NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA373; Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis

Original publication date:	16 December 2015
Review date	December 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA373, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

There has been no change to the marketing authorisations relating to juvenile idiopathic arthritis for the 4 treatments. There is no new evidence that is likely to lead to a change in the current recommendations.

3. Summary of new evidence and implications for review

The evidence identified includes long-term efficacy and safety data on the 4 biologic therapies compared with placebo/standard treatment. Data from these trials would not address the uncertainty associated with the relative effectiveness between the 4 treatments. Overall, no new evidence has been identified that could be expected to lead to a change in the recommendations.

Has there been any change to the price of the technology(ies) since the guidance was published?
Biosimilar products for etanercept and adalimumab have been introduced since the guidance was published. The availability of biosimilars will increase the cost-effectiveness of the technologies when compared with standard treatment. The guidance states 'when more than 1 technology is suitable (taking into account extra articular manifestations) treatment should be started with the least expensive technology, taking into account administration costs, the dose needed and the product cost per dose.' The NICE website also states that the recommendations in TA373 'also apply to biosimilar products of the technologies that have a marketing authorisation allowing the use of the biosimilar for the same indication.'

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There are no existing or proposed changes to the marketing authorisations that would affect the existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
The uncertainties in the original guidance related to obtaining utility values for juvenile idiopathic arthritis, and the relative effectiveness of the biologic therapies when compared with each other. The new evidence identified does not address uncertainty relating to utility values for juvenile idiopathic arthritis. There is no new evidence directly comparing the therapies with each other. The cost-effectiveness of the biologic treatments compared with each other was not analysed in TA373 because the differences between the trials prevented a robust indirect comparison of clinical effectiveness, and there was no evidence of any difference in the effectiveness of the 4 treatments when compared with placebo/standard treatment. There is 1 new meta-analysis of biologic treatments but it only includes 1 trial for each treatment which suggests these are the same trials included by the Assessment Group in their indirect comparison. Furthermore, the results of the meta-analysis show that the treatments are similarly effective which matches the conclusion of the committee in TA373.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
Not applicable.
Additional comments
None.

The search strategy from the original Assessment Report was adapted and re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2015 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 the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues were raised in relation to the original guidance.

GE paper sign off: **Helen Knight, 06/12/2018**

Contributors to this paper:

Information Specialist: Tom Hudson
Technical Analyst: Anna Brett
Associate Director: Sheela Upadhyaya
Project Manager: Emily Richards

Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of etanercept, adalimumab, tocilizumab and abatacept within their licensed indications for treating juvenile idiopathic arthritis.

6. Current guidance

1.1 Abatacept, adalimumab, etanercept and tocilizumab are recommended, within their marketing authorisations, as options for treating polyarticular juvenile idiopathic arthritis (JIA), including polyarticular-onset, polyarticular-course and extended oligoarticular JIA. That is:

- for abatacept, people 6 years and older whose disease has responded inadequately to other disease-modifying anti-rheumatic drugs (DMARDs) including at least 1 tumour necrosis factor (TNF) inhibitor
- for adalimumab, people 2 years and older whose disease has responded inadequately to 1 or more DMARD
- for etanercept, people 2 years and older whose disease has responded inadequately to, or who are intolerant of, methotrexate
- for tocilizumab, people 2 years and older whose disease has responded inadequately to previous therapy with methotrexate.

Abatacept and tocilizumab are recommended only if the companies provide them with the discounts agreed in the patient access schemes for these technologies.

1.2 Adalimumab and etanercept are recommended, within their marketing authorisations, as options for treating enthesitis-related JIA, that is, for people 6 years and older (adalimumab) and 12 years and older (etanercept) whose disease has responded inadequately to, or who are intolerant of, conventional therapy.

1.3 Etanercept is recommended, within its marketing authorisation, as an option for treating psoriatic JIA, that is, in people aged 12 years and over whose disease has responded inadequately to, or who are intolerant of, methotrexate.

1.4 When more than 1 technology is suitable (taking into account extra-articular manifestations) treatment should be started with the least expensive technology, taking into account administration costs, the dose needed and the product cost per dose.

7. Research recommendations from original guidance

The Committee noted a paucity of data on the effect of biological treatments for JIA on long-term outcomes and quality of life. It noted that continued collection of data

on long‑term outcomes and quality of life would improve the evidence base for juvenile idiopathic arthritis.

8. Cost information from original guidance

See appendix C below.

Appendix B – 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 should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisals process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to a specific date or trial.	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
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

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	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.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

None for comparable indications.

2. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Abatacept Indicated (in combination with methotrexate) for treating moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years and older whose disease has responded inadequately to other disease‑modifying antirheumatic drugs (DMARDs) including at least 1 tumour necrosis factor (TNF) inhibitor Price: £302.40 for a 250 mg vial	No changes.
Adalimumab Indicated for… • treating active polyarticular JIA in patients 2 years and older whose disease has responded inadequately to 1 or more DMARDs • treating active enthesitis‑related arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy Price: £352.14 for a 40 mg prefilled pen or prefilled syringe and for a 40 mg/0.8 ml vial	No changes to indications. The patent for the original version of adalimumab (Humira brand) expired in October 2018. Biosimilar versions have therefore only recently become available. The Hyrimoz-branded adalimumab biosimilar (produced by Sandoz) is currently available in a 40mg/0.8ml pre-filled pen at £323.09 [source: C+D data, accessed 24th October 2018]
Etanercept Indicated for: • treating polyarthritis (rheumatoid factor positive or negative) and	No changes to indications.

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
extended oligoarthritis in children and young people 2 years and older whose disease has responded inadequately to, or who cannot tolerate, methotrexate • treating psoriatic arthritis in young people 12 years and older whose disease has responded inadequately to, or who cannot tolerate, methotrexate • treating enthesitis-related arthritis in young people 12 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. Price: £35.75 for a 10 mg vial and £89.38 for a 25 mg vial	Biosimilar versions of etanercept are available. No equivalent biosimilar preparation was found for the 10 or 25 mg formulations mentioned in the original TA For comparison: a four-pack of 50 mg per 1 ml pre-filled syringes, which have a marketing authorisation for the treatment of JIA, is available at a cost of £715 for the reference medicine (Enbrel brand) or £643.50 for a biosimilar version (Erelzi brand) [source: C+D data, accessed 24th October 2018]
Tocilizumab Indicated in combination with methotrexate (or as monotherapy if methotrexate is not tolerated for… • treating juvenile idiopathic polyarthritis (rheumatoid factor positive or negative, and extended oligoarthritis) in patients 2 years and older whose disease has responded inadequately to methotrexate • treating active systemic JIA in patients 2 years and older whose disease has responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs and systemic corticosteroids *[covered separately by NICE TA238]*. Price: £102.40 for an 80 mg vial, £256.00 for a 200 mg vial and £512.00 for a 400 mg vial	No changes.

3. Registered and unpublished trials

No directly relevant trials found.