysis of the open-label phase up to week 49 suggested that efficacy of tocilizumab SC was maintained over this period. The proportion of patients who achieved ACR20/50/70, DAS28 and HAQ-DI scores were similar in both groups.³

Summary of evidence on comparative safety

In the SUMMACTA study, the proportions of all adverse events (AEs) and serious adverse events (SAEs) were similar between the two treatment groups.²

Infection was reported in 36% of patients in the tocilizumab SC group versus 39% in the tocilizumab IV group. The rate of serious infections was similar between the groups ($n=9$; 1.4%) for both tocilizumab SC and tocilizumab IV.²

Injection site reactions were reported more frequently with tocilizumab SC ($n=64$; 10%) than tocilizumab IV ($n=15$; 2.4%). The most common symptoms associated with injection site reaction were erythema, pain, pruritis and haematoma.²

Summary of clinical effectiveness issues

Tocilizumab subcutaneous injection is a new formulation of tocilizumab that is administered as a fixed dose (162mg). It is an alternative to tocilizumab intravenous infusion, which has a variable dose according to patient weight.

The SUMMACTA study demonstrated that tocilizumab SC was non-inferior to tocilizumab IV in adult patients with rheumatoid arthritis. The response was similar between groups across the body weight categories. The majority of patients in the study were taking concurrent methotrexate (80% for tocilizumab SC and 82% for tocilizumab IV) and 22% and 21% respectively had previously failed a TNF inhibitor. The mean DAS28 score at baseline (6.6 and 6.7 respectively) indicated that patients had high disease activity. The primary outcome of ACR20 response is a validated outcome in studies in rheumatoid arthritis.

There is limited information available regarding switching patients from tocilizumab IV to tocilizumab SC and there are no studies comparing tocilizumab SC with other biologic therapies in patients with rheumatoid arthritis.

Tocilizumab SC offers an alternative to tocilizumab IV and is administered as a fixed dose once weekly, in contrast to tocilizumab IV, which has a variable dose according to patient weight and is administered once every 4 weeks as an intravenous infusion over one hour. Tocilizumab SC has an advantage over tocilizumab IV in that there is no need to calculate individualised doses.

Clinical experts consulted by SMC considered that the introduction of this medicine may impact favourably on service delivery, as patients may self-administer tocilizumab SC at home.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing tocilizumab SC to tocilizumab IV in adult patients who have either responded inadequately to or who were intolerant to previous therapy with one or more DMARDs or TNF antagonists. The time period for the analysis was a one year horizon. A patient weight of 70kg was assumed.

The evidence used to support the cost-minimisation analysis was the SUMMACTA non-inferiority study. Additionally, the submitting company indicated that by using a bridging argument and the non-inferiority evidence, all available clinical data in adult RA can be applied to the two formulations of tocilizumab. By extrapolation, this would then imply that the company would wish any economic evidence where the IV formulation of tocilizumab has shown cost-effectiveness to apply to the SC preparation for its licensed indications. SMC has previously accepted tocilizumab IV in combination with MTX or as a monotherapy against a range of treatment sequences including other biologic agents.

The costs included in the analysis related to the drug acquisition costs and any associated administration costs. For IV tocilizumab, the administration cost was based on a published study. For tocilizumab SC, it was assumed that for 90% of patients treatment would be administered free of charge to the NHS through a home delivery scheme and in the remaining 10% of patients, a district nurse would administer the treatment. The company assumed that there would be no difference in monitoring costs between each treatment option.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount is applied to the list price of the medicine.

The result, without the PAS, was that SC tocilizumab was not the cost-minimising treatment. Based on drug acquisition costs and administration costs, IV tocilizumab cost £11,690

compared to £12,047 per patient per year for SC tocilizumab. With the PAS, tocilizumab SC became a cost-effective treatment option.

The company provided sensitivity analysis varying the % of patients who receive their medicine from a district nurse, the costs associated with IV administration and patient weight. The results showed that tocilizumab SC remained cost-effective when the PAS was taken into account unless the cost of IV administration was reduced by 10% or more.

There were some limitations noted with the analysis:

- The analysis assumed that there will be no additional monitoring costs associated with tocilizumab SC. In previous tocilizumab IV submissions to SMC where comparator medicines were administered by SC injection, the company considered that additional monitoring visits and tests were applicable for the SC arm (but no additional monitoring cost for IV tocilizumab was included as this was assumed to be integral to the IV administration cost). While SMC experts at that time suggested that the monitoring levels they had assumed were excessive and that the zero cost assumption for IV tocilizumab may not have been correct, some additional allowance for outpatient visits would be relevant for SC administered treatments and it could be argued should have been included here on consistency grounds. As such, the company was asked to provide analysis where some monitoring costs for tocilizumab SC were included. The company provided threshold analysis which showed that if more than 1.5 additional outpatient visits were required, tocilizumab SC was no longer cost-effective (with PAS). However, it was also acknowledged that there are potentially other assumptions included in the analysis that may underestimate the savings with tocilizumab SC, i.e. the % of patients receiving treatment from a district nurse may be lower in practice and the average weight of patients may be higher (which would increase the cost of tocilizumab IV).
- There are no directly comparative studies for tocilizumab SC against other SC medicines for RA (e.g. adalimumab, etanercept or certolizumab). Instead, the company has used a bridging argument to link the SC medicine to the previous evidence base that would exist versus other active comparators. A similar argument has been used in previous submissions to SMC for other products.

The medicine may be associated with small additional overall costs if additional monitoring costs are incorporated into the analysis but these may be offset by plausible variation in other assumptions. In addition, the new formulation may offer patient and service benefits given the mode of administration. Given this, the economic case has been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

The following information reflects the views of the specified patient group.

- A submission was received from the National Rheumatoid Arthritis Society (NRAS) which is a registered charity.
- NRAS has received some pharmaceutical company funding in the past two years, including from the submitting company.
- Rheumatoid Arthritis (RA) is a chronic, progressive and disabling autoimmune disease which mainly impacts on the joints, but can affect other organs such as the heart, eyes and lungs.
- RA can cause severe disability and greatly affects a person's ability to carry out everyday living activities, with many having to give up employment. It can affect the person's self-esteem and self image, confidence and emotional wellbeing as well as impacting upon relationships and sexuality. People often experience symptoms of pain, fatigue and depression.
- Tocilizumab is currently administered by infusion in hospital, which can require time off work. Those with long standing disease may also experience difficulty being cannulated.
- This submission for an alternative administration of tocilizumab via sub-cutaneous injection is advantageous to patients as they can inject at home at their convenience rather than attending hospital. It will also reduce pressure on NHS day-case facilities and transport costs.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 123 Management of early rheumatoid arthritis in February 2011. All patients with moderate to severe disease activity should receive treatment with DMARDs, adjusted with the aim of achieving remission or a low disease activity score (DAS)/28-joint disease activity score (DAS28). Use of TNF α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.

The Royal College of Physicians published a national clinical guideline for the management and treatment rheumatoid arthritis in adults in 2009. These state that in patients with established active disease despite conventional DMARDs, the addition of a biologic drug generally adds significant benefits for symptom control, function and quality of life, and that the combination of biological drug to methotrexate compared to methotrexate alone favours the combination.

The National Institute for Health and Care Excellence (NICE) currently has guidance in development on biologics (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab) in rheumatoid arthritis (ID537).

Additional information: comparators

Tocilizumab 20mg/mL concentrate for solution for infusion.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Tocilizumab 162mg solution for injection in pre-filled syringe	162mg subcutaneously once every week	£11,870
Tocilizumab 20mg/mL concentrate for solution for infusion	8mg/kg intravenously every 4 weeks	£9,318

Cost for tocilizumab SC is from the company submission (without PAS). Cost for tocilizumab IV is from dm+d on 05/05/14 and assumes a patient weight of 70kg.

Additional information: budget impact

The submitting company estimated there to be 5146 patients eligible for treatment with tocilizumab each year, with an estimated uptake rate of 2% in year 1 and 18% in year 5 and a 12% discontinuation rate.

Without the PAS, the submitting company estimated the gross medicines budget impact to be £1.3m in year 1 and £9.6m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £278k in year 1 and £2.06m in year 5. These figures do not take account of any non-cash releasing savings associated with reduced use of resources for treatment administration given the move from an IV to a SC medicine.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Roche Products Ltd. Summary of Product Characteristics tocilizumab RoActemra® 162mg solution for injection in pre-filled syringe, last updated 29/04/13.

2. Burmester GR, Rubbert-Roth A, Cantagrel A et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). Ann. Rheum Dis 2014; 73 (1): 69 to 74.

3. Burmester GR, Rubbert-Roth A, Cantagrel A et al. The efficacy and safety of tocilizumab subcutaneous versus tocilizumab intravenous, in combination with traditional DMARDs, in patients with RA at 49 weeks (SUMMACTA). Arthritis and Rheumatism 2013; 65 (10); supplement; Abstract number 464.

This assessment is based on data submitted by the applicant company up to and including 11 June 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the

considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.