NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA238; Tocilizumab for the treatment of systemic juvenile idiopathic arthritis, and TA302; Canakinumab for treating systemic juvenile idiopathic arthritis (terminated appraisal)

Final recommendation post consultation
A review of the guidance for the intravenous formulation should be planned into the appraisal work programme to coincide with the timing of any future extension of the marketing authorisation for the subcutaneous formulation of tocilizumab for systemic juvenile idiopathic arthritis. Canakinumab should also be included in the review of tocilizumab for systemic juvenile idiopathic arthritis at that time. Tocilizumab intravenous and subcutaneous formulations and canakinumab will be appraised through the MTA process.

1. Background

TA238 was issued in December 2011.

The termination advice in TA302 was issued in November 2013.

At the GE meeting of 20 January 2015 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

A review of the guidance for the intravenous formulation should be planned into the appraisal work programme to coincide with the timing of any extension of the marketing authorisation for the subcutaneous formulation of tocilizumab for systemic juvenile idiopathic arthritis. Canakinumab should also be included in the review of tocilizumab for systemic juvenile idiopathic arthritis. Tocilizumab intravenous and subcutaneous formulations and canakinumab will be appraised through the MTA process.

3. Rationale for selecting this proposal

Confidential information has been removed.

Although there is no evidence that would change the current recommendations of T238, there is, however, a new subcutaneous formulation of tocilizumab with a marketing authorisation for patients with moderate to severe RA, but this is not licensed for use in systemic JIA. Should the marketing authorisation be extended to include systemic JIA, it will be important to review the TA238 NICE recommendations and consider any new evidence at that time, including a comparison of the subcutaneous and intravenuous formulations. A review of the guidance for the intravenous formulation should be planned into the appraisal work programme to coincide with the timing of any extension of the marketing authorisation to include the subcutaneous formulation of tocilizumab for systemic JIA and any new evidence for adolescents at that time reconsidered.

NICE was unable to make a recommendation about the use in the NHS of canakinumab for systemic juvenile idiopathic arthritis because no evidence submission was received from the manufacturer of the technology. However, further information may be available in future to allow an appraisal submission for canakinumab, and this should also be considered to coincide with the timing of any extension of the marketing authorisation for the subcutaneous formulation of tocilizumab. Both intravenous and subcutaneous tocilizumab formulations and canakinumab will be appraised through the MTA process.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Novartis **Response to proposal:** Disagree Novartis disagrees with the NICE Guidance Executive proposal to incorporate a review of TA302 (canakinumab for treating systemic juvenile idiopathic arthritis [terminated appraisal]) into an MTA for tocilizumab and canakinumab. The sole reason for NICE proposing to undertake this MTA is the future potential of a subcutaneous formulation of tocilizumab to be made available in addition to the existing intravenous formulation. Aside from this, NICE acknowledges in its proposal that there is no new evidence for tocilizumab that would change its current recommendation (TA 238). However, it is also doubtful that accounting for a change of formulation alone would materially alter the recommendations. Regarding canakinumab, Novartis is not aware of any changes to the evidence base that would alter the negative recommendation of TA302, even if this was to be reviewed in an MTA rather than being based on a manufacturer non-submission for an STA. Canakinumab use in sJIA is very limited in the UK [redacted] Thus, for sJIA, canakinumab does not represent routine or established clinical practice in the UK. Based on the lack of new evidence (and the usage information provided above for canakinumab), we do not agree with the proposal that a combined review of the TA 302 guidance for canakinumab and TA 238 guidance for tocilizumab should be undertaken. In our view, the proposed MTA would not be a good use of resources for NICE or its stakeholders.	**Comment from Technology Appraisals** Thank you for your response and for the usage information provided for canakinumab. We would like to clarify that NICE is not proposing to undertake an immediate MTA; rather, it is proposing that a review of the guidance will be conducted at some point in the future to coincide with any future extension to the marketing authorisation for the subcutaneous formulation of tocilizumab for systemic JIA. The review at that time will include an assessment of the evidence to determine whether equivalence in cost and clinical effectiveness for the subcutaneous formulation compared with the intravenous formulation is suggested. Regarding the comment about TA302, canakinumab did not receive, as stated, a 'negative recommendation'. NICE was unable to make a recommendation about the use of canakinumab because no evidence submission was received.

Respondent: Royal College of Nursing **Response to proposal:** No comment The Royal College of Nursing invited members who work in this area of health to review and comment on this review consultation. The feedback received suggests that there are no additional comments to make on behalf of the RCN.	**Comment from Technology Appraisals** Comment noted.

Respondent: Royal College of Pathologists **Response to proposal:** • There is an error in the middle of the page 3 (of the GE proposal paper), it doesn't make sense to read: "In August 2013, the licensed indication for canakinumab was granted for the treatment of active the timing of any extension of the marketing authorisation for the subcutaneous formulation of tocilizumab for systemic juvenile idiopathic arthritis,in patients aged 2 years and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids." • There should be a discussion about extending the license of Tocilizumab in JIA from being only licensed in the subgroup of systemic JIA to other subgroups of JIA patients, including the polyarticular JIA. There is evidence from the CHERISH study1 that Tocilizumab treatment results in significant improvement, maintained over time, of polyarticular JIA signs and symptoms and has a safety profile consistent with that for adults with rheumatoid arthritis. CHERISH study was a three-part study, conducted by members of the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG) at 58 centres in Australia, Canada, Europe, Latin America, Russia and the USA, to evaluate the efficacy and safety of tocilizumab in patients with active polyarticular JIA and inadequate responses to MTX. • The subcutaneous formulation of Tocilizumab is an advancement. The SUMMACTA study2 demonstrated that the response to Tocilizumab SC was similar to Tocilizumab IV in adult patients with rheumatoid arthritis. Tocilizumab SC 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 IV infusion over one hour as a day case in the hospital. Tocilizumab SC has an advantage over tocilizumab IV in that it can be self-administered at home by the patient. • No comments on Canakinumab	**Comment from Technology Appraisals** Comments noted. Any future extension to the license of tocilizumab would need to be approved by EMA/MHRA before a NICE technology appraisal could appraise it as a separate STA or MTA in that indication. As stated in section 6.1.12 of the guide to methods of technology appraisal the Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics.

Respondent: Roche Products **Response to proposal:** Disagree We are surprised the review of sJIA is to be conducted separately to the review of the other juvenile arthritis indications [ID738]. As many of the same stakeholders are involved in the pJIA review (which includes a number of indications across product licences), it seems unnecessary to conduct two separate reviews of rare paediatric conditions. We had also raised this point during our response to the consultation on the draft scope of review ID738 and at the recent Stakeholder meeting. In our view, the proposed review of TA238 does not seem a particularly prudent use of resources. As stated in the Guidance Executive's report, *'there does not appear to be any evidence that would change the current recommendations of TA238'. Furthermore, the Guidance Executive states that if tocilizumab were to receive an sJIA licence for the subcutaneous formulation '... the new evidence available at this time is unlikely to lead to a change in the recommendations of the original guidance.'* [Guidance Executive; 7. Summary of evidence and implications for review]. It is also important to note that the cost-effectiveness of the subcutaneous formulation which will become available for sJIA in 2017, will be equivalent or improved on the IV formulation. This was demonstrated in the recent SMC appraisal of the subcutaneous formulation of tocilizumab for rheumatoid arthritis [SMC Guidance; tocilizumab subcutaneous formulation 982/14]. In the GE, there appears to be an error in the first sentence of the 2nd paragraph in Section 7; *'In August 2013, the licensed indication for canakinumab was granted for the treatment of active the timing of any extension of the marketing authorisation for the subcutaneous formulation of tocilizumab for systemic juvenile idiopathic arthritis,in patients aged 2 years and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids'*. In Appendix 3, the Hospital Pharmacy Audit Index presents the volume of the number of tocilizumab packs used across England. The graph does not indicate which indications are represented, but appears to represent the all use in JIA, and not sJIA on its own.	**Comment from Technology Appraisals** The patient population in the decision problem of the ongoing appraisal for ID783 (not ID738 as stated) is as follows: • People with the following forms of juvenile idiopathic arthritis:polyarthritis (rheumatoid factor positive, rheumatoid factor negative and extended oligoarthritis, both onset and course); enthesitis related arthritis; and psoriatic arthritis. The scope for ID783 does not include systemic JIA as tocilizumab is not included as an intervention and it is the only drug licensed for use in systemic JIA. The scope notes 'An appraisal of treatments for systemic juvenile idiopathic arthritis will be considered separately when a review proposal for TA238 is developed'. The review that coincides with any future extension to the tocilizumab marketing authorisation for the subcutaneous formulation for systemic JIA .The review at that time will include an assessment of the evidence to determine whether equivalence in cost and clinical effectiveness for the subcutaneous formulation compared with the intravenous formulation is suggested.

Accepting there would not be a change in the recommendations for tocilizumab, and based on the decision by the manufacturer of canakinumab not to submit for sJIA in November 2013, it would seem of little value to conduct a review of sJIA when considering the significant resource required to complete an MTA.	

Respondent: Abbvie **Response to proposal:** Request change to matrix As adalimumab does not have a licence for the treatment of systemic JIA we consider that it should not be included as a comparator in this appraisal and therefore have no further comments in regard to this proposed topic given the current scope covering systemic JIA only.	**Comment from Technology Appraisals** Comment noted.

Paper signed off by: Frances Sutcliffe, 25 March 2015

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