1 Executive Summary

1.1 Product characteristics, license, existing HTA guidance in the UK

Product

Tocilizumab (RoActemra®)

Licensed Indications

Rheumatoid arthritis

Tocilizumab, 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 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.

Systemic juvenile idiopathic arthritis

Tocilizumab is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Tocilizumab can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.

Mode of action

Tocilizumab is a humanised anti IL-6 receptor antibody, which blocks the function of the pleiotropic cytokine IL-6, considered to play a central role in chronic inflammation in RA. It was initially approved for use in RA by the European Medicines Agency (EMA) in January 2009

Available formulations

Vial containing 80 mg of tocilizumab in 4 ml (20 mg/ml).
Vial containing 200 mg of tocilizumab in 10 ml (20 mg/ml).
Vial containing 400 mg of tocilizumab in 20 ml (20 mg/ml).

Current HTA recommendations from NICE and SMC

NICE: Tocilizumab, in combination with MTX, is recommended for the treatment of severely active RA in patients:

- after the failure of two conventional DMARDs including methotrexate (DMARD-IR population)
- after the failure of two conventional DMARDs and a TNF inhibitor (TNF-IR population)
- after the failure of a TNF inhibitor and rituximab (BIO-IR population)

NICE guidance stipulates that tocilizumab should be used in line with existing NICE guidance for biologics in the DMARD-IR and TNF-IR settings [NICE TA130, TA225 and TA195]. A simple discount patient access scheme is offered by Roche. [NICE TA247, February 2012].

SMC has accepted tocilizumab for use in adult RA, both as combination therapy with MTX as well as monotherapy [SMC guidance 593/09 and 774/12 respectively for combination and monotherapy].

1.1 Overview and submission focus

This submission focuses on providing new data on the clinical and cost-effectiveness of tocilizumab monotherapy in the treatment of RA patients for whom methotrexate is contraindicated or inappropriate.

We present results from the ADACTA study [Gabay et al, 2012], the first head-to-head randomised controlled trial (RCT) of tocilizumab monotherapy compared to an anti-TNF monotherapy in this setting.

Our economic model is driven by results from ADACTA as well as from relevant placebo-controlled monotherapy studies of certolizumab pegol and etanercept. A network meta-analysis was created to allow indirect comparison of all biologic monotherapies and produce adjusted efficacy estimates to drive the economic model.

The submission has also summarised the clinical effectiveness data for tocilizumab in combination with MTX. No new cost-effectiveness estimates for tocilizumab in combination with MTX have been produced in this submission. We are not aware of any new evidence that would change the ICER published in TA247 [NICE, 2012].

1.2 Moderately active rheumatoid arthritis

TCZ is licensed and proven to be effective in the treatment of moderate to severe RA.

An illustrative subgroup analysis of the ACT-SURE study suggests that patients with a baseline DAS28 between 5.1 and 3.2 (moderately active RA) have outcomes not dissimilar to patients with higher baseline DAS28 > 5.1 (severely active RA). This suggests that patients with moderately active RA are equally likely to benefit from treatment with tocilizumab as patients with severe disease.

1.3 The role of tocilizumab monotherapy in rheumatoid arthritis

Up to 30 per cent of RA patients may require biologic monotherapy because they cannot tolerate MTX

A significant proportion of RA patients cannot tolerate MTX and following the failure of two conventional DMARDs up to 30 per cent will require biologic monotherapy [Soliman et al, 2011].

Currently biologic monotherapy treatment options are restricted by NICE to TNF inhibitors, however, a number of studies have demonstrated that TNF inhibitors are less effective when administered as monotherapy compared to use with MTX. This finding highlights the unmet need in those patients where continued use of MTX is not considered appropriate.

1.4 Monotherapy efficacy data for tocilizumab

Since the publication of NICE TA247, we are able to provide new data about tocilizumab monotherapy, including a head-to-head RCT

New data presented in this submission includes the head-to-head study, ADACTA (tocilizumab versus an active comparator adalimumab), as well as evidence from eight Phase III/IV/long-term extension trials assessing the use of tocilizumab as monotherapy. A network analysis was also conducted to provide an indirect comparison of biologic monotherapies.

The ADACTA study found that TCZ was superior to adalimumab on DAS28 score and ACR response outcomes

This head-to-head trial was designed specifically to test superiority of tocilizumab (TCZ) monotherapy versus adalimumab (ADA) monotherapy, in patients with RA of six months or greater duration, who were MTX intolerant or for whom continued treatment with MTX was inappropriate.

ADACTA was a multicentre, randomized, double-blind, 24-week trial involving RA

patients with a DAS28 score of more than 5.1 ('severely active' disease). A total 326 patients were randomized (1:1 ratio) to receive ADA or TCZ monotherapy. The primary endpoint was change in mean DAS28 score from baseline (BL).

The study met its primary endpoint demonstrating that TCZ was statistically significantly superior to ADA in reducing the signs and symptoms of RA as measured by DAS28. Clinically meaningful and statistically significant benefit over ADA was also observed on other outcomes including ACR response category and DAS28 remission

Adalimumab monotherapy is currently recommended by NICE as a cost-effective treatment option for RA patients who cannot tolerate MTX or in whom continued use of MTX would be inappropriate.

Table 1. Selected efficacy endpoints from ADACTA at week 24 (intent–to-treat population[a])

	TCZ	ADA	p-value[b]
N	163	162	
Change from baseline in DAS28, mean	-3.3[c]	-1.8	<0.0001
Patients achieving DAS28 reduction of 1.2, %	86.5	59.9	<0.001
DAS28 remission, %	39.9	10.5	<0.0001
DAS28 low disease activity, %	51.5	19.8	<0.0001
ACR20, %	65.0	49.4	<0.01
ACR50, %	47.2	27.8	<0.01
ACR70, %	32.5	17.9	<0.01

NOTES: [a]LOCF and imputation of non-response were applied to continuous and categorical endpoints, respectively, to handle missing data and data after withdrawal and escape. [b]p values were adjusted for region and duration of RA for all endpoints and additionally baseline DAS28 for the primary endpoint. [c]Two patients in the TCZ arm with no post-baseline data were excluded from the primary endpoint analysis.

A network meta-analysis found that TCZ monotherapy is superior to adalimumab, certolizumab pegol and etanercept monotherapies

This bespoke analysis was conducted to allow adjusted indirect comparison of all biologic monotherapies with one another. Results from the analysis suggest that TCZ monotherapy was associated with superior outcomes on ACR20, ACR50 and ACR70 response measures, compared with ADA, certolizumab pegol (CTZ) and etanercept (ETA) monotherapy.

1.5 Decision problem

Monotherapy focus

In this submission we have focussed on the cost-effectiveness of tocilizumab monotherapy in the treatment of RA in the DMARD-IR setting. With respect of combination therapy, we are not aware of any relevant clinical or economic evidence published since NICE issued its HTA guidance for tocilizumab in 2012 (TA247).

Our trial results suggest that patients with 'moderate' RA have treatment outcomes not dissimilar to patients with 'severe' RA.

The patient population in the pivotal studies includes patients with moderate to severe rheumatoid arthritis. We have presented an illustrative subset analysis for patients with moderate disease only (5.1≥DAS>3.2).

This analysis found few clinically or statistically significant differences in the 'moderate' RA group from the general population.

1.6 Economic model

The model design builds on the structure previously used in

The economic model was designed to demonstrate the cost-effectiveness of tocilizumab when used as the first option relative to currently available biologic monotherapy treatment options in the DMARD-IR setting.

TA247

The model design and approach mirror that used in TA247. The model is driven by ACR response outcomes, which create a simulated distribution of HAQ scores – these in turn allow the estimation of utility values according to established mapping algorithms.

In our base case analysis, a 'standard care' sequence of biologic treatments, followed by 'palliation' (that is, non-biologic therapy once those options have been exhausted) is compared to the same sequence with tocilizumab added to the front of the sequence.

A simple discount patient access scheme (PAS) is in operation already

As with the rapid review TA247, our submission presents cost-effectiveness estimates which take the existing PAS into account.

Results suggest that adding TCZ monotherapy as a treatment option in patients who cannot have MTX is cost-effective both with and without a PAS

A summary of the total costs, outcomes (QALYs gained) and incremental cost effectiveness ratio (ICER) for our base case analysis can be found in Table 2**.**

Table 2: Base case: cost-effectiveness results (with PAS)

	Standard of Care	Standard of care + TCZ	Incremental Difference	ICER (£/QALY)
Total QALYs	8.42	9.26	0.84	
Total Cost	£123,492	£135,104	£11,611	£13,856

The ICER estimates for tocilizumab is well within a range normally considered cost-effective by NICE. Results are robust to changes in the clinical and cost components of the model.

We strongly believe that patients who cannot tolerate MTX need a better treatment pathway. **Our clinical results suggest that tocilizumab is a superior monotherapy agent in the DMARD-IR setting; our economic model suggests that adding it as a first treatment ahead of TNF-inhibitors may improve long-term outcomes for monotherapy-eligible patients.**