

tocilizumab, 20mg/mL concentrate for solution for infusion (RoActemra®) SMC No. (754/12)

Roche Products Limited

13 January 2012

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

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

Indication under review: treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tocilizumab can be given as monotherapy (in case of intolerance to methotrexate or where treatment with methotrexate is inappropriate) or in combination with methotrexate.

Tocilizumab was superior to placebo in reducing disease activity and fever in patients with persistent active systemic juvenile idiopathic arthritis despite treatment with NSAIDs and corticosteroids.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of tocilizumab. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients two years of age and older, who have responded inadequately to previous therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tocilizumab can be given as monotherapy (in case of intolerance to methotrexate or where treatment with methotrexate is inappropriate) or in combination with methotrexate.

Dosing Information

The recommended dose is 8mg/kg once every two weeks as an intravenous infusion in patients weighing ≥ 30 kg or 12mg/kg once every two weeks in patients weighing < 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

The summary of product characteristics (SPC) details laboratory abnormalities where dose interruptions of tocilizumab are recommended in sJIA patients.

Available data suggest that clinical improvement is observed within six weeks of initiation of treatment with tocilizumab. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of rheumatoid arthritis or sJIA. All patients treated with tocilizumab should be given the Patient Alert Card.

Product availability date

03 August 2011

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 considered to play a central role in maintaining inflammation in rheumatoid arthritis that also include IL-1 and tumour necrosis factor alpha (TNF α). Tocilizumab has a marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis 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 TNF α antagonists. SMC has previously accepted tocilizumab for restricted use in rheumatoid arthritis, in combination with methotrexate, in adults.

Tocilizumab has recently been granted a marketing authorisation for the treatment of systemic juvenile idiopathic arthritis (sJIA). In addition to arthritis in the joints, systemic JIA is associated with a range of additional symptoms including fever, rash, swollen glands, tiredness and lack of energy, weight loss and muscle pain. It can lead to joint damage and permanent disability. Tocilizumab is the first medicine to be licensed specifically for this indication although the TNF-

alpha inhibitors etanercept and adalimumab are licensed for polyarticular juvenile idiopathic arthritis and have previously been accepted by SMC in this setting.

The evidence for the new indication comes from two placebo-controlled studies. The pivotal TENDER study ^{1, 2} recruited 112 children aged 2 to 17 years with sJIA according to the International League of Associations for Rheumatology (ILAR) classification (2001). Patients had at least 6 months documented persistent sJIA activity prior to screening, an inadequate response to NSAIDs and corticosteroids because of toxicity or lack of efficacy, and high sensitivity C-reactive protein (CRP) >4.3 mg/L. Concomitant treatment with stable doses of NSAIDs, methotrexate and low to medium doses of corticosteroids was allowed but other DMARDs and biologics were not permitted.

The TENDER study consisted of three phases. Part I was a 12-week, randomised, double-blind, placebo-controlled phase that included an escape option (if protocol-specified criteria were met) for patients receiving placebo to receive open-label tocilizumab. Patients who completed Part I of the study could enter Part II, where all patients received open-label tocilizumab for 92 weeks. Patients who received escape treatment during Part I and who were benefiting from tocilizumab could also enter Part II. Part III is a further 3-year, open-label extension that is ongoing.

In the controlled phase, Part I, patients were randomised in a 2:1 ratio, with stratification by body weight, disease duration, background corticosteroid dose and background methotrexate use to intravenous infusions of tocilizumab or placebo. The tocilizumab dose depended on body weight: <30 kg received 12mg/kg and ≥30 kg received 8mg/kg every 2 weeks for six doses. The primary outcome was the proportion of patients with a JIA American College of Rheumatology (ACR) 30 response and absence of fever assessed at Week 12 in the intention to treat (ITT) population. ACR30 response is a validated paediatric response criterion defined as improvement by at least 30% in at least three of six core components (physician global assessment of disease activity; parent/patient global assessment of overall well-being; number of joints with active arthritis; number of joints with limitation of movement; erythrocyte sedimentation rate; functional ability (Childhood Health Assessment Questionnaire [CHAQ])), with no more than one component worsening by more than 30%. Absence of fever was defined as no temperature recording ≥37.5° C in the preceding 7 days. This was achieved by significantly more tocilizumab than placebo patients: 85% (64/75) versus 24% (9/37) respectively (weighted difference: 62% [95% confidence interval: 45 to 78], p<0.0001). The primary outcome was reported in 76% (28/37) patients in the tocilizumab 8mg/kg group and 95% (36/38) in the tocilizumab 12mg/kg group.

Patients receiving tocilizumab achieved significant results over placebo in all 22 secondary endpoints which included objective and subjective outcomes and measures of arthritis and systemic disease. Tocilizumab patients had a greater chance of achieving JIA ACR30/50/70/90 responses (corresponding percentage improvements in ACR criteria) at Week 12 compared with placebo patients. Significantly positive effects were shown on joint inflammation, systemic effects, laboratory endpoints and physical function in tocilizumab patients compared with placebo patients. Corticosteroid use could be reduced in patients by more than 20% after reaching a JIA ACR70 response without experiencing a disease flare. Results from the open-label extension phase show that most patients maintained the response for JIA ACR30 and absence of fever, with 82% (78/95) patients still responding at weeks 48. JIA ACR90 was met by 69% (66/95) patients at 48 weeks. ^{1, 3}

In a supportive, withdrawal design, Japanese study⁴ 44 out of 56 children recruited with active sJIA responded to three doses of tocilizumab 8mg/kg every 2 weeks and were then randomised in a double-blind manner to continue active treatment or to receive placebo for 12 weeks. Significantly more tocilizumab patients compared with placebo patients, 80% versus 17% respectively, achieved the primary endpoint of maintaining ACR30 response and CRP concentrations <15mg/L.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In general, adverse events (AE) in sJIA patients in the pivotal study were similar to those seen in rheumatoid arthritis patients e.g. infections, leucopenia, thrombocytopenia, increased AST, ALT, bilirubin, cholesterol and infusion reactions. The rates of AE, particularly infection and leucopenia, appeared to be higher in children. AE were reported in 88% (66/75) versus 62% (23/37) patients in the tocilizumab versus placebo groups respectively. The majority of AE were of mild to moderate intensity and the most common in the tocilizumab group were upper respiratory tract infection, headache, nasopharyngitis, and diarrhoea. Serious AE were reported in 4% (3/75) tocilizumab patients and in no placebo patients.¹

The infection rate in the 12-week, double-blind phase was 345 versus 287 per 100 patient years for the tocilizumab versus placebo groups, respectively and remained at a similar level in the ongoing open label extension phase at 307 per 100 patient years. The rate of serious infection in the tocilizumab group in the double blind phase was 11.5 per 100 patient years and remained stable in the open-label extension phase. Clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported in 1 of 112 patients treated with tocilizumab during the controlled and open-label extension phases (angioedema).¹

Long-term safety data are not available.

Summary of clinical effectiveness issues

Systemic JIA is a subtype of JIA characterised by systemic manifestations of disease in addition to arthritis. The prevalence of all types of JIA is thought to be around 1 in 1,000 children, equating to around 10,000 children in the UK. Around 10 to 20% of children with JIA have the systemic sub-type. Tocilizumab is the first medicine to be licensed in the UK specifically for the treatment of sJIA.

The pivotal TENDER^{1,2} study population had fairly high disease activity with approximately 70% of patients receiving methotrexate in combination with study drug. The supportive withdrawal study⁴ was conducted in Japan and it is not clear if similar results would be seen in the Scottish population. Controlled data are limited to 12 weeks. Safety concerns with tocilizumab include the risk of angioedema during treatment and the lack of safety data on long-term use.

Clinical experts consulted by SMC have indicated that there is significant unmet need for a treatment for sJIA. They have advised that off-label anakinra is the main treatment currently used in Scotland. The SPC for anakinra states that the safety and efficacy in children aged 0 to

18 years have not been established. Anakinra is administered as daily subcutaneous injections whereas tocilizumab requires one intravenous infusion every two weeks. The use of tocilizumab may therefore provide both patient and service benefits.

Two indirect comparisons, using the Bucher method, were included in the company submission: tocilizumab versus infliximab and tocilizumab versus anakinra. The indirect comparison with infliximab was not considered appropriate since the infliximab study used did not correspond to the licensed population (sJIA). The indirect comparison versus anakinra found no significant difference between treatments for the ACR30 and absence of fever outcome deemed acceptable by the European Medicines Agency for assessing drugs in sJIA. The comparison had several limitations, however, as it included only two studies: the pivotal TENDER study and a placebo-controlled anakinra study⁵ which was small (24 patients) and of short duration (controlled phase was 1 month). There were also differences between the studies in baseline disease severity and use of concomitant methotrexate.

The economic evaluation also compared tocilizumab with methotrexate. This comparison is not considered valid because tocilizumab should only be given as monotherapy when methotrexate is not tolerated or is inappropriate.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of tocilizumab with and without concurrent methotrexate compared to:

- I. methotrexate alone in children and adolescents with sJIA which has not responded adequately to prior NSAID(s) and systemic corticosteroids.
- II. anakinra in patients who were inadequate responders to NSAID(s), systemic corticosteroids and methotrexate.

The analysis used a Markov model with 12-week cycles with the health states consisting of ACR30, 50, 70 and 90 response to treatment, no response, uncontrolled disease or death. In the model, patients start treatment with tocilizumab or the comparator at age 2, and on non-response go on to receive up to a further three lines of treatment with biologic agents (etanercept, adalimumab, abatacept) until age 18. In an alternative scenario, anakinra was replaced with etanercept as the first choice biologic agent. However, information from SMC clinical experts confirmed that the predominant biologic agent currently used in Scotland for sJIA is anakinra, and it tends to be positioned after other conventional treatments including methotrexate.

The analysis comparing tocilizumab with and without methotrexate with methotrexate alone was considered invalid as the licence for tocilizumab in sJIA allows use as monotherapy (i.e. without methotrexate) only in patients who are intolerant to methotrexate or where treatment with methotrexate is inappropriate.

For the comparison versus anakinra, as there was no head to head clinical data, the relative ACR response state probabilities were derived via an adjusted indirect comparison of TENDER versus an anakinra study, as described in the clinical effectiveness section. The relative efficacy of etanercept and the other biologics were derived from an indirect comparison performed of the TENDER study versus an infliximab study, with the infliximab results representing a proxy for the other biologics. As only 16% of the infliximab study patients were specifically sJIA patients,

a further efficacy adjustment using an observational dataset in etanercept patients with sJIA and other types of JIA was applied, that had the impact of reducing the relative efficacy of the comparator biologic agents. These adjustments introduce additional uncertainty.

In the model, data on withdrawals due to lack of efficacy and mortality associated with sJIA were based on published single study sources. Using data from the indirect comparison average child HAQ (CHAQ) scores were calculated for each response health state and a utility estimate derived for each state based on the CHAQ score. However, specific sJIA CHAQ-based utilities were not available so a non-linear mapping function for adult HAQ and EQ-5D in rheumatoid arthritis patients was used instead. Drug and administration costs were included and for the biologic agents that require weight-based dosing, these costs were dependent on the age and weight of the patients. The cost of drug wastage was included. Healthcare resource-use costs estimates were based on published schedules adapted by expert clinical opinion. This produced average per cycle costs of between £374 -and £545 for ACR90 to ACR30 response respectively, and a substantially higher cost of £3,641 for the no-response or uncontrolled disease state. This high cost was driven by the assumption that 90% of patients in these states are estimated to have an inpatient stay of average duration of 24.5 days per 12 week cycle. As tocilizumab had a substantially lower proportion of patients in the no-response state, this was an important driver improving the cost-effectiveness results in favour of tocilizumab. Clinical experts confirmed that this assumption is reasonable.

A patient access scheme 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 discount was offered on the list price of tocilizumab.

The ICERs were sensitive to the estimates for resource use costs and drug administration costs. Tocilizumab is administered intravenously and the submitting company assumed a 1-hour infusion would be required in an outpatient setting, whereas anakinra is a subcutaneous injection and was assumed to be self administered without nurse visits (by carers) in 70% of cases. The model results were also relatively sensitive to age at start of treatment, so the ICER increases if it is assumed all patients start treatment at age 5. The results were not highly sensitive to using alternative utility mapping or no drug wastage scenarios.

There were some limitations associated with the economic analysis, in particular:

- Concerns over the robustness of the Markov model structure, in that it did not allow patients to move between ACR response health states within each treatment line. This could introduce bias of an uncertain direction.
- Comparisons versus anakinra and etanercept were based on an indirect comparison with challengeable assumptions required to produce probabilities for each health state, and questionable robustness of the results, as described in the clinical effectiveness section.

In response to concerns raised by the New Drugs Committee the submitting company provided a revised model, this addressed the main weaknesses in the economic case. The model compares tocilizumab followed by anakinra and palliative care with anakinra followed by palliative care. This new model contains different health states defined as severe, moderate, mild and controlled based on Child HAQ (CHAQ) score with associated utility linked to ACR response, whereas the original model was based on ACR response category linked to CHAQ and associated utility. It is difficult to assess whether this model is more robust overall, as it is

still limited by data available. However, the revised model may have advantages in terms of how utilities are assessed in the model. In addition, the differences in average costs across health states appear to be more reasonable in this model, to some extent addressing some of the concerns relating to high relative resource use costs in the DAD associated with no-response. The resulting cost per QALY estimate in the comparison versus anakinra, based on the PAS, was £16,923 with the PAS.

Despite the limitations outlined above, the economic case was considered demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Arthritis Care in Scotland
- SNAC

Additional information: guidelines and protocols

The American College of Rheumatology has recently published (2011) Recommendations for the Treatment of Juvenile Idiopathic Arthritis. It divides systemic JIA into two separate groups:

- systemic arthritis with active systemic features (and without active arthritis) and
- systemic arthritis with active arthritis (and without systemic features)

The recommendations do note that the appropriate treatment of patients with concurrent active arthritis and active systemic features may be expected to incorporate elements of both recommendations.

Anakinra was the only biologic drug recommended in patients with active systemic features. Anakinra, TNF α inhibitors and abatacept were recommended in specific situations in systemic arthritis with active arthritis and without systemic features. TNF α inhibitors were not considered owing to their reported relatively poor effectiveness. These guidelines predate the availability of tocilizumab for use in this indication.

The British Society for Paediatric and Adolescent Rheumatology (BSPAR) published Standards of care for children and young people with juvenile idiopathic arthritis in 2010. However this document does not include treatment recommendations.

Additional information: comparators

Tocilizumab is the first medicine to be licensed in the UK specifically for the treatment of sJIA. Other biologic drugs have been used off-label. Anakinra is the main comparator although its safety and efficacy in children has not been established.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Tocilizumab	By intravenous infusion once every two weeks: 8mg/kg if $\geq$ 30kg or 12mg/kg if $<$ 30kg.	5,325 to 15,974*
Anakinra	By subcutaneous injection once daily 2mg/kg up to a maximum of 100mg**	9,548

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 07.11.11. *Costs based on body weight range 12kg to 60kg. ** Dose is from the ANAJIS study. Aankinra is not licensed for use in this indication.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 40 patients in year 1 and 41 patients in year 5. Based on a forecast uptake of tocilizumab of 20% in year 1 (8 patients), and 60% in year 5 (24 patients), the gross impact on the medicines budget was estimated at £75K in year 1 and £229K in year 5 (without the PAS). The net impact after displacement of methotrexate (60%), anakinra (30%) and etanercept (10%) was estimated to be £47K in year 1 and £144K in year 5. Additional net costs would be incurred primarily associated with the IV drug administration costs associated with tocilizumab. The budget impact estimates are likely to be inaccurate as they include uptake in patients who are not inadequate responders to methotrexate; this positioning has not been supported by the economic case presented versus methotrexate, or by the licence for tocilizumab which precludes the displacement of methotrexate by tocilizumab monotherapy.

Other data were also assessed but remain commercially confidential.*

The undernoted references were supplied with the submission.

1. European Medicines Agency Variation Assessment Report for tocilizumab EMEA/H/C/955/II/15 www.ema.europa.eu
2. De Benedetti F, et al. 2011 Efficacy and safety of tocilizumab (TCZ) in patients (PTS) with systemic juvenile idiopathic arthritis (sJIA): Tender 52-Week Data. European League Against Rheumatism 2011. Abstract and oral presentation OP0006 <http://www.ped-rheum.com/content/pdf/1546-0096-9-S1-P164.pdf>
3. European Medicines Agency Type II Variation Committee for Medicinal Products for Human Use (CHMP) Overview and Request for Supplementary Information RoActemra (tocilizumab) EMEA/H/C/955/II/15 16 December 2010
4. Yokota S, Imagawa T, Mori M et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial Lancet 2008; 371: 998–1006 <http://www.sciencedirect.com/science/article/pii/S0140673608604547>
5. Quartier P, Allantaz F, Cimaz R et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011 70:747-54. 2010 December 20 Epub ahead of print <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3070271/?tool=pubmed>

This assessment is based on data submitted by the applicant company up to and including 13 December 2011.

**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. These have been confirmed from the eVadis drug database. 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.