

Friday, 28 October, 2011

██████████ ██████████
National Institute for Health and Clinical Excellence
Level 1A, City Tower
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Manchester
M1 4BD

BY E-MAIL

Dear ██████████,

SINGLE TECHNOLOGY APPRAISAL
Rheumatoid arthritis - tocilizumab (rapid review TA198)

We welcome the opportunity to comment on the ACD for this appraisal.

As this is a rapid review, we have only provided comments with regard to evidence and guidance which are newly added or changed from the original appraisal.

Should you have any questions regarding this response, please do not hesitate to contact me.

Kind Regards,

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Roche responses

Has all of the relevant evidence been taken into account?

No comment.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We would like to comment on sections 4.7 to 4.9 in the ACD. These three sections concern the Appraisal Committee's considerations of the relative efficacy of etanercept, tocilizumab and rituximab.

In Section 4.7 it is stated that the Appraisal Committee noted that "etanercept appeared at least equal to, and possibly had higher efficacy than, tocilizumab" once the Klareskog trial was removed from the indirect comparison analysis initially presented by Roche. Section 4.8 subsequently concludes that results from this indirect comparison should not be used as the basis for decision-making, because the adjustment method in the analysis appears to preferentially improve ACR responses associated with tocilizumab whilst reducing the ACR responses of rituximab and etanercept. Section 4.9 finally notes the Committee's conclusion, based on unadjusted trial estimates of ACR rate, that "the evidence was not conclusive of a benefit of any one drug over another".

Taken together, we believe the statements in 4.7 and 4.8 could be interpreted to mean that the Committee considered etanercept to be equally if not more efficacious than tocilizumab, a difference which they found was 'masked' by Roche's initially-submitted indirect comparison analysis. This interpretation runs contrary to the Committee's final approach to efficacy in section 4.9, which allowed use of unadjusted trial statistics in the final economic model but considered that there was little to distinguish the treatments with regard to ACR response.

The comments in 4.7 through 4.9 also do not acknowledge that by using unadjusted trial statistics, slight differences in the placebo response rate seen in the etanercept and tocilizumab trials are unchecked and allowed to influence the results. Furthermore, no description is provided of the direction or magnitude of any bias which could potentially arise through this approach.

To improve clarity, we would recommend that the wording in 4.7 about relative efficacy of etanercept and tocilizumab be changed to more closely reflect the conclusion in 4.9.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

We welcome the Appraisal Committee's preliminary recommendations on the use of tocilizumab in rheumatoid arthritis (RA).

However, we believe that the layout of the guidance, its conditions and wording could be

simplified to avoid confusion and challenges in the NHS in implementing the guidance. Below, we highlight the key parts of the guidance which we feel could be improved for clarity.

Description of disease severity

There is a lack of consistency in the description of disease severity. “Active disease” is referred to on pages 3 and 4 of this document, but on pages 44 and 45 of the document the term “severe active disease” is used. We would recommend using the same wording for both. For your information, tocilizumab is licensed for moderate to severe active RA.

Conditionality and wording in main recommendations

We note that each of the Institute’s three guidance points for tocilizumab contain conditions under which the product is recommended for use.

Use of word “only”

We note that in section 1.2 the phrase ‘only recommended’ is used prior to a list of conditions under which tocilizumab may be used in people whose disease has responded inadequately to one or more tumour necrosis alpha (TNF- α) inhibitors.

We cannot see a particular semantic need for using the word “only” ahead of the conditions listed in 1.2, when all recommendations include bullet-lists of conditions, preceded by the word “if.”

In case NICE considers it important to emphasise the conditionality of guidance in 1.2 through use of the word “only”, we would suggest that this word be moved such that the bullet lists are each preceded by the words “only if.”

Use of wording “other TNF-inhibitors” in 1.1 and 1.3.

In section 1.1, tocilizumab is recommended for use in the DMARD-IR population. The condition for use in this population is that tocilizumab is used as per guidance set out for TNF- α inhibitors in TA130. Since tocilizumab acts on the IL-6 pathway and does not directly inhibit TNF- α , we suggest that the word “other” be removed from the guidance point in order to be clinically accurate.

The same wording is used in section 1.3 to refer to the TA195 guidance for use of TNF- α inhibitors. Our suggestion would be to make a similar amendment in that section.

Conditions in sections 1.1, 1.2, 1.3

Overall, we would comment that the current draft guidance wording may be confusing and difficult for clinicians to follow. To ensure we have correctly understood the preliminary recommendations, we would like to provide our interpretation of each of the guidance points in sections 1.1 through 1.3:

Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults with active disease:

- Where their disease has responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs), **providing that** tocilizumab is used as described for TNF- α inhibitor treatments in NICE TA130

or

- Where their disease has responded inadequately to one or more biologic treatments including a TNF- α inhibitor, **providing that** their rheumatoid arthritis has also responded inadequately to rituximab, or rituximab was contraindicated or withdrawn because of an adverse event

or

- As an alternative to rituximab, **providing that**
 - Their disease has responded inadequately to DMARDs, including a TNF- α inhibitor **and**
 - They cannot receive rituximab because they have a contraindication or rituximab was tried and withdrawn due to an adverse event **and**
 - Tocilizumab is used as described for TNF- α inhibitor treatments in NICE TA195.

These recommendations are only valid if the manufacturer provides the discount agreed as part of the patient access scheme.

If at all possible, we would be grateful to receive the Institute's confirmation that this interpretation is correct. We would also encourage the Institute to consider simplifying the guidance wording, in order to ensure that tocilizumab is used correctly and in compliance with the recommendations made in the ACD.

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 gender, race, disability, age, sexual orientation, religion or belief?

No comment.

Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?

No comment.

If you wish to comment on the evaluation report, please do so under a separate heading from your comments on the ACD.

N/A (no new evaluation report created).