NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Tocilizumab for treating giant cell arteritis

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using tocilizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using tocilizumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 4 January 2018

Second appraisal committee meeting: 23 January 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Tocilizumab is not recommended for treating giant cell arteritis in adults.

1.2 This recommendation is not intended to affect treatment with tocilizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Giant cell arteritis is usually treated with a high dose of corticosteroids, which is gradually reduced over time. High doses of corticosteroids may cause skin problems and weight gain, and long-term use can lead to diabetes and osteoporosis.

Clinical trial results show that after having tocilizumab plus corticosteroids for 1 year, more people are able to sustain a remission and need lower doses of corticosteroids compared with people having corticosteroids alone.

Including the committee's preferred assumptions, the most likely cost-effectiveness estimate for tocilizumab is at least £65,800 per quality-adjusted life year gained. This is much higher than the range normally considered to be a cost-effective use of NHS resources. This estimate also assumes that treatment with tocilizumab is for 2 years at most, but some people may have tocilizumab for more than 2 years. This would increase the cost-effectiveness estimate further. Because of this, tocilizumab is not recommended.

2 Information about tocilizumab

Marketing authorisation indication	Tocilizumab (RoActemra, Roche) has a marketing authorisation for 'the treatment of adults with giant cell arteritis'.
Dosage in the marketing authorisation	162 mg subcutaneous injection once every week in combination with a tapering course of glucocorticoids. Tocilizumab can be used alone following discontinuation of glucocorticoids, but monotherapy should not be used for the treatment of acute relapses. Treatment beyond 52 weeks should be guided by disease activity, physician discretion and patient choice.
Price	£913.12 for 4 syringes containing 162 mg tocilizumab (excluding VAT). The company has agreed a patient access scheme with the Department of Health. If tocilizumab had been recommended, this scheme would provide a simple discount to the list price of tocilizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Possible new treatment option

People would welcome a new treatment that reduces the cumulative amount of steroids needed

3.1 Giant cell arteritis causes inflammation in the walls of the arteries in the head and neck, and less commonly the aorta (known as large vessel giant cell arteritis). The patient experts explained that this causes symptoms such as headache, jaw pain, fatigue and muscle and joint pains. More serious complications include vision loss and stroke, and it is with visual symptoms that people often first present to health services. Initial treatment in the NHS is with high-dose corticosteroids, usually

prednisolone. The dose is tapered gradually over 18 to 24 months to minimise the risk of the disease flaring up. The clinical experts explained that although corticosteroids are effective at managing the disease, large cumulative doses can cause serious side effects such as diabetes and osteoporosis. The patient experts also noted unpleasant side effects with corticosteroids such as skin changes and weight gain. They highlighted that because the disease is most common in people over 80 years old, these side effects are often in addition to existing health problems. The committee concluded that people with giant cell arteritis would welcome a new treatment option that reduces flares of the disease and the cumulative amount of corticosteroids needed.

Subgroups

There may be other relevant subgroups based on disease severity or other patient characteristics

3.2 The marketing authorisation for tocilizumab is for adults with giant cell arteritis. The company presented clinical- and cost-effectiveness analyses which divided the overall population into 2 subgroups: people with newly diagnosed disease and people with relapsing disease. The clinical experts explained that newly diagnosed giant cell arteritis is treated differently to relapsing disease. People with a new diagnosis are usually offered high doses of corticosteroids (40 mg to 60 mg). This is because the priority is to prevent vision loss, and at this stage people have not been exposed to a high cumulative dose of corticosteroids, so there are fewer concerns about steroid-related adverse events. People with relapsing disease are usually offered lower doses of corticosteroids in an attempt to manage flares and minimise additional steroid exposure; as such, the clinical experts considered that tocilizumab would be most valuable to people with relapsing disease. The committee agreed that there were important differences between the 2 subgroups. It considered how many people with newly diagnosed disease would then go on to have relapsing disease. The clinical experts explained that it is difficult to identify people whose

disease may relapse, although there are some whose disease does not respond to initial high doses of corticosteroids and that never achieve remission. The committee also acknowledged differences within the subgroup of people with relapsing disease: for example, some people's disease may relapse frequently, whereas for others relapses may be rare. Furthermore, the clinical experts explained there were differences in the severity of flares in this subgroup. The committee concluded that there may be other relevant subgroups of people with giant cell arteritis, based on disease severity or other patient characteristics, but these have not been robustly identified.

Clinical evidence

The weekly tocilizumab and 52-week corticosteroid taper arms of GiACTA are most relevant to clinical practice in England

3.3 The main clinical evidence for tocilizumab came from GiACTA, a multicentre, double-blind, randomised controlled trial. The trial followed patients for 52 weeks, at which point they were enrolled in an open-label extension study which is still ongoing. The primary outcome of the trial investigated whether more people achieve sustained disease remission at 52 weeks with tocilizumab and corticosteroids compared with corticosteroids alone. Secondary outcomes included time to first flare after disease remission and cumulative steroid dose. The trial included 4 arms:

- tocilizumab every week with 26-week prednisone taper (n=100)
- tocilizumab every 2 weeks with 26-week prednisone taper (n=50)
- placebo with 26-week prednisone taper (n=50)
- placebo with 52-week prednisone taper (n=51).

The company presented clinical-effectiveness data for all 4 arms, but in its economic model used only the weekly tocilizumab and the placebo with 52-week prednisone taper arms. This is because weekly tocilizumab reflects the marketing authorisation, and the 52-week corticosteroid taper reflects the minimum tapering regimen recommended in British Society for

Rheumatology guidelines on giant cell arteritis. The committee noted that splitting the trial into 4 arms meant that the numbers in each arm were small, especially when the population was further divided into newly diagnosed and relapsing subgroups. It also noted that prednisolone, not prednisone, is usually used in the NHS, but considered that the 2 drugs are very similar. The committee concluded that the 2 arms included in the company's economic model (that is, weekly tocilizumab and placebo with 52-week prednisone taper) are most relevant to clinical practice in England.

Patients in GiACTA reflect those with giant cell arteritis in England

3.4 The committee noted a number of differences in the baseline characteristics between the treatment groups in GiACTA, but the ERG explained that these generally balanced out with no obvious skew. However, the committee was concerned that the mean age in the trial was lower than the mean age of people with the disease in the UK (69 years and 73 years respectively). In addition, 40% of patients in GiACTA had large vessel disease, compared with only around 5% of people with giant cell arteritis seen in clinical practice in England. Large vessel disease tends to be associated with a longer disease duration and more relapses than giant cell arteritis affecting the head and neck. However, the clinical experts explained that most people with giant cell arteritis affecting the head and neck also have large vessel disease. It is less likely to be diagnosed in the NHS because there is a lower availability of advanced imaging than in the trial. As such, the proportion in the trial is likely to reflect the true proportion with large vessel disease in England. The committee concluded that the patients in the trial reflect those with giant cell arteritis in England.

The 52-week steroid taper does not reflect clinical practice in England and might bias the results in favour of tocilizumab

3.5 The committee was concerned that 52 weeks (12 months) is the minimum steroid taper recommended in the British Society for Rheumatology

guidelines. The clinical experts explained that in clinical practice, corticosteroids would usually be tapered over 18 to 24 months. The committee considered that this might mean that the number of flares in the comparator arm (that is, placebo with 52-week steroid taper) may be higher, and the time to first flare shorter, than in clinical practice in England. The committee was also aware that 49% of patients in the comparator arm did not have disease remission after the 6 week screening phase of the trial, but that nonetheless they had to start the 52-week tapering regimen. The committee was concerned that this might bias the primary end point of the trial (sustained remission at 52 weeks) in favour of tocilizumab, because it is less likely that people whose disease has not responded to high-dose steroids would achieve remission with lower doses. The committee concluded that the 52-week steroid taper arm of the trial does not reflect clinical practice in England and might bias the results in favour of tocilizumab.

Tocilizumab plus corticosteroids is more effective than corticosteroids alone

3.6 The company presented results for the overall intention-to-treat population of GiACTA, as well as for both the newly diagnosed and relapsing subgroups. The results showed that tocilizumab plus corticosteroids was more effective than corticosteroids alone at increasing the proportion of patients sustaining remission at 52 weeks, and increasing the time to first flare for the overall population and both subgroups (see table 1). The committee recalled that in clinical practice, newly diagnosed disease and relapsing disease are managed differently, but the results were similar across both subgroups. The committee concluded that tocilizumab is more effective than corticosteroids alone at increasing sustained remission and time to first flare.

Table 1 GiACTA trial results

	Overall population		Newly diagnosed subgroup		Relapsing subgroup	
	Tociliz. (n=100)	Placebo (n=51)	Tociliz. (n=47)	Placebo (n=23)	Tociliz. (n=53)	Placebo (n=28)

Sustained remission at 52 weeks (%)	56.0	17.6	59.6	21.7	52.8	14.3
Time to first flare hazard ratio (99% confidence interval)	0.39 (0.18 to 0.82)		0.44 (0.29 to 1.59)		0.33 (0.14 to 0.81)	
Median cumulative steroid dose (mg)	1,862	3,818	1,942	3,817	1,385	3,785

Adverse events

Because tocilizumab is taken with corticosteroids, the extent to which steroid-related adverse events are reduced is unclear

3.7 One of the main perceived benefits of tocilizumab is a reduction in cumulative steroid dose and risk of steroid-related adverse events. The committee noted that although the initial tapering regimen with tocilizumab is shorter than when corticosteroids are used alone, disease flare ups are treated by increasing the steroid dose, and a tapering regimen restarted. As such, people taking tocilizumab could still be exposed to large cumulative doses of corticosteroids. The committee acknowledged that the median cumulative steroid dose was lower in the tocilizumab arm of GiACTA (see table 1), but noted that this was over the relatively short 52-week follow-up. It was concerned that despite the lower median cumulative steroid dose in the tocilizumab arm, the rate of steroid-related adverse events was similar between arms (50% vs. 49%). The committee concluded that because corticosteroids still need to be taken with tocilizumab, the extent to which steroid-related adverse events are reduced is unclear.

The company's economic model

The structure of the model is adequate for decision-making

3.8 The company's economic model had a 30-year time horizon and included separate health states for remission based on whether patients are having corticosteroids or not. Patients in the model could also have a flare, giant

cell arteritis-related adverse events and steroid-related adverse events. Both taking corticosteroids and disease flares were associated with a utility decrement. The committee concluded that the structure of the model was adequate for decision-making.

Duration of tocilizumab treatment

Average treatment duration is likely to be at least 2 years and could be much longer

3.9 The company assumed in their economic model that treatment with tocilizumab stops after 2 years. However, the committee was concerned that in clinical practice treatment may continue well beyond 2 years. This is because the risk of relapse continues, and there is no evidence that tocilizumab modifies the underlying disease when treatment stops (it may just supress it for the duration of treatment). The committee was aware that in both the preliminary results of the GiACTA follow-up study and in a smaller phase II study (NCT01450137), around half the patients' disease relapsed after stopping tocilizumab. The clinical experts commented that if the disease was controlled after 2 years of treatment, the interval between treatments could potentially be increased. In addition, tocilizumab treatment may be stopped and only restarted in the event of a relapse. The committee concluded that the average treatment duration with tocilizumab was likely to be at least 2 years, and could be much longer.

Extrapolation of time to first flare

The company's extrapolation after 52 weeks lacks validity

3.10 In order to extrapolate time to first flare beyond the 52 weeks of the trial, the company fitted separate parametric models to the 2 arms in its economic model. It used a Weibull distribution for the weekly tocilizumab arm (implying a decreasing risk of flare over time) and an exponential distribution for the comparator arm (implying a constant risk of flare over time). The committee was concerned that extrapolating in this way meant that the benefit of tocilizumab over corticosteroids alone was assumed to

continue for the 30-year time horizon of the model, despite tocilizumab treatment stopping at 2 years. Moreover, the extrapolation for the comparator arm was based on the corticosteroid taper period, when the risk of flare is highest. The committee was concerned that this would exaggerate the risk of flare for patients in the comparator arm that had successfully completed the 52-week steroid taper. The clinical experts explained that they would expect around 25% of people who had successfully completed a steroid taper to not have disease relapse by 10 years; in contrast, at the same time point the company's model predicts that almost all patients in the comparator arm would have disease relapse. Longitudinal cohort data also suggests that at 5 years, around 30% to 50% of people having corticosteroids alone will not have disease relapse, whereas at the same time point the model predicts this proportion is less than 2%. The committee concluded that the company's extrapolation of time to first flare lacked validity.

The ERG's approach to extrapolation is more appropriate

3.11 The ERG suggested an alternative approach to extrapolating time to first flare, for the comparator arm, in which it switches to the same Weibull distribution as the weekly tocilizumab arm after 2 years. The committee considered that this addressed the issue of the relative benefit of tocilizumab continuing after treatment stops, because all patients that have successfully completed the taper in either arm have the same decreasing risk of disease relapse. Using this approach, the ERG predicted that at year 5 around 12% of patients in the comparator arm would not have relapsed disease (this falls to 8% by year 10). The committee concluded that the ERG's approach may still overestimate the risk of flare in the comparator arm, but that it provided more clinically realistic estimates of the proportion of patients with disease relapse after having corticosteroids alone.

Estimating rates of subsequent flares

The ERG's approach results in more realistic estimates of subsequent flares

3.12 The company used GiACTA data to estimate rates of subsequent flares. The ERG noted that the company's estimate for the tocilizumab newly diagnosed subgroup was higher than for the relapsing subgroup, which is clinically implausible. In addition, the company's model predicted a high number of flares for people having corticosteroids alone, which lacks validity. For example, over the same period of 10 years, a longitudinal cohort study of people with giant cell arteritis taking corticosteroids alone (Labarca et al. 2016) reported less than half the flares predicted by the company's model. The ERG derived probabilities based on this study that were logically consistent across the subgroups. The committee considered that when the ERG's probabilities for subsequent flare are combined with its approach to time to first flare extrapolation (section 3.11), the predicted mean number of flares over the model time horizon for the comparator arm is more plausible. The committee concluded that the ERG's approach to estimating the probability of subsequent flares is more appropriate.

Utility values in the model

The company's model adequately captures the negative impact of flares and corticosteroids on quality of life

3.13 The company used a common utility value for the remission health state in both treatment arms, and applied a utility decrement of –0.13 for 4 weeks to capture how a flare negatively affects quality of life. The company accounted for the negative effects of corticosteroids by including increased probabilities of diabetes and fracture in the model, which are associated with costs and disutilities. In addition, all patients having corticosteroids in the model were assigned a utility decrement of –0.07 for the duration of their treatment, reflecting the negative effects of common side effects such as weight gain and skin changes. The committee

concluded that the company's model adequately captures the negative impact of flares and corticosteroids on quality of life.

Cost-effectiveness results

The most plausible ICER is higher than the company's and the ERG's base-case ICER

3.14 The company's base-case deterministic incremental cost-effectiveness ratio (ICER) for the overall population was £28,272 per quality-adjusted life year gained (QALY). The ERG's base-case probabilistic ICER was £65,801 per QALY gained. Both the company's and the ERG's analyses incorporated the confidential patient access scheme discount for tocilizumab. The committee preferred the ERG's base-case estimate, because it reflected some of its preferred assumptions. Specifically:

- the mean age was 73 years (section 3.4)
- the time to first flare extrapolation for corticosteroids alone switched to the same Weibull function as tocilizumab after 2 years (section 3.10)
- the probabilities of subsequent flares were based on longitudinal cohort data (see section 3.12).

However, the ERG's base case did not address the uncertainties arising from the fact that the 52-week steroid taper used in the comparator arm of the trial does not reflect clinical practice in the NHS (section 3.5). In addition, the ERG's base case assumed that the average duration of tocilizumab treatment was 2 years, but the committee noted that treatment could be much longer and potentially include cycles of stopping and restarting treatment (section 3.9). Both the company's and ERG's scenario analyses show that duration of treatment is one of the main factors influencing the ICER, with longer treatment increasing the ICER substantially. Because of this, the committee concluded that the most plausible ICER was likely to be higher than the ERG's base-case ICER. Having concluded that the ICER is significantly higher than the range

normally considered to be a cost-effective use of NHS resources, the committee did not recommend tocilizumab.

Innovation

There are no additional benefits that are not captured in the QALY calculations

3.15 The clinical experts highlighted that tocilizumab is the first new treatment for giant cell arteritis in several years. The committee was aware that before its marketing authorisation was granted, tocilizumab received a Promising Innovative Medicines designation for this indication. The patient experts explained that high doses of corticosteroids are needed to treat flares and afterwards the tapering regimen must be restarted. This can have a large negative effect on quality of life which may not be captured in the modelling. However, the committee noted that in the model, patients have a substantially lower utility during a flare which is assumed to last for 4 weeks (section 3.8). In addition, after a disease flare, all patients have corticosteroids and this is associated with a utility decrement (section 3.13). The committee concluded that there were no additional benefits that had not been captured in the QALY calculation.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, appraisal committee
November 2017

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ross Dent
Technical lead

Alexandra Filby
Technical adviser

Stephanie Yates
Project manager

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