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)

TA238 was issued in December 2011. The review date for this guidance was December 2014.

TA302 was issued in November 2013.

1. Recommendation

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. That we consult on this proposal.

2. Original remit(s)

TA238

To appraise the clinical and cost-effectiveness of tocilizumab within its licensed indication for juvenile idiopathic arthritis.

TA302

To appraise the clinical and cost-effectiveness of canakinumab within its licensed indication for the treatment of systemic juvenile idiopathic arthritis.

3. Current guidance

TA238

1.1 Tocilizumab is recommended for the treatment of systemic juvenile idiopathic arthritis in children and young people aged 2 years and older whose disease has responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids and methotrexate if the manufacturer makes tocilizumab available with the discount agreed as part of the patient access scheme.

1.2 Tocilizumab is not recommended for the treatment of systemic juvenile idiopathic arthritis in children and young people aged 2 years and older whose disease continues to respond to methotrexate or who have not been treated with methotrexate.

1.3 Children and young people currently receiving tocilizumab for the treatment of systemic juvenile idiopathic arthritis who do not meet the criteria in 1.1 should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinicians, and the child or young person and/or their parents or carers.

TA302

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

4. Rationale[1]

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.

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2011 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

the ‘Summary of evidence and implications for review’ section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The marketing authorisation for tocilizumab relevant to TA238 has remained the same since the publication of guidance, that is, for the treatment of active systemic juvenile idiopathic arthritis (JIA) in patients aged 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 patients intolerant to methotrexate or if treatment with methotrexate is inappropriate) or in combination with methotrexate. In addition to indications for systemic JIA and rheumatoid arthritis, the drug has expanded to include other indications since the publication of TA238, including the approval in June 2013 for children with polyarticular juvenile idiopathic arthritis (PJIA), a rare form of childhood arthritis however this indication is not relevant to scope of TA238. For the indications of RA, systemic JIA and PJIA, tocilizumab is administered as an intravenous infusion over 1 hour. As an infusion, tocilizumab has been available in the UK since January 2009. In addition to TA 238, tocilizumab was also the subject of TA 247: Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). In April 2014 Roche received EU approval for a new subcutaneous formulation of tocilizumab for patients with moderate to severe RA. TA 247 relates only to the use of the intravenous infusion, and provides no guidance specific to the use of subcutaneous tocilizumab, which was not available at the time of publication. Subcutaneous tocilizumab is not recommended for use in children under 18 years of age and is therefore not available for use in systemic JIA or PJIA.

[redacted]

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. Canakinumab was due to be appraised by NICE, and tocilizumab was listed as a comparator in the NICE scope. It should be noted that biologic anti-TNF alpha inhibitors were not included in the NICE scope for canakinumab due to their ‘poor efficacy’ in this condition. Given the similar licensed indications between canakinumab and tocilizumab, it is likely that the anti-TNF inhibitors would also no longer be considered relevant comparators for tocilizumab. In November 2013, NICE stated that it 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 for systemic juvenile idiopathic arthritis. Canakinumab should be included in any MTA review of tocilizumab for systemic juvenile idiopathic arthritis.

The price of tocilizumab for intravenous infusion remains unchanged: £102.40 for 80mg (4ml vial) – BNF Children October 2014.

[redacted], which is a simple discount scheme and applies to all populations for which tocilizumab has EMA marketing authorisation in both RA and systemic JIA indications. The cost of anakinra (£26.23 per 100mg) remains unchanged.

There were no specific further research recommendations made in the guidance for TA238. New evidence since the publication of TA238 for the indication of systemic JIA consists largely of publications reporting the long-term open-label extension results of TENDER, (the phase 3 trial that was the main study for the appraisal), or post-hoc analyses of TENDER. Other studies include a Japanese long term extension study of a phase II (11 patients) and phase 3 (56 patients) study. There is a relevant ongoing open-label study researching the effect of reducing the dosing frequency of tocilizumab, which is due to complete December 2018. The evidence since the publication of TA238 in systemic JIA has continued to show that tocilizumab is efficacious in this condition there has been no evidence to suggest a change in the recommendations of TA238.

In summary, there have been no changes to the marketing authorisation for the systemic JIA indication, the acquisition cost of tocilizumab or the patient access scheme. In addition, there does not appear to be any 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 currently licensed for use in systemic JIA. [redacted] The subcutaneous formulation would offer a more convenient treatment for the patient, who can self-administer, bringing care closer to home for the patient, and reducing the burden on hospital based services. 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. Overall, the new evidence available at this time is unlikely to lead to a change in the recommendations of the original guidance. 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, and should also include canakinumab. Tocilizumab intravenous and subcutaneous formulations and canakinumab will be appraised through the MTA process at that time.

8. Implementation

A submission from Implementation is included in Appendix 3.

9. Equality issues

No equalities issues were raised in the appraisal.

GE paper sign off: Frances Sutcliffe, 14 January 2015

Contributors to this paper:

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance for the intravenous formulation should be planned into the appraisal work programme to co-incide with the timing of any extension of the marketing authorisation for the subcutaneous formulation of tocilizumab to adolescents. Canakinumab should be included in any MTA review of tocilizumab for systemic juvenile idiopathic arthritis. Both intravenous and subcutaneous tocilizumab formulations and canakinumab will be appraised through the MTA process.	A review of the appraisal will be planned into the NICE's work programme.	Yes
The decision to review the guidance should be deferred to	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

NICE technology appraisals [TA35]. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. Published date: March 2002. Review date: November 2013 (a review of TA35 will be planned into the appraisals work programme).

In progress

Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (including review of TA35). Anticipated publication date: February 2016

Suspended/terminated

Abatacept for the treatment of juvenile idiopathic arthritis. Referral date: June 2008. The marketing authorisation for abatacept in this therapeutic area suggests limited use of this drug for a small population of those with juvenile idiopathic arthritis. Following discussions with the Department of Health, NICE concluded that this topic should be removed from the work programme (July 2010).

Adalimumab for the treatment of juvenile idiopathic arthritis. Referral date: June 2008. Following on from the licence extension for adalimumab for juvenile idiopathic arthritis an additional draft scope consultation was conducted in November 2010. As a result of the consultation this topic will not be re referred onto the technology appraisals work programme (July 2011).

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Tocilizumab has a marketing authorisation for the treatment of active systemic juvenile idiopathic arthritis (JIA) 'in patients aged 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 patients intolerant to methotrexate or if treatment with methotrexate is inappropriate) or in combination with methotrexate.	[redacted]

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
[redacted]	[redacted]

Registered and unpublished trials

Trial name and registration number	Details
A Study of RoActemra/Actemra (Tocilizumab) in Patients With Active Systemic Juvenile Idiopathic Arthritis (JIA) (NCT00642460)	Enrolment: 112 Estimated Study Completion Date: August 2014 This study is ongoing, but not recruiting participants.
A Study of Decreased Dose Frequency in Patients With Systemic Juvenile Arthritis Who Experience Laboratory Abnormalities During Treatment With RoActemra/Actemra (Tocilizumab) (NCT01734382)	Estimated Enrolment: 20 Estimated Study Completion Date: January 2016 This study is currently recruiting participants

Relevant services covered by NHS England specialised commissioning

PAEDIATRIC MEDICINE: RHEUMATOLOGY (E03/S/b): PARTICULARS, SCHEDULE 2 – THE SERVICES, A – SERVICE SPECIFICATIONS

Additional information

[redacted]

Appendix 3 – Implementation submission

Contents

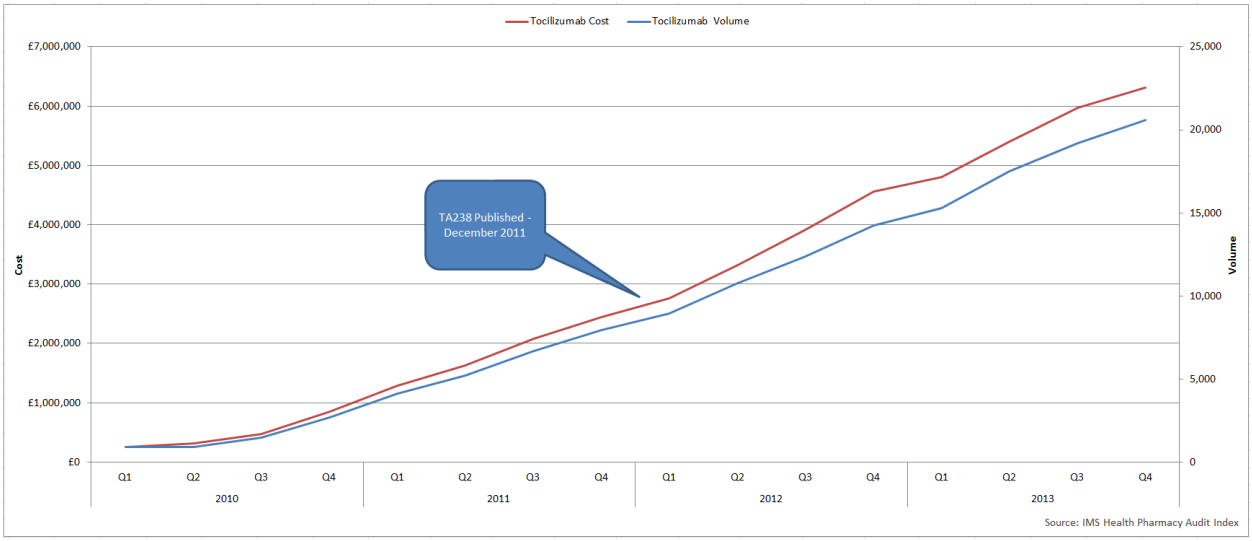
Please contact Liesl Millar regarding any queries Liesl.Millar@nice.org.uk

Routine healthcare activity data

Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of tocilizumab prescribed and dispensed in hospitals in England between January 2010 and December 2013. The volume relates to the number of packs used and should not be added together across various preparations due to differences in dosages/pack sizes.

Figure 1 Cost and volume of tocilizumab prescribed in hospitals in England between January 2010 and December 2013.



2. Implementation studies from published literature

No uptake information was found on the uptake database website for TA 238.

3. Qualitative input from the field team

The implementation field team have not recorded any feedback in relation to this guidance.

4. Implementation studies from shared learning

A search of the shared learning website highlighted no examples of TA238 being implemented.

Appendix A: Healthcare activity data definitions

IMS HEALTH Hospital Pharmacy Audit Index

The hospital dispensing information is provided by IMS Health. It is based on information collected by IMS Health from the majority of hospitals in England. A minimum of 99% of acute English hospitals supply data to IMS Health about all medicines issued by hospital pharmacy departments. National figures are grossed up to give England level estimates on the basis of bed numbers. However sub-national figures are not adjusted in any way and will be an under estimate if trusts do not contribute data. Note that IMS Health revise figures as new data becomes available and so any figures may be different when extracted on a different occasion.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.