NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of NICE Technology Appraisal; Adalimumab, etanercept, infliximab, rituximab, abatacept (review of TA195), golimumab (part review of TA225) and tocilizumab (part review of TA247) for the treatment of rheumatoid arthritis after failure of disease-modifying anti-rheumatic drugs including a TNF-inhibitor

The guidance was issued in:

TA195 – August 2010

TA225 – June 2011

TA247 – February 2012

The review date for all of these is June 2013.

1. Recommendation

The guidance should be transferred to the 'static guidance list' for NICE to proactively monitor future developments. That we consult on this proposal.

2. Original remit(s)

TA195 – To appraise the clinical and cost effectiveness of adalimumab, etanercept, infliximab, rituximab and abatacept, within their respective licensed indications, for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (TA195 included a part review of Technology Appraisal No. 36, March 2002, Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis'; and reviews of Technology Appraisal No. 126, August 2007, Rituximab for the treatment of rheumatoid arthritis; and Technology Appraisal No. 141, April 2008, Abatacept for the treatment of rheumatoid arthritis).

TA225 – To appraise the clinical and cost effectiveness of golimumab within its licensed indication for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs.

TA247 – To appraise the clinical and cost effectiveness of tocilizumab within its licensed indication for the treatment of rheumatoid arthritis *(TA247 is a rapid review of guidance number TA198. The remit is from the scope of the original appraisal, TA198).*

3. Current guidance

TA195, TA225 and TA247 cover the following recommendations for treating adults with severe active rheumatoid arthritis who have had an inadequate response to, or

are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor.

- Rituximab is recommended in combination with methotrexate.

- Adalimumab, etanercept, infliximab, abatacept, golimumab and tocilizumab each in combination with methotrexate, are recommended as treatment options only for adults who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event

- Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event.

See appendix 2, relevant institute work for full guidance sections.

4. Rationale[1]

There are a number of contradictory arguments for and against an update of the guidance:

- Ongoing or completed relevant trials are either not reporting until end of 2015 or contain uncertain evidence only.

- Subcutaneous formulations and biosimilars will be emerging in the next couple of years, some of which may affect the cost effectiveness of the current drugs. However, the emergence of biosimilars for rituximab, which is recommended in TA195, is not expected to alter the recommendation for rituximab.

- There is currently no NICE guidance for use of certolizumab pegol after failure of a first line biologic. However, certolizumab pegol is currently recommended for 1st line biologics treatment, and the absence of recommendations for 2nd line biologics treatment would not preclude it being used stage of the treatment pathway. Carrying out a full MTA to explicitly explore the use of one of many treatment option is not appropriate use of NICE's resources.

- There are no significant changes in marketing authorisation indications that would alter the current guidance. A large number of new biologics are awaiting marketing authorisations, but are most appropriately considered in separate appraisals.

- NICE is currently reviewing the guidance for first use of a biologic (Rheumatoid arthritis - adalimumab, etanercept, infliximab (TA130), certolizumab pegol (TA186) and golimumab (TA225 part review) - review

[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

[ID537]). This is expected to be issued in January 2014. There is potential for the starting and stopping rules applied to treatment decisions to be updated in the guidance. However, starting and stopping rules for 1st line biologics treatment would not affect a 2nd line treatment recommendations.

- The NICE clinical guideline for rheumatoid arthritis will be considered for review again after the publication of the MTA (scheduled to review and update TA130, TA186, TA234 and part review of TA225), and may provide for an opportunity for consideration to update TA195, TA225 and TA247 within the guideline.

Bearing in mind that several technologies are currently recommended for 2nd line biologics treatment, none of the above issues points towards the need to review the technology appraisals.

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 January 2007 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 below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

Marketing authorisation changes

The marketing authorisations for each of the interventions in TA195 and TA247 have not changed since the guidance was released. Since the publication of TA225 in June 2011 the marketing authorisation for golimumab has been updated to (changes in bold italicised text) "Golimumab is licensed in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis when response to disease-modifying antirheumatic drug (DMARD) therapy (including methotrexate) has been inadequate; ***it is also licensed in combination with methotrexate for patients with severe, active, and progressive rheumatoid arthritis not previously treated with methotrexate***." This extension to the marketing authorisation has not been appraised as the manufacturer did not submit evidence (terminated appraisal TA224), but is being reviewed in the ongoing MTA review covering the first use of a biologic DMARD.

At the time of TA195 rituximab was estimated to be given on average once every 9 months. The administration schedule section of the SPC for rituximab received an amendment at the end of 2010 to state: "***The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment***

should be delayed until disease activity returns". This amendment may place greater emphasis on more frequent re-treatment which could affect the cost effectiveness of the product.

Details of new products

Since release of the TA195, TA225 and TA247, several new products have been launched or are being developed.

Inflectra

Inflectra is an infliximab biosimilar which has been studied in a phase 3 trial of people with rheumatoid arthritis who have previously been treated with DMARDs (including MTX) and compared with infliximab. People who had received previous treatment with TNF inhibitors were not excluded from this trial. Recent data published at the EULAR congress in 2012 indicated equivalence between inflectra and infliximab in clinical efficacy at week 30 (Yoo 2012), and that the safety profiles were comparable (Yoo et al. 2012). The anticipated date of patent expiry for infliximab is August 2014 (Generics and Biosimilars Initiative online 2013), and therefore it is expected that inflectra will be launched in the second half of 2014. [redacted] The price of inflectra may be different from infliximab, and therefore assessment of its cost-effectiveness may alter the current guidance. It should be noted that the number of patients in the trial who had received previous TNF inhibitors is not known.

Rituximab biosimilar

The patent for rituximab is due to expire in Nov 2013 (Generics and Biosimilars Initiative online 2013). A phase 3 clinical trial, investigating the efficacy of a rituximab biosimilar in patients the rheumatoid arthritis which has had an inadequate response to other DMARDs including one or more TNF inhibitors is currently recruiting patients. This trial has an estimated completion date of 2014. The addition of a rituximab biosimilar would not alter the guidance, as rituximab was concluded to be the most cost effective treatment in TA195.

Novel formulations of abatacept, golimumab and tocilizumab

Subcutaneous abatacept was launched in the UK in February 2013. This offers a different route of administration from the intravenous method which was included in TA195, and results from a phase 3b clinical trials show that subcutaneous abatacept provides efficacy and safety comparable with that of intravenous abatacept (Genovese et al. 2011). An intravenous formulation of golimumab (TA225 appraised a subcutaneous formulation), and the subcutaneous formulation of tocilizumab (TA247 appraised an intravenous formulation) are currently being investigated in Phase 3 clinical trials. The different administration methods may impact on cost and patient outcomes, and therefore the cost-effectiveness of these products. The anticipated marketing authorisation dates for intravenous golimumab and subcutaneous tocilizumab are currently unknown.

Tofacintib

Tofacitinib is an oral Janus kinase inhibitor. It has been studied in combination with methotrexate and as a monotherapy in adults whose rheumatoid arthritis has had an inadequate response to, or who are intolerant to conventional non-biological DMARDs including methotrexate and have had an inadequate response to, or who are intolerant to, TNF inhibitors. Tofacitinib was referred for appraisal in May 2012. the manufacturer received negative CHMP opinion in April 2013.

Fostamatinib disodium sarilumab, secukinumab Baricitinib, masitinib, and sirukumab

A number of new drugs are expected in the coming years (Fostamatinib disodium sarilumab, secukinumab Baricitinib, masitinib, and sirukumab). These are currently being investigated in clinical trials, and the results are not yet available. These would not be expected to be ready for appraisal until the end of 2014 at the earliest.

New evidence

Efficacy of TNF inhibitors compared to other agents.

One of the important areas of uncertainty in TA195, TA225 and TA247 was the relative efficacy of the TNF inhibitors compared to rituximab, abatacept or tocilizumab (which have a different mechanism of action to the TNF inhibitors) due to the lack of direct head to head data. Three trials have been identified that could provide further evidence to reduce this uncertainty:

- A randomised, open label trial, SWITCH, is on-going. SWITCH investigates switching to alternative TNF blocking drugs or abatacept or rituximab in patients (n=870) with rheumatoid arthritis who have failed an initial TNF blocking drug. The study lasts 6 months and has 3 arms: TNF inhibitors (etanercept, adalimumab, certolizumab pegol, infliximab), abatacept (intravenous formulation), rituximab. The primary outcomes are reduction in disease activity with no toxicity, and the proportion of patients who achieve a reduction in disease activity score 28 of at least 1.2 at 6 months with no toxicity. The study completion date is expected to be December 2015, and is currently at only 1% recruitment.

- A phase 4 clinical trial, that investigates rotation or change of biotherapy after first anti-TNF treatment failure for rheumatoid arthritis, is currently on-going. The trial compares moving to an alternative TNF inhibitor (infliximab, etanercept, or adalimumab) with moving to a treatment with a different mechanism of action (abatacept, rituximab, or tocilizumab). There are two study arms: TNF inhibitors and other biotherapy. The time frame of the study is 6 months and its primary outcome is the proportion of EULAR responders. The estimated study completion date is May 2013. No results have been published from this trial as yet. The use of this study in informing a guidance update is limited by its design in that abatacept, rituximab and tocilizumab are grouped together in one study arm.

- It was noted in TA247 that there was no available evidence to compare the clinical effectiveness of tocilizumab with TNF inhibitors. Since which a

randomized, open-label, parallel-group study of the reduction of signs and symptoms during treatment with tocilizumab versus adalimumab (both in combination with methotrexate) in patients with moderate to severe active rheumatoid arthritis and an inadequate response to treatment with a TNF inhibitor has been conducted. The study completion date was February 2013 however study results have not yet been published.

Uncertainty in the efficacy of TNF inhibitors after failure of a TNF inhibitor

It was concluded in TA195 that the available evidence on the effectiveness of TNF inhibitors after failure of a TNF inhibitor was mainly derived from observational studies with short follow-up periods that included small numbers of participants. Since release of this guidance, some studies have been completed, or are on-going, that could add to the evidence base. This may enable inclusion of further data, adding power to a mixed treatment comparison and reducing the uncertainty associated with the clinical effectiveness of using further TNF inhibitors after failure of a first TNF inhibitor:

- A randomised, double blind, placebo controlled study comparing the safety and efficacy of etanercept in individuals with rheumatoid arthritis that has had an inadequate response to adalimumab or infliximab. The completion date for this study is May 2014.

- A phase 4, open label, one arm study investigating the efficacy and safety of infliximab in individuals with active rheumatoid arthritis that has responded inadequately to adalimumab or etanercept. This study completed in June 2010. Results have been published, however, no statistical analysis is provided. The results indicate that 49.7% of patients achieved a EULAR response at week 10, and 22.3% maintained the response until week 26 without a dose increase. The mean change from baseline in physical function (HAQ) at week 26 was -0.223 +/- 0.4968. The percentage of patients who achieved ACR20 at week 26 it was 26 35.5% (Clinical Trials.gov 2013).

- A phase 4 multicenter, single-blind, randomized parallel-group study to assess the short- and long-term efficacy of certolizumab pegol plus methotrexate compared to adalimumab plus methotrexate in people with moderate to severe active rheumatoid arthritis responding inadequately to methotrexate. This study has 4 arms: certolizumab pegol plus methotrexate, adalimumab plus methotrexate, certolizumab pegol plus methotrexate followed by adalimumab plus methotrexate, adalimumab plus methotrexate followed by certolizumab pegol plus methotrexate. No results have yet been published for this study. It started in December 2011 and is anticipated to complete January 2016

Uncertainty in the efficacy of rituximab

In developing TA195, the Committee reviewed an indirect comparison and concluded that the clinical efficacy of rituximab was not significantly different to that of abatacept, but that both were clinically effective compared to placebo. Four open label or non-interventional studies have been completed or are on-going since the publication of the guidance. The results of which have not been published. These are

not randomised, placebo controlled trials and therefore these data are unlikely to be any more certain than the data reviewed for TA195, and could not be incorporated into a mixed treatment comparison.

Summary

The following issues could possibly lead to a change in the current guidance:

- There are some trials on-going that could address the uncertainty relating to the difference in efficacy between the TNF inhibitors and non TNF inhibitors. These data could alter the guidance however the most appropriate data will not be available until December 2015.

- The placebo controlled trials investigating etanercept, infliximab, certolizumab pegol and adalimumab in the relevant population could add to the evidence base and support a mixed treatment comparison. Of note, the data that has been published relating to infliximab does not indicate a large clinical effect. However, as no statistical analyses have been published the conclusions are uncertain.

- The emergence of an infliximab biosimilar into the market towards the end of 2014 could alter the cost effectiveness of infliximab. However, as infliximab is an intravenous agent, the costs will be driven by administration costs as well as drug price.

- The development of different formulations of abatacept, golimumab and tocilizumab may impact their cost effectiveness. The subcutaneous abatacept and tocilizumab could reduce their associated costs substantially.

- The impact in clinical practice of the change in the SPC for rituximab would need to be evaluated in the review.

The following would not alter the guidance:

- There are no significant changes in marketing authorisation indications that would alter the current guidance.

- Tofacitinib, fostamatinib disodium, sarilumab, seckinumab, baricitnib, masitinib and sirkumab are awaiting marketing authorisations. But the timings for these marketing authorisations mean that these products are most appropriately considered in separate appraisals.

- Additional trials investigating the efficacy of rituximab have been conducted or are on-going. However, these are non-RCT trials and therefore associated with more uncertainty than the data reviewed in TA195.

- The emergence of a rituximab biosimilar would not alter the guidance, as rituximab was concluded to be the most cost-effective treatment in TA195.

Other considerations

- Certolizumab pegol has the same licence as other TNF inhibitors, but hasn't previously been considered by NICE in this position. It wasn't included within TA195 due to marketing authorisation timings. It could be appropriate to include certolizumab pegol in this review proposal, alongside the other TNF inhibitors.

- The current NICE guidance for first use of a biologic allows use of both TNF inhibitors and non TNF inhibitors. However, guidance for second line biologics is only available following first line biologic treatment with TNF inhibitors; there is no current guidance for second line biologics treatment where the first line biologic was a non TNF inhibitor. The current guidance therefore does not allow for the range of scenarios that may occur in clinical practice, when following NICE guidance.

- NICE is currently reviewing the guidance for rheumatoid arthritis treatment before failure of a TNF inhibitor (Rheumatoid arthritis - adalimumab, etanercept, infliximab (TA130), certolizumab pegol (TA186) and golimumab (TA225 part review) - review [ID537]). This is expected to be issued in January 2014. There is potential for the starting and stopping rules applied to treatment decisions to be updated in the guidance.

- The NICE guideline on the management of rheumatoid arthritis that refers to technology appraisal guidance updated by TA 195, will be considered for review again after the publication of the MTA (scheduled to review and update TA130, TA186, TA 234 and part review of TA 225). This will provide for an opportunity for consideration of review of TA195, TA225 and TA247 within the context of the guideline.

8. Implementation

A submission from Implementation is included in Appendix 3.

Data from ePACT indicates that the use of adalimumab, etanercept and golimumab have increased following the release of NICE guidance TA195 and TA225, which shows that these are being used in clinical practice. The use of golimumab increased rapidly after release of NICE guidance TA225. However, this guidance includes the use of golimumab after failure of DMARDs as well as after failure of a first TNF inhibitor and therefore the impact of guidance relating to the later indication only is not clear. Adalimumab and etanercept are used for other conditions, therefore masking the impact of TA195 on their update. The rate of the increase of their use wasn't largely affected by the release of TA195. The cost and volume of infliximab, rituximab and abatacept and tocilizumab was zero, suggesting that these drugs are not prescribed in primary care or by hospitals dispensing in the community.

A study across 10 hospital and community sites showed that although NICE recommends combination with DMARDS, the vast majority of patients (90% of 337 case notes and 331 surveys) were receiving monotherapy (Gordon 2010).

An audit of rituximab use showed that results of DAS-28 were always recorded at screening, but not always at follow-up. It was concluded that NICE guidance was consistently followed for initiation of rituximab, but not always for continuation (Khurshid 2010).

There is insufficient evidence to draw firm conclusions on how NICE guidance is being adhered to, any variation in practice, or any changes in clinical practice since publication of the previous guidance.

9. Equality issues

The following equality issues were raised and discussed in the previous guidance:

- DAS28 is not an appropriate tool for people with specific disabilities of the lower limbs. DAS44 would be a better tool to use for people with greater lower limb disease burden. The Committee agreed that it was important to allow clinicians to adjust the assessment of disease severity depending on the characteristics of the disease, and that the recommendations should reflect this.

- People with mobility problems or visual impairment may find travel to hospital onerous or inconvenient. However, the Committee concluded that it was not clear that travelling to receive infusions one or two times per year (for rituximab treatment) would necessarily be more onerous or inconvenient than the alternative of much more frequent injections. In any event, the Committee did not consider that the need to travel would make it impossible or unreasonably difficult for these people to obtain treatment with rituximab, and noted that they would need to travel to other hospital or healthcare appointments in relation to their condition. The Committee concluded that rituximab would still be the most appropriate treatment option, taking into account its cost-effectiveness data and the infrequent dosing interval, but that all reasonable steps should be taken to provide practical support and assistance to ensure access to treatment for this group of people.

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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 should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	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.	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.	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
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

Options	Consequence	Selected – 'Yes/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

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

Current guidance

TA195:

1.1 Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Treatment with rituximab should be given no more frequently than every 6 months.

1.2 Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following retreatment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more.

1.3 Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.

1.4 Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event.

1.5 Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response (as defined in 1.2) 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.

1.6 When using DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.

1.7 A team experienced in the diagnosis and treatment of rheumatoid arthritis and working under the supervision of a rheumatologist should initiate, supervise and assess response to treatment with rituximab, adalimumab, etanercept, infliximab or abatacept.

TA225:

Relevant guidance to position after the failure of a TNF inhibitor only.

1.2 Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if:

- it is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' (NICE technology appraisal guidance 195), **and**

- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.

1.3 When using the disease activity score (DAS28), healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.

TA247:

Relevant guidance to position after the failure of a TNF inhibitor only.

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

- the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, **and** tocilizumab is used as described for TNF inhibitor treatments in Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (NICE technology appraisal guidance 195), specifically the recommendations on disease activity **or**

- the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab

- **and** the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.

Published

Technology Appraisal TA130 Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (issued October 2007). Status: a review is currently in development as Rheumatoid arthritis - adalimumab, etanercept, infliximab (TA130), certolizumab pegol (TA186) and golimumab (TA225 part review) - review [ID537] (expected January 2014).

Technology Appraisal TA234 Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (issued August 2011), subject to rapid review (expected April 2013).

Clinical Guideline CG79 Rheumatoid arthritis: the management of rheumatoid arthritis in adults (issued February 2009). Review decision January 2012:

- *"The Rheumatoid arthritis guideline should not be considered for an update at this time*
- *The guideline will be reviewed again after the publication of the MTA (scheduled to review and update TA130, TA186, TA 234 and part review of TA 225)."*

In progress

Abatacept for the treatment of rheumatoid arthritis only after the failure of conventional disease-modifying anti-rheumatic drugs (rapid review of TA234). Expected date of issue: April 2013.

Referred - QSs and CGs

Rheumatoid Arthritis QS - in development. Expected date of issue: June 2013.

Suspended/terminated

Technology Appraisal TA224 Golimumab for the treatment of methotrexate-naive rheumatoid arthritis. Status: terminated (June 2011) *"because no evidence submission was received from the manufacturer or sponsor of the technology*."

Rheumatoid arthritis (after the failure of conventional DMARDs) -rituximab [ID333]. Status: terminated (March 2011) because *"The manufacturer has informed us that they will not be seeking a license for this particular indication at the present time."*

Tofacitinib for the treatment of rheumatoid arthritis after the failure of disease modifying anti-rheumatic drugs [ID526]. Status: paused (December 2012) because *"Due to an update from the manufacturer, this appraisal is currently paused as the regulatory process is ongoing*."

Details of changes to the indications of the technology

Indication considered in original appraisal	**Proposed indication (for this appraisal)**
The indications remain the same except for the following:	

Indication considered in original appraisal	Proposed indication (for this appraisal)
In October 2009, golimumab, in combination with methotrexate, received a marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including methotrexate has been inadequate. The summary of product characteristics (SPC) notes that golimumab has also been shown to improve physical function in this population. In February 2011, the marketing authorisation was amended to indicate that golimumab has also been shown to reduce the rate of progression of joint damage as measured by X-ray when given in combination with methotrexate.	Golimumab is licensed in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis when response to disease-modifying antirheumatic drug (DMARD) therapy (including methotrexate) has been inadequate (see also NICE guidance below); it is also licensed in combination with methotrexate for patients with severe, active, and progressive rheumatoid arthritis **not previously treated with methotrexate**. (eBNF March 13)

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
CT P13 / Inflectra (Hospira)	Infliximab biosimilar. Filed in the EU according to NDO. Phase III trial results were reported at EULAR 2012.
Abatacept SC (Bristol-Myers Squibb).	Launched in the UK February 2013.
Golimumab IV (Schering Plough (MSD).	PIII Go-Further study results are in publication.
Tocilizumab SC (Roche).	"Topline results from the PIII study BREVACTA" are being reported (NDO, July 2012).
Baricitinib (Eli Lilly.)	Phase III trial stage.
Fostamatinib disodium (AstraZeneca).	"Topline results" are being reported (NDO, April 2013).
Masitinib (AB Science)	"The PII/III study (NCT01410695)…is due to complete August 2014" (NDO, August 2011).

Drug (manufacturer)	Details (phase of development, expected launch date,)
Sarilumab SC (Sanofi)	Phase III trial stage.
Secukinumab (Novartis)	Phase III trial stage.
Sirukumab (Centocor)	Phase III trial stage.

Registered and unpublished trials

Trial name and registration number	Details
General: Rotation or Change of Biotherapy After First Anti-TNF Treatment Failure for Rheumatoid Arthritis NCT01000441	Phase IV, currently recruiting. Estimated Enrollment: 300 Estimated study completion date: May 2013.
Randomised-controlled Trial of Switching to Alternative Tumour-necrosis Factor (TNF)-Blocking Drugs or Abatacept or Rituximab in Patients With Rheumatoid Arthritis Who Have Failed an Initial TNF-blocking Drug. NCT01295151 and UKCRN 12343.	Phase IV, not yet recruiting, but on UKCRN 12343 says 1% recruitment. Estimated Enrollment: 870 Estimated study completion date: December 2015.
Formation of Antibodies and Subsequent Prediction of Clinical Response in Patients With Rheumatoid Arthritis Treated With a Tnf-α Blocking Agent NCT01691014	"The rationale for this study is to further explore if development of antibodies against TNF-α blocking agents is associated with reduced clinical effect/worsened clinical outcome and, if patients with high-level antibodies may benefit from early shift to other therapies. An important aspect of the study is to carry out head-to-head analyses of the immunogenicity in RA patients of the 4 most commonly used TNF-α blockers in the Nordic countries." These four are adalimumab, etanercept, infliximab and golimumab. Phase IV, not yet open to recruitment. Estimated Enrollment: 144 Estimated study completion date: October 2014.

Trial name and registration number	Details
A Retrospective Chart Review on the Use of Biologics in Monotherapy for the Treatment of Patients With Rheumatoid Arthritis. no phase given, recruiting NCT01640548	NB it says this: Primary Outcome Measures: "Percentage of patients receiving biologics in monotherapy according to National Institute for Health and Care Excellence (NICE) guidelines." "This non-interventional, retrospective, cross sectional chart review study will evaluate the management of rheumatoid arthritis patients with a biologic in monotherapy." Estimated Enrollment: 300 Estimated study completion date: May 2013.
Adalimumab (as a comparator): A Multicenter, Single-blind, Randomized Parallel-group Study to Assess the Short- and Long-term Efficacy of Certolizumab Pegol Plus Methotrexate Compared to Adalimumab Plus Methotrexate in Subjects With Moderate to Severe Rheumatoid Arthritis Responding Inadequately to Methotrexate. . NCT01500278 and also UKCRN 12147	Phase IV, recruiting. Estimated Enrollment: 892 Estimated study completion date: January 2016.
Etanercept A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Etanercept in Subjects With Rheumatoid Arthritis Who Have Had an Inadequate Response to Adalimumab or Infliximab Plus Methotrexate. NCT01783015	Phase IV, not yet open for recruitment. Estimated Enrollment: 168 Estimated study completion date: May 2014.
Infliximab A Phase 4, Multicenter, Open-Label, Assessor-Blinded Switch Study of the Efficacy and Safety of Infliximab (REMICADE) in Patients With Active Rheumatoid Arthritis Who Are Responding Inadequately to Etanercept (ENBREL) or Adalimumab (HUMIRA).. NCT00714493	Phase IV, completed. (No publication found, estimated study completion date June 2010)

Trial name and registration number	Details
Infliximab biosimilar Program evaLuating the Autoimmune Disease iNvEstigational Drug cT-p13 in RA Patients(PLANETRA) NCT01217086	Phase III, completed. (No publication found, estimated study completion date July 2012)
Rituximab An Open Label Study to Evaluate the Safety and Effect on Treatment Response of MabThera in Patients With Rheumatoid Arthritis Following Inadequate Response to One Prior Anti-TNF Inhibitor. NCT00576433	Phase IV, ongoing not recruiting. Estimated Enrollment: 60 Estimated study completion date: December 2012.
An Open Label Study to Assess the Safety and Effect on Disease Activity of MabThera in Patients With Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Prior Treatment With DMARDs and/or One Anti-TNF Alpha Agent. NCT00503425	Phase III, ongoing not recruiting. Estimated Enrollment: 215 Estimated study completion date: April 2013.
Non-interventional, Prospective, Multicenter Study to Assess Efficacy and Safety of MabtheRA (Rituximab) in Patients With Active Rheumatoid Arthritis Who Have Had an Inadequate Response or Intolerance to One Anti-TNF Agent - FAST 2 SWITCH Program. NCT01641952	Phase not given, currently recruiting. Estimated Enrollment: 200 Estimated study completion date: December 2013.
A Long-Term Study of the Safety of Rituxan in Patients With Rheumatoid Arthritis After an Inadequate Response to Previous Anti-TNF Therapy (SUNSTONE). NCT00443443	Phase IV, ongoing not recruiting. Estimated Enrollment: 1026 Estimated study completion date: December 2013.
Rituximab biosimilar Double Blind Randomized Clinical Study Evaluating Efficacy and Safety of BCD-020 and MabThera in Patients With Rheumatoid Arthritis Who Had an Inadequate Response or Intolerance to Other DMARDs Including One or More TNF Inhibitor Therapies. NCT01759030	Biosimilar phase III, currently recruiting. Estimated Enrollment: 160 Estimated study completion date: December 2014.

Trial name and registration number	Details
Tocilizumab A Randomized, Open-label, Parallel-group Study of the Reduction of Signs and Symptoms During Treatment With Tocilizumab Versus Adalimumab, Both in Combination With MTX, in Patients With Moderate to Severe Active Rheumatoid Arthritis and an Inadequate Response to Treatment With Only One TNF Inhibitor. NCT01283971	Phase IV, ongoing not recruiting. Estimated Enrollment: 100 Estimated study completion date: February 2013.

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Yoo D, Miranda P, Piotrowski M et al. (2012) A randomised, double blind, phase 3 study demonstrates clinical equivalence of CT-P13 to infliximab when co-administered with methotrexate in patients with active rheumatoid arthritis. Annals of the Rheumatic Diseases. 71 (suppl3): 359-.

Implementation feedback: review of NICE technology appraisal guidance 195, 225 & 247

NICE Technology Appraisal 195; Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor NICE Technology Appraisal 225; Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs NICE Technology Appraisal 247; Tocilizumab for the treatment of rheumatoid arthritis
Implementation input required by 25/02/2013
Please contact Rebecca Lea regarding any queries rebecca.lea@nice.org.uk

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1 Routine healthcare activity data

1.1 ePACT data

Figure 1 below presents the net ingredient cost (NIC) and the number of prescription items of Adalimumab prescribed in primary care and hospitals that have been dispensed in the community in England between January 2008 and December 2012. In addition to the NICE guidance indicated in Figure 1, NICE has published other Technology Appraisal guidance on Adalimumab for indications other than Rheumatoid Arthritis[2].

Figure 1 Net ingredient cost and volume of Adalimumab prescribed in primary care and hospitals that have been dispensed in the community

[2] NICE TA146 Psoraisis – adalimumab (June 2008)

NICE TA199 Psoriatic arthritis – adalimumb (August 2010)

NICE TA143 Ankylosing spodylitis – adalimumab (May 2008)

NICE TA187 Crohn's disease – adalimumab (May 2010)

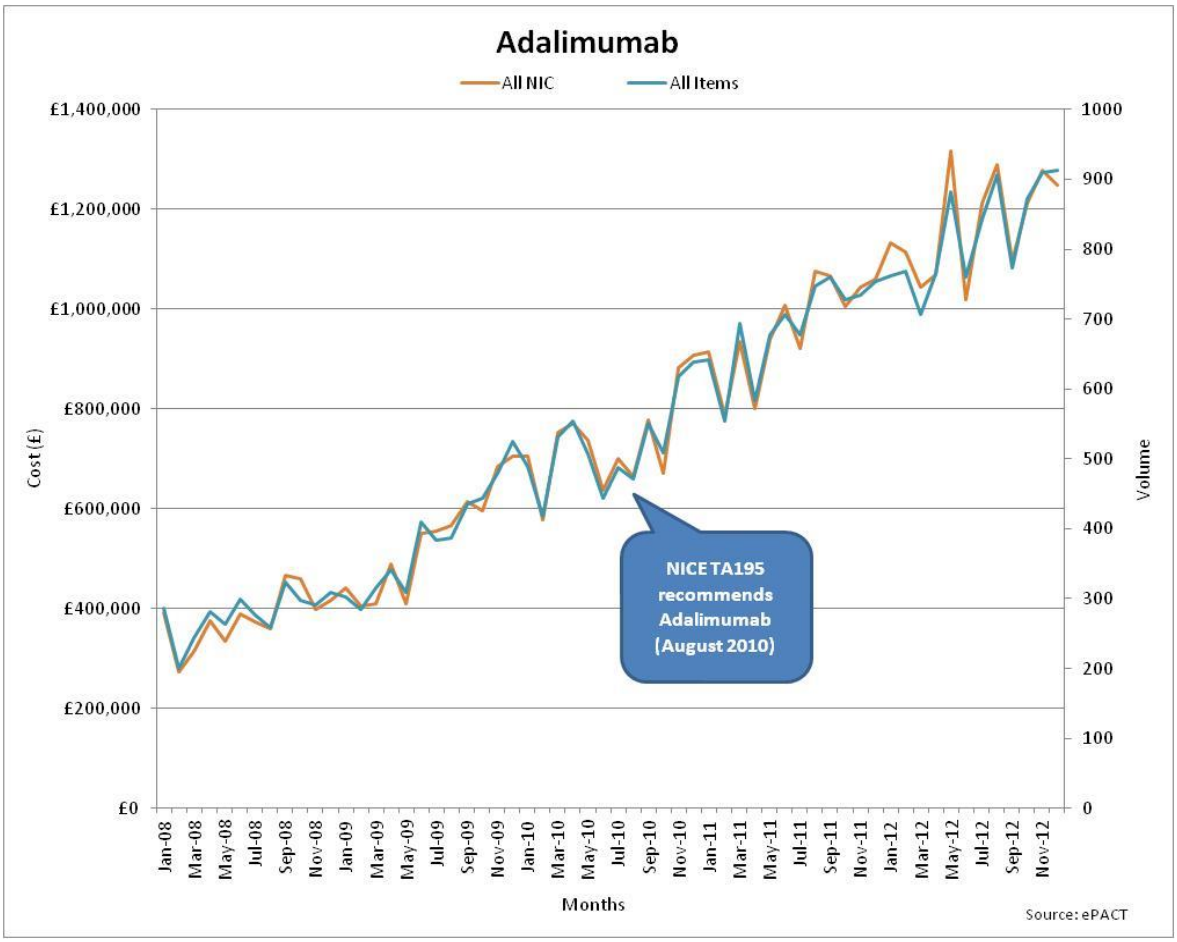


Figure 2 presents the net ingredient cost (NIC) and the number of prescription items of Etanercept prescribed in primary care and hospitals that have been dispensed in the community in England between January 2008 and December 2012. In addition to the NICE guidance indicated in Figure 2, NICE has published other Technology Appraisal guidance on Etanercept for indications other than Rheumatoid Arthritis[3].

Figure 2 Net ingredient cost and volume of Etanercept prescribed in primary care and hospitals that have been dispensed in the community

[3] NICE TA103 Psoriasis – etanercept (July 2006)

NICE TA199 Psoriatic arthritis – etanercept (August 2010)

NICE TA143 Ankylosing spodylitis – etanercept (May 2008)

NICE TA35 Arthritis (juvenile idiopathic) –etanercept (March 2002)

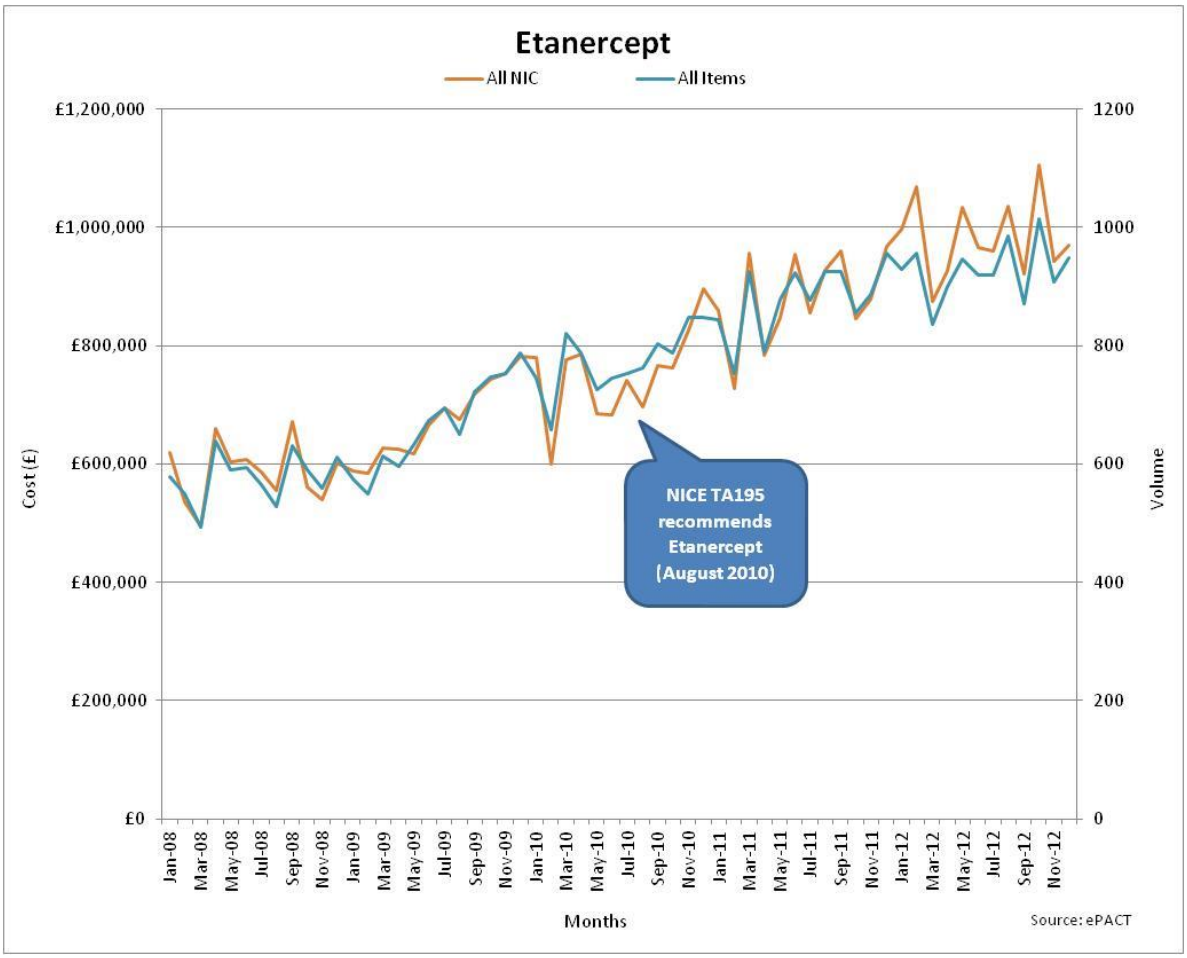
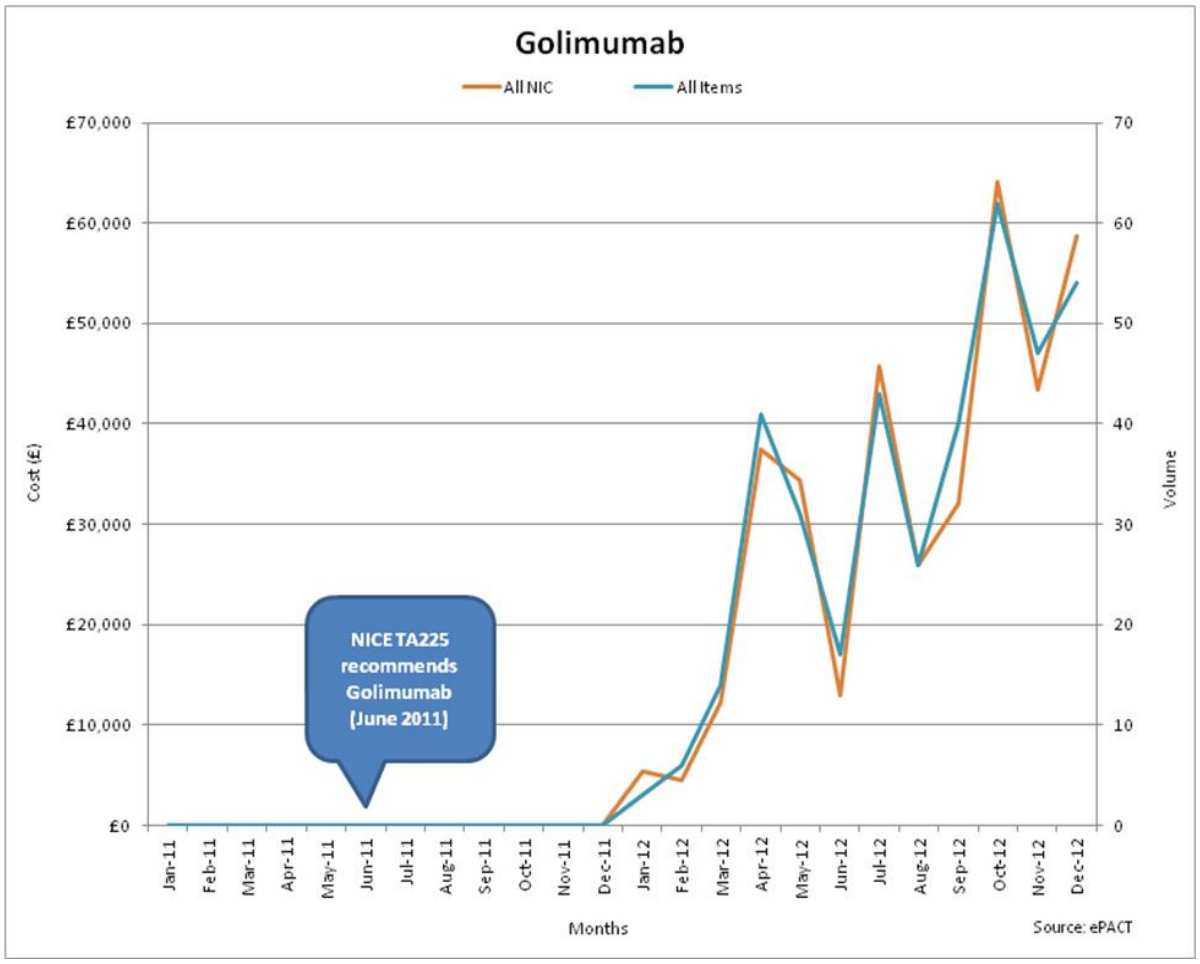


Figure 3 presents the net ingredient cost (NIC) and the number of prescription items of Golimumab prescribed in primary care and hospitals that have been dispensed in the community in England between January 2008 and December 2012. In addition to the NICE guidance indicated in Figure 3, NICE has published other Technology Appraisal guidance on Golimumab for indications other than Rheumatoid Arthritis[4].

Figure 3 Net ingredient cost and volume of Golimumab prescribed in primary care and hospitals that have been dispensed in the community

[4] NICE TA220 Psoriatic arthritis – Golimumab (April 2011)

NICE TA233 Ankylosing spondylitis – Golimumab (August 2011)



ePACT data on the cost and volume of infliximab, rituximab, abatacept and tocilizumab was zero, suggesting that these drugs are not prescribed in primary care or by hospitals for dispensing in the community.

2 Implementation studies from published literature

Information is taken from the uptake database (ERNIE) website.

2.1 Gordon R et al (2010) A supra-district audit of the management of rheumatoid arthritis in adults (2009 NICE guidance) *Rheumatology* 49

Rheumatology services based at 10 hospital and community sites across Greater Manchester were asked to collect data on up to 60 outpatients with inflammatory arthritis. Data was collected from 337 sets of case notes and patients completed and returned 331 (33%) of surveys distributed. Although NICE recommends combination

therpay with DMARDs, the vast majority (90%) of patients were receiving monotherapy.

2.2 Khurshid M A et al (2010) Rituximab; data from audit on 43 patients at Queen Alexandra Hospital, Portsmouth, UK *International Journal of Rheumatic Diseases* 13

53 patients on Rituximab were identified and 43 finally audited. Results found that DAS-28 (a composite score) was always recorded at screening but not always at follow-up. NICE guidance was consistently followed for initiation of Rituximab but not always for continuation. 70% of patients fulfilled NICE response criteria at 3-4 months but <10% achieved remission.

2.3 National Rheumatoid Arthritis Society & Chartered Society of Physiotherapy (2011) RA and physiotherapy: A national survey

The National Rheumatoid Arthritis Society sent out 2,303 electronic questionnaires to their members with RA in August 2011, and 248 questionnaires were returned. Results found 32.2% of respondents to the survey said they waited over one year for a referral from a medical practitioner to see a physiotherapist, while 31% of respondents said they had never been offered a referral to a physiotherapist. Only 10.6% of respondents reported waiting less than one month for a referral.

2.4 National Audit Office (2009) Services for people with rheumatoid arthritis

This report evaluates services provided for people with rheumatoid arthritis in England. Data was collected between October 2008 and February 2009 using a variety of means, including two censuses of NHS Trusts and surveys of people with rheumatoid arthritis. Findings relating to access to treatment and care after diagnosis show that of the estimated 11,900 patients eligible to receive NICE recommended biologics in 2007-08, all but approx. 350 people across all acute trusts were receiving them.

2.5 Health and Social Care Information Centre (2012) https://catalogue.ic.nhs.uk/publications/prescribing/primary/use-nice-app-med-nhs-exp-stat-eng-10-11/use-nice-app-med-nhs-exp-stat-eng-10-11-rep.pdf

This is the 3rd report published by the HSCIC on behalf of the DH to look at the variation in use of positively appraised medicines in relation to the expected use as predicted by NICE. In all, 52 medicines in 25 groups, relating to 35 technology appraisals were considered. Out of the 12 groups where a comparison could be made, observed use by the NHS in England was higher than the predicted use for 6 and lower for 6. For one drug group use was lower on one measure, and higher on another.

2.6 Kobelt, G et al (2009) Access to innovative treatments in Rheumatoid Arthritis In Europe

This report compares usage of NICE positively appraised Rheumatoid Arthritis drugs in England (abatacept, rituximab, adalimumab, infliximab, etanercept), with other countries drug usage. Cost and volume data from IMS data and average annual dose per patient and drug were used to estimate the patient numbers treated by country. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

2.7 Richards, M (2010) Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.