Review of TA375; Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

<table>
<thead>
<tr>
<th>Original publication date:</th>
<th>26 January 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review date:</td>
<td>January 2019</td>
</tr>
<tr>
<td>Existing recommendations:</td>
<td>Optimised</td>
</tr>
<tr>
<td></td>
<td>To see the complete existing recommendations and the original remit for TA375, see Appendix A.</td>
</tr>
</tbody>
</table>

1. Proposal
We propose that a partial review of TA375 for patients with moderate disease only should be planned into the appraisal work programme. To consult on this proposal.

2. Rationale
TA375 includes optimised positive recommendations for patients with severe disease only. It concluded that biological disease-modifying antirheumatic drugs (DMARDs) are not a cost-effective use of NHS resources for people with moderate active disease because the committee’s preferred median ICER was around £51,100 per QALY gained.

Although TA375 included biosimilar infliximab, since its publication, new biosimilars for adalimumab and etanercept have become available and there have been changes in the confidential prices paid by NHS England for all treatments considered in TA375 (see table 1 in Appendix E). The availability of cheaper treatments may reduce the committee’s preferred ICER to £20,000 to £30,000 per QALY gained for people with moderate active disease (that is, the range that is considered a cost-effective use of NHS resources). No new evidence has been found to address the other uncertainties identified in TA375.

It is therefore proposed that a partial review of TA375 for people with moderate active disease only should be planned into the appraisal work programme because the price reductions may change the existing, negative recommendations in TA375 for patients with moderate disease.
3. Process for the update

A partial update of TA375 should be planned into the appraisal work programme. The update will focus on the population with moderate active disease only. As the main driver for the review is the price reduction for the treatments included in the original appraisal, it is proposed that NICE takes a pragmatic approach to the update without going through a full appraisal process. The proposed steps are outlined below:

- using the original Assessment Group economic model from TA375 (owned by the School of Health and Related Research, Sheffield (ScHARR)) model the new confidential price information of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, following the introduction of the biosimilars
- Seek short, succinct submissions from stakeholders regarding the potential for a change to the current recommendations for moderate active disease in TA375
- Conduct a short engagement step on the results of the Assessment Group work prior to committee consideration
- the NICE Resource Impact Assessment team will compile the relevant information regarding the Budget Impact Test and provide this to both NHS England and the companies
- seek committee consideration of the results of the modelling of the confidential prices for the treatments and develop recommendations regarding moderate active disease
- issue the new recommendations as an update to TA375, in a FAD for appeal.

The approach outlined above could be completed in approximately 6 months instead of a 14-month process that a standard Multiple Technology Appraisal would take.

4. Charging for technology appraisals

If it is agreed that this is an appropriate approach to take, the part review of TA375 will commence post 01 April 2019. Therefore, this review will be subject to the charging mechanism for technology appraisals.

5. Summary of new evidence and implications for review

Optimised recommendation for TA375

TA375 recommends biological DMARDs for severe disease that has not responded to intensive therapy with a combination of conventional DMARDs. In TA375, the committee concluded that it was not cost-effective to use biological DMARDs to treat moderate disease because the median ICER was around £51,100 per QALY gained. It acknowledged lower ICERs for moderate disease when:

- using American College of Rheumatology (ACR) rather than European League Against Rheumatism (EULAR) as a response measure
- assuming the fastest health assessment questionnaire (HAQ) progression for conventional DMARDs (that is, assuming a linear rate of HAQ progression rather than non-linear data from the Early Rheumatoid Arthritis Study [ERAS])
• using alternative utility values from Malottki et al (2011) to map HAQ (instead of Hernandez et al 2013)
• using alternative discounts rates of 6% for costs and 1.5% for QALYs

However, the committee did not consider these changes to be plausible and preferred to use the EULAR response measure using data from ERAS, which assumed non-linear disease progression with conventional DMARDs. Non-linear HAQ progression and utility data using Hernandez et al (2013) were also accepted by the committee in the most recent technology appraisal in the same disease area (TA485 sarilumab for moderate to severe rheumatoid arthritis).

In TA375, the committee also understood that in clinical practice, treatment was aimed at rapidly progressing disease and was not convinced this would be targeted by treating moderate disease. Therefore, TA375 does not recommend biological DMARD treatment for moderate disease because it is not cost-effective in this group.

New evidence and changes since TA375

Since TA375 was published in 2016, cheaper biosimilar versions of adalimumab, etanercept and rituximab have become available. In addition, there have been changes to the confidential prices of all the treatments included in TA375 paid by the NHS (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept).

A recent review of the cost-effectiveness of biological DMARDs in England using the model from TA375 (Stevenson et al 2017) reported exploratory analyses showing that the cost of biological DMARDs would need to be lowered by around 50% to reduce the most plausible ICER for moderate disease (£51,100) to a range that is considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained). However, it is noted that the analyses compared biological DMARDs with no additional treatment and did not account for any people with moderate disease, whose disease becomes severe, at which point the treatments recommended in TA375 would be started. It is likely that the cost reduction would need to be more than 50% to address this relevant treatment strategy in some people, but these analyses were not reported. Table 1 (see appendix E) shows that although the changes in list prices are small, the price reductions in the confidential prices paid by NHS England are much larger compared to the original costs used in TA375. Therefore, cheaper medicines may change the existing recommendations in TA375 for patients with moderate disease.

No relevant new evidence was identified to address uncertainty in HAQ progression with conventional DMARDs and calculating EQ-5D from HAQ. The approach for long-term disease progression in TA375 used registry data from the UK biologics register for rheumatoid arthritis (BSRBR-RA study) and it is unlikely that other UK based data sources would result in any changes.

It is proposed that a partial review of TA375 for people with moderate active disease only should be planned into the appraisal work programme because price reductions may change the existing recommendations in TA375 for patients with moderate disease.
Has there been any change to the price of the technologies since the guidance was published?

<table>
<thead>
<tr>
<th>TA375 considered 4 patient access schemes; golimumab and certolizumab pegol were complex schemes and were not confidential and tocilizumab and abatacept were simple discounts and were confidential. These discounts have not changed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA375 considered biosimilar infliximab but biosimilar versions of rituximab, adalimumab and etanercept are now available (see Appendix C and E for costs).</td>
</tr>
</tbody>
</table>

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

None

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

Uncertainties in TA375

In TA375 the committee identified uncertainty in the long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D utility values, but still made decisions based on the evidence presented to it.

Specifically, it noted limitations with the ERAS data but preferred to use this data to model disease progression with conventional DMARDs rather than assume a linear progression because it was considered to be more clinically plausible. The committee also preferred to use Hernandez et al (2013) to calculate EQ-5D values because the alternative method using Malottki et al (2011) inappropriately used a linear regression to estimate EQ-5D when these scores are not normally distributed, included more patients at the severe end of the HAQ scale and was associated with the biggest range of EQ-5D values compared with other equations.

Recent technology appraisal for rheumatoid arthritis

More recently published appraisal in this disease area (TA480 tofacitinib for moderate to severe rheumatoid arthritis and TA485 sarilumab for moderate to severe rheumatoid arthritis) use the same approach as TA375 for utilities and disease progression. Specifically, the committee accepted the non-linear approach to HAQ progression and Hernandez (2013) to calculate EQ-5D as appropriate for decision-making. Therefore, new evidence on these areas of uncertainty have not been identified in more recent appraisals.

In TA485, the committee also accepted a model that allowed patients treated for moderate disease to progress to treatment for severe disease and this was not used in TA375. It is uncertain how including this would impact on the existing recommendations for TA375.

New evidence and ongoing trials

Systematic reviews and meta-analyses published after TA375 (for example Combe et al 2018, Singh et al 2016, Alfonso-Cristancho et al 2017, Buckley et al 2015) generally support the existing recommendations and show biological
DMARDs in combination with methotrexate are more effective compared with conventional DMARDs and there is little difference in effectiveness between the different biological treatments.

Some newly published and on-going trials identified in the literature search (Appendix C) include EQ-5D data, which may help to address one of the uncertainties identified in TA375. However as reported in TA485, it is unlikely that EQ-5D data would be available for all comparators across all patient populations. Therefore, it is likely that a utility mapping approach will still be needed in future appraisals in the same disease area.

Overall, it is the price reductions that may change the existing recommendations in TA375 for patients with moderate disease.

**Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?**

*See Appendix C for a list of related NICE guidance.*

**Additional comments**

None

The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from May 2013 to December 2018 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.

**6. Equality issues**

No specific equality issues were raised during the development of TA375.

**GE paper sign off:**  Helen Knight, 29 March 2019

**Contributors to this paper:**

Information Specialist:  Toni Shaw

Technical Analyst:  Abi Senthinathan

Technical Adviser:  Alex Filby

Associate Director:  Frances Sutcliffe / Janet Robertson

Project Manager:  Emily Richards
Appendix A – Information from existing guidance

7. Original remit
To appraise the clinical and cost effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept within their licensed indications for the treatment of rheumatoid arthritis

8. Current guidance

1.1 Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs) and
- the companies provide certolizumab pegol, golimumab, abatacept and tocilizumab as agreed in their patient access schemes.

1.2 Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in section 1.1 are met.

1.3 Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.

1.4 After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

1.5 Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for some people because of differences in the mode of administration and treatment schedules.

1.6 People whose treatment with adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab or abatacept is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
9. Research recommendations from original guidance

6.1 The Committee agreed that further research would be of value to investigate factors which can predict the likelihood of rapid progression of disease and response to treatment with biological DMARDs. Factors to investigate include:

- persistent elevation of inflammatory markers (such as C-reactive protein [CRP])
- presence of erosions on X-ray and
- positive for anti-citrullinated protein antibodies (ACPA; see section 4.94).

The Committee felt that how these factors interact with each other and to what extent the likelihood of progression is affected by the use of different thresholds would be of value.

10. Cost information from original guidance

- The net price of adalimumab is £352.14 per 40-mg prefilled pen or prefilled syringe, or £352.14 per 40-mg/0.8-ml vial (British national formulary [BNF], July 2015). Assuming 26 doses per year, the annual cost of adalimumab is £9155.64. For adalimumab monotherapy, the dose may be increased up to 40 mg per week for people who have a decrease in response.

- The net price of etanercept is £89.38 per 25-mg prefilled syringe, or £178.75 per 50-mg prefilled pen or prefilled syringe (BNF, July 2015). Assuming 52 doses per year, the annual cost of etanercept is £9295.

- The NHS list price of originator infliximab (Remicade) is £419.62 per 100-mg vial (BNF, July 2015). Assuming a weight per person of 70 kg, vial wastage and 3 initial doses followed by treatment every 8 weeks, the cost in the first year is £10,070.88, and then £8812.02 per year.

- The NHS list price of infliximab biosimilars (Remsima, Inflectra) is £377.66 per 100-mg vial (BNF, December 2015). Assuming a weight per person of 70 kg, vial wastage, and 3 initial doses in the first year followed by treatment every 8 weeks, the cost in the first year is £9063.84, and then £7930.86 per year.

- The net price of certolizumab pegol is £357.50 per 200-mg prefilled syringe (BNF, July 2015). Assuming 3 initial doses of 400 mg followed by maintenance doses every 2 weeks, the cost (without the patient access scheme) in the first year is £10,367.50, (or with the patient access scheme, £6793) and then £9295 per year.
Appendix A

- The net price of **golimumab** is £762.97 per 50-mg prefilled pen or prefilled syringe (BNF, July 2015). For people weighing less than 100 kg and assuming 12 doses per year, the annual cost of golimumab is £9155.64.

- The net price of **abatacept for intravenous infusion** is £302.40 per 250 mg vial (BNF, July 2015). For people weighing between 60 and 100 kg, the cost of treatment for the first year is £12,700.80 and then £11,793.60 per year (without the patient access scheme).

- The net price of **abatacept for subcutaneous injection** is £302.40 per 125-mg prefilled syringe (BNF, July 2015). Assuming a weight per person of 70 kg, 1 intravenous loading dose followed by subcutaneous treatment doses every week, the cost (without the patient access scheme) of the initial intravenous dose is £907.20, and then £15,724.80 per year.

- The net price of **tocilizumab** is £102.40 per 4-ml (80-mg) vial, £256.00 per 10-ml (200 mg) vial, or £512.00 per 20-ml (400-mg) vial (BNF, July 2015). Assuming a weight per person of 70 kg, vial wastage, and 13 doses each year, the annual cost (without the patient access scheme) of tocilizumab is £9318.40.
# 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:

<table>
<thead>
<tr>
<th>Options</th>
<th>Consequence</th>
<th>Selected – ‘Yes/No’</th>
</tr>
</thead>
<tbody>
<tr>
<td>A partial review of the guidance should be planned into the appraisal work programme.</td>
<td>A review of the appraisal will be planned into the NICE’s work programme.</td>
<td>Yes</td>
</tr>
<tr>
<td>The decision to review the guidance should be deferred</td>
<td>NICE will reconsider whether a review is necessary at the specified date.</td>
<td>No</td>
</tr>
<tr>
<td>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.</td>
<td>A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.</td>
<td>No</td>
</tr>
<tr>
<td>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.</td>
<td>A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.</td>
<td>No</td>
</tr>
<tr>
<td>The guidance should be incorporated into an on-going guideline.</td>
<td>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 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.</td>
<td>No</td>
</tr>
<tr>
<td><strong>Options</strong></td>
<td><strong>Consequence</strong></td>
<td><strong>Selected – ‘Yes/No’</strong></td>
</tr>
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<tr>
<td>The guidance should be updated in an on-going guideline&lt;sup&gt;1&lt;/sup&gt;.</td>
<td>Responsibility for the updating the technology appraisal passes to the NICE 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).</td>
<td>No</td>
</tr>
<tr>
<td>The guidance should be transferred to the 'static guidance list'.</td>
<td>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.</td>
<td>No</td>
</tr>
<tr>
<td>The guidance should be withdrawn</td>
<td>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.</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>1</sup> Information on the criteria for NICE allowing a technology appraisal in an ongoing 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

Published

Rheumatoid arthritis in adults: management (2018) NICE guideline NG100

Rheumatoid arthritis (2015, last updated July 2018) NICE Pathway

Sarilumab for moderate to severe rheumatoid arthritis (2017) NICE technology appraisal guidance 485

Tofacitinib for moderate to severe rheumatoid arthritis (2017) NICE technology appraisal guidance 480

Baricitinib for moderate to severe rheumatoid arthritis (2017) NICE technology appraisal guidance 466

Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (2016) NICE technology appraisal guidance 415

Tocilizumab for the treatment of rheumatoid arthritis (2012) NICE technology appraisal guidance 247 (partially replaced by TA375)

Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs (2011) NICE technology appraisal guidance 225

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (2010) NICE technology appraisal guidance 195 (partially replaced by TA375)

In progress

Upadacitinib for treating moderate to severe rheumatoid arthritis. NICE technology appraisal guidance. Publication date to be confirmed.

2. Details of changes to the indications of the technology

<table>
<thead>
<tr>
<th>Indication and price considered in original appraisal</th>
<th>Proposed indication (for this appraisal) and current price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira, AbbVie), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe, active rheumatoid arthritis in adults</td>
<td>The indication for adalimumab is the same (eBNF, accessed 17 December 18). The price is the same in the current eBNF (accessed 17 December 18)</td>
</tr>
</tbody>
</table>
### Indication and price considered in original appraisal

when the response to DMARDs, including methotrexate, has been inadequate and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

The net price of **adalimumab** is £352.14 per 40 mg prefilled pen or prefilled syringe, or £352.14 per 40 mg/0.8 ml vial (British national formulary [BNF], July 2015).

### Proposed indication (for this appraisal) and current price

Amgevita (a biosimilar) was launched in the UK in October 2018 for "rheumatoid arthritis and other Humira indications", according to SPS (accessed 17 December 18). On SPS the price information says:

"Amgevita 20mg/0.4ml soln for inj in pre-filled syringe, Price =£158.40. Amgevita 40mg/0.8ml soln for inj in pre-filled syringe or pre-filled pen, Price =£633.60"

Similarly SPS lists Hyrimoz (by Sandoz) and Imraldi (Samsung Bioepsis) as launched in October 2018. In SPS the price for Hyrimoz is given as "2 x 40mg/0.8ml soln for inj in pre-filled syringe or pre-filled pen=£646.18" and for Imraldi it is given as " 40mg/0.8ml soln for inj in pre-filled syringe or pre-filled pen, Price = £633.85". Neither are currently on eBNF, as of 10 Jan 19.

Mylan are listed in SPS as having a biosimilar called Huilio approved in the UK, and launched in Europe, while an entry for another biosimilar (Cyltezo) says: "Dec 18: Boehringer Ingelheim has said that it will not commercialize its approved adalimumab biosimilar Cyltezo (BI 695501) in Europe and is discontinuing all biosimilar development activities outside the US".

Other adalimumab biosimilars in development are listed on SPS.

**Etanercept** (Enbrel, Pfizer), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate (unless

The indication for **etanercept** is the same (eBNF, accessed 17 December 18).

The price is the same in the current eBNF (accessed 17 December 18).
<table>
<thead>
<tr>
<th>Indication and price considered in original appraisal</th>
<th>Proposed indication (for this appraisal) and current price</th>
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<tbody>
<tr>
<td>contraindicated), has been inadequate, and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Etanercept can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. The net price of <strong>etanercept</strong> is £89.38 per 25 mg prefilled syringe, or £178.75 per 50 mg prefilled pen or prefilled syringe (BNF, July 2015).</td>
<td>eBNF lists Benepali (BioGen Idec) for the same indication. The date of first authorisation is given as 14 January 2016. It also lists Erelzi (Sandoz, June 2017). Other etanercept biosimilars in development are listed on SPS.</td>
</tr>
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</table>

**Infliximab** (Remicade, Merck Sharp & Dohme; Remsima, Napp Pharmaceuticals and Inflectra, Hospira UK), in combination with methotrexate, has a UK marketing authorisation for the reduction of signs and symptoms of rheumatoid arthritis as well as the improvement in physical function in adults with active disease when the response to DMARDs, including methotrexate, has been inadequate. It is also licensed for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs. The contraindications, adverse reactions and administration schedule are the same for all infliximab products (see sections 3.9 and 3.10), but both biosimilars are subject to additional monitoring in line with standard European Medicines Agency recommendations.

The NHS list price of originator **infliximab (Remicade)** is £419.62 per 100 mg vial (BNF, July 2015).

The NHS list price of **infliximab biosimilars** (Remsima, Inflectra) is £377.66 per 100 mg vial (BNF, December 2015). | The indication for **infliximab** is the same in the current SPC (accessed 17 December 18). The prices for remicade, remsima and inflectra are the same in the current eBNF (accessed 17 December 18). SPS also lists Zessly (Sandoz, launched December 2018). Other infliximab biosimilars in development are listed on SPS. |
<table>
<thead>
<tr>
<th>Indication and price considered in original appraisal</th>
<th>Proposed indication (for this appraisal) and current price</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Certolizumab pegol</strong> (Cimzia, UCB Pharma), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate, has been inadequate. Certolizumab pegol can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. The net price of <strong>certolizumab pegol</strong> is £357.50 per 200 mg prefilled syringe (BNF, July 2015).</td>
<td>The indication for <strong>certolizumab pegol</strong> is the same but also includes &quot;the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs&quot; (<a href="https://www.eMC.org.uk/">eMC, accessed 17 December 18</a>). The price is the same in the current eBNF (accessed 17 December 18).</td>
</tr>
<tr>
<td><strong>Golimumab</strong> (Simponi, Merck Sharp &amp; Dohme), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to DMARD therapy including methotrexate has been inadequate, and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. The net price of <strong>golimumab</strong> is £762.97 per 50 mg prefilled pen or prefilled syringe (BNF, July 2015).</td>
<td>The indication for <strong>golimumab</strong> is the same (<a href="https://www.medicines_complete.com/products/116166">SPC, accessed 17 December 18</a>). The price is the same in the current eBNF (accessed 17 December 18).</td>
</tr>
<tr>
<td><strong>Abatacept</strong> (Orencia, Bristol–Myers Squibb) in combination with methotrexate has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease responded inadequately to previous therapy with 1 or more DMARDs including methotrexate or a TNF-alpha inhibitor. The net price of <strong>abatacept for intravenous infusion</strong> is £302.40 per 250 mg vial (BNF, July 2015).</td>
<td>The indication for <strong>abatacept</strong> is the same and also includes &quot;the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate&quot; (<a href="https://www.medicines_complete.com/products/116166">SPC, accessed 17 December 18</a>). The price is the same in the current eBNF (accessed 17 December 18).</td>
</tr>
</tbody>
</table>
### Indication and price considered in original appraisal

<table>
<thead>
<tr>
<th>Proposed indication (for this appraisal) and current price</th>
</tr>
</thead>
<tbody>
<tr>
<td>The net price <strong>of abatacept for subcutaneous injection</strong> is £302.40 per 125 mg prefilled syringe (BNF, July 2015).</td>
</tr>
</tbody>
</table>

**Tocilizumab** (RoActemra, Roche), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has responded inadequately, or adults who were intolerant, to previous therapy with 1 or more DMARDs or TNF-alpha inhibitors. In these people, tocilizumab can be given as monotherapy in cases of intolerance to methotrexate or if continued treatment with methotrexate is inappropriate. In July 2014 the marketing authorisation for tocilizumab was extended to include treatment of severe active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. A marketing authorisation for a subcutaneous formulation was granted in February 2014.

The net price of **tocilizumab** is £102.40 per 4 ml (80 mg) vial, £256.00 per 10 ml (200 mg) vial, or £512.00 per 20 ml (400 mg) vial (BNF, July 2015).

3. Registered and unpublished trials

<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adalimumab</strong>:</td>
<td></td>
</tr>
<tr>
<td>Trial name and registration number</td>
<td>Details</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>A Randomized, Double-blind, Parallel-group Study Assessing the Efficacy and Safety of Sarilumab Monotherapy Versus Adalimumab Monotherapy in Patients With Rheumatoid Arthritis (SARIL-RA-MONARCH)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>NCT02332590; EFC14092; 2014-002541-22 (EudraCT Number)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>U1111-1160-6154 (Other Identifier: UTN)</strong></td>
<td></td>
</tr>
<tr>
<td>Phase: III</td>
<td></td>
</tr>
<tr>
<td>Enrolment: 369 participants</td>
<td></td>
</tr>
<tr>
<td>Status: active not recruiting</td>
<td></td>
</tr>
<tr>
<td>Start date: February 2015</td>
<td></td>
</tr>
<tr>
<td>Estimated completion date: December 2020</td>
<td></td>
</tr>
<tr>
<td><strong>OBJECTIVES:</strong> To compare efficacy and safety of sarilumab monotherapy with adalimumab monotherapy in patients with active rheumatoid arthritis (RA) who should not continue treatment with methotrexate (MTX) due to intolerance or inadequate response.</td>
<td></td>
</tr>
<tr>
<td><strong>Study results are available on the trial record.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>MIRACLE (Methotrexate Inadequate Response Patient With Rheumatoid Arthritis Treated by Adalimumab in Combination With Low-dose Methotrexate) Study</strong></td>
<td></td>
</tr>
<tr>
<td><strong>NCT03505008; D2E7-C000-401</strong></td>
<td></td>
</tr>
<tr>
<td>&quot;Evaluation of the Optimal MTX Dose as an Add-on Therapy to Adalimumab for RA Patients in Japan, South Korea and Taiwan.&quot;</td>
<td></td>
</tr>
<tr>
<td>Phase: IV</td>
<td></td>
</tr>
<tr>
<td>Enrolment: 300 participants</td>
<td></td>
</tr>
<tr>
<td>Status: recruiting</td>
<td></td>
</tr>
<tr>
<td>Start date: April 2018</td>
<td></td>
</tr>
<tr>
<td>Estimated completion date: February 2022</td>
<td></td>
</tr>
<tr>
<td><strong>A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects With Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>NCT02629159; M14-465</strong></td>
<td></td>
</tr>
<tr>
<td>2015-003333-95 (EudraCT Number)</td>
<td></td>
</tr>
<tr>
<td>SELECT-COMPARE</td>
<td></td>
</tr>
<tr>
<td>Phase: III</td>
<td></td>
</tr>
<tr>
<td>Enrolment: 1630 participants</td>
<td></td>
</tr>
<tr>
<td>Status: active not recruiting</td>
<td></td>
</tr>
<tr>
<td>Start date: December 2015</td>
<td></td>
</tr>
<tr>
<td>Estimated completion date: August 2020</td>
<td></td>
</tr>
<tr>
<td>Trial name and registration number</td>
<td>Details</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------</td>
</tr>
</tbody>
</table>
| Phase 3b/4 Randomized Safety Endpoint Study Of 2 Doses Of Tofacitinib In Comparison To A Tumor Necrosis Factor (Tnf) Inhibitor In Subjects With Rheumatoid Arthritis | Three arms: tofacitinib 5 mg; tofacitinib 10mg; adalimumab or etanercept  
Phase: IV  
Enrolment: 4400 participants  
Status: recruiting  
Start date: March 2014  
Estimated completion date: March 2020 |
| A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks in Combination With Methotrexate to Subjects With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate | Investigation / treatment:  
- Drug: Filgotinib  
- Drug: Placebo to match filgotinib  
- Drug: Adalimumab  
- Drug: Placebo to match adalimumab  
- Drug: MTX  
Phase: III  
Enrolment: 1759 participants  
Status: active not recruiting  
Start date: August 2016  
Estimated completion date: April 2019 |
| Etanercept: |  
A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis | Phase: III  
Enrolment: 371 participants  
Status: Active not recruiting  
Start date: February 2015  
Estimated completion date: November 2019 |
<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Multicenter Extension Study To 104 Weeks To Assess The Efficacy, Safety And Immunogenicity Of Enanceptan® In Combination With Methotrexate For The Treatment Of Patients With Rheumatoid Arthritis**<br>NCT03403140; GEMENE002 | "This is a prospective study, single treatment arm of 72 weeks of duration. Patients who completed the original study GEMENE001 may enroll in the study."
Phase: III
Enrolment: 141 participants
Status: active not recruiting
Start date: October 2016
Estimated completion date: October 2018 |
| **Effectiveness of a Combination of Methotrexate and a Step Down Glucocorticoid Regimen (COBRA-Slim) for Remission Induction in Patients With Early Rheumatoid Arthritis (RA), With or Without Fast Access to 24 Weeks of Tumor Necrosis Factor (TNF) Blockade in Insufficient Responders, a Randomized, Multicenter, Pragmatic Trial**<br>NCT03649061; KCE-16002; 2017-004054-41 (EudraCT Number) CareRA2020 | "In the Care in Rheumatoid Arthritis (CareRA) trial (NCT01172639) about 70% of early RA patients are in remission at the 2 year evaluation point independent of the combination scheme used. Interesting to see is that the 30% of insufficient responders can be identified in an early stage of the treatment course.

The purpose of the present study is to investigate if, for patients with an insufficient response to a COBRA-Slim regimen, accelerated access to a short course of anti-TNF therapy already early after treatment initiation (from w8 until w32) could improve outcomes compared to a more traditional treat to target sequence."

Intervention / treatment:
- Drug: Etanercept 50 MG/ML
- Drug: Leflunomide 10 milligram

Phase: IV
Enrolment: 442
Status: recruiting
Start date: June 2018
Estimated completion date: December 2022 |
### Treatments Against RA and Effect on FDG-PET/CT (The TARGET Trial)

**Trial name and registration number**

<table>
<thead>
<tr>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;In a randomized controlled clinical trial, investigators will compare the effects on [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET/CT) from two treatment regimens in rheumatoid arthritis (RA) patients deemed methotrexate inadequate responders (MTX-IRs). Two common RA treatments will be compared: triple therapy (sulfasalazine, methotrexate, and hydroxychloroquine) versus tumor necrosis factor (TNF) inhibitor (etanercept or adalimumab, plus background methotrexate for all subjects and hydroxychloroquine for subjects who were taking this at screening).&quot;</td>
</tr>
</tbody>
</table>

**Intervention / treatment:**

- Drug: Methotrexate
- Drug: Sulfasalazine
- Drug: Hydroxychloroquine
- Drug: Etanercept
- Drug: Adalimumab

**Phase:** IV

**Enrolment:** 200 participants

**Status:** recruiting

**Start date:** July 2016

**Estimated completion date:** March 2022

### Infliximab:

**A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety Between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients With Active RA**

**Details:**

"This Phase I/III Study randomized, open-label, multicenter, parallel-group study is designed to evaluate efficacy, pharmacokinetics and safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis"

**Phase:** I/III

**Enrolment:** 412 participants

**Status:** active not recruiting

**Start date:** September 2016

**Estimated completion date:** February 2019
### A NORwegian Multicentre Randomised Controlled Trial Assessing the Effectiveness of Tailoring Infliximab Treatment by Therapeutic DRUg Monitoring - The NOR-DRUM Study

<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
</table>
| NCT03074656; DIA2016-1            | "The NOR-DRUM study is planned as a national, randomised controlled multicentre trial in two parts aiming to assess the effectiveness of therapeutic drug monitoring in order to achieve remission in patients with immunological inflammatory diseases starting infliximab treatment (part A) and in order to maintain disease control in patients on maintenance infliximab treatment (part B). The results of the NOR-DRUM study will hopefully contribute to an implementation of a personalised medicine approach to treatment with infliximab and other biological drugs."

This trial includes people with any of the following conditions/diseases:

- Rheumatoid Arthritis
- Spondyloarthritis
- Ankylosing Spondylitis
- Crohn Disease
- Ulcerative Colitis
- Psoriasis
- Psoriatic Arthritis

- Phase: n/a
- Enrolment: 600 participants
- Status: recruiting
- Start date: March 2017
- Estimated completion date: March 2022

### Certolizumab pegol:

| Prediction of Response to Certolizumab Pegol Treatment by Functional MRI of the Brain. A Multi-center, Randomized Double-blind Controlled Study Prediction of Response to Certolizumab-Pegol in RA (PreCePRA) | "The rationale of this study is to test whether response to TNFi can be predicted by using functional MRI."

- Phase: III
- Enrolment: 156 participants
- Status: recruiting
- Start date: July 2013
- Estimated completion date: June 2019

### Golimumab:

No relevant active trials were found in searching.
<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abatacept:</strong></td>
<td></td>
</tr>
</tbody>
</table>
| A Phase 3, Randomized, Active-Controlled, Double Blind Study Comparing Upadacitinib (ABT-494) to Abatacept in Subjects With Moderately to Severely Active Rheumatoid Arthritis With Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs) on Stable Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs) | "The comparison of safety and efficacy of upadacitinib versus abatacept in participants with rheumatoid arthritis on a stable background conventional synthetic Disease Modifying Anti-Rheumatic Drug (csDMARD) who have an inadequate response or intolerance to biologic DMARDs."
Phase: III
Enrolment: 550 participants
Status: recruiting
Start date: May 2017
Estimated completion date: March 2021 |
| **Abatacept to Silence Anti-citrullinated Protein Antibody-expressing B Cells in Rheumatoid Arthritis (ASCARA).** | "To investigate the effect of CTLA4-Ig (abatacept) on phenotype, transcriptional profile, B cell receptor usage and functional parameters of circulating B cells expressing anticitrullinated protein antibodies (ACPA) in patients with early, methotrexate-naïve, ACPA positive rheumatoid arthritis."
Phase: IV
Enrolment: 46 participants
Status: not yet recruiting
Start date: May 2018
Estimated completion date: September 2021 |
<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Tapering Abatacept or Tocilizumab in Rheumatoid Arthritis in Remission. An Evaluation of Disease Activity, Relapse Risk, Structural Progression and the Economic Impact of a Tapering Strategy**<br>NCT01557374; AOM 11061<br>TOLEDO | "As the expected result, this study is aimed to test the feasibility of a step down strategy on 2 biological agents, Abatacept and Tocilizumab, in RA patients in remission."
Phase: IV
Enrolment: 232 participants
Status: active not recruiting
Start date: April 2012
Estimated completion date: June 2021 |
| **Abatacept Versus Tocilizumab by Subcutaneous Administration for the Treatment of Rheumatoid Arthritis in TNF Alpha Inhibitor Inadequate Responder Patients: A Randomized, Open-labeled, Superiority Trial**<br>NCT03227419; RC-P0055<br>SUNSTAR | Phase: IV
Enrolment: 224 participants
Status: recruiting
Start date: January 2018
Estimated completion date: November 2022 |
| **Tocilizumab:**<br>Open-label, Randomized Controlled Trial Comparing Tocilizumab to Anti-TNF Treatment and Discovery of Biomarkers for Treatment Selection in Rheumatoid Arthritis Patients With Inadequate Response to a First Anti-TNF<br>NCT03100253; IRFMN-RA-6453<br>RAFTING | "To compare the efficacy of switching to a different molecular target (from TNF to IL6) versus cycling to a second TNF inhibitor in patients with active RA, who have not adequately responded to a previous treatment with a first anti-TNF."
Phase: IV
Enrolment: 400 participants
Status: recruiting
Start date: March 2018
Estimated completion date: October 2021 |
### Trial name and registration number

| Details |
|------------------|--------------------------------------------------|
| A Randomized, Multi-Center, Double Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Subcutaneous (SC) Tocilizumab (TCZ) in Combination With Methotrexate (MTX) and as Monotherapy Versus MTX in Patients With Moderate to Severe Rheumatoid Arthritis With Inadequate Response to Current DMARD Therapy |
| **NCT03155347**; YA29359 |
| "This is a randomized, double-blind, multi-center, parallel-group study to evaluate the efficacy and safety of subcutaneous (SC) tocilizumab (162 milligrams [mg] every 2 weeks [Q2W]) given as monotherapy and in combination with MTX versus MTX given as monotherapy, in participants with moderate to severe active rheumatoid arthritis (RA) who have inadequate response to current DMARD therapy. The study comprises a 24-week double-blind treatment phase, followed by a 24-week extension phase." |
| Phase: III |
| Enrolment: 300 participants |
| Status: recruiting |
| Start date: August 2017 |
| Estimated completion date: June 2020 |

| Details |
|------------------|--------------------------------------------------|
| Therapeutic Drug Monitoring of Tocilizumab in Rheumatoid Arthritis |
| **NCT03781310**; 0563-18-TLV |
| "A wide range of serum trough concentrations is observed in tocilizumab-treated rheumatoid arthritis (RA) patients, while 1 mg/L tocilizumab is sufficient to block systemic interleukin-6 receptor. A substantial proportion of patients has higher serum tocilizumab concentrations and is likely to be overexposed. We expect that patients can at least reduce the dose aiming for a concentration of 5 mg/L without reducing efficacy." |
| Phase: IV |
| Enrolment: 80 participants |
| Status: recruiting |
| Start date: December 2018 |
| Estimated completion date: December 2019 |

### Trials with multiple relevant technologies:
<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
</table>
| Stopping Tumor Necrosis Factor-Alpha Inhibitors in Rheumatoid Arthritis (STARA) Clinical Trial  
NCT01793519; CER-1402-10522  
STARA | Objectives:  
- To see whether RA remission can continue after discontinuing use of a TNF inhibitor.  
- To determine if clinical, imaging and immunological measurements can predict which participants will flare and which will remain in remission after discontinuing TNF inhibitor.  
Drug: Etanercept  
Drug: Infliximab  
Drug: Adalimumab  
Drug: Placebo  
Phase: IV  
Enrolment: 290 participants  
Status: recruiting  
Start date: January 2013  
Estimated completion date: August 2020 |
### Trial name and registration number

<table>
<thead>
<tr>
<th>Trial name and registration number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compare Efficacy and Safety Between Biologics + Methotrexate (MTX) vs Biologics + Tacrolimus (TAC) (Switched From Biologics + Methotrexate (MTX)) in the Patients With Rheumatoid Arthritis (RA): Randomized, Interventional, Open, Active Controlled, Parallel Group, Multicenter-designed, Phase 4 Clinical Trial</td>
<td>“The purpose of this study is to compare the efficacy of Biologics + Methotrexate with Biologics + Tacrolimus measured by the disease activity score 28 (DAS28) erythrocyte sedimentation rate (ESR) and the American College of Rheumatology (ACR) scores. The study will also assess the safety of the combinations.”</td>
</tr>
<tr>
<td><strong>NCT03737708</strong>: 506-MA-3187</td>
<td>Experimental: tacrolimus + biologics: tacrolimus; adalimumab; tocilizumab; abatacept</td>
</tr>
<tr>
<td></td>
<td>Active comparator: methotrexate + biologics: methotrexate; adalimumab; tocilizumab; abatacept</td>
</tr>
<tr>
<td></td>
<td>Phase: IV</td>
</tr>
<tr>
<td></td>
<td>Enrolment: 148 participants</td>
</tr>
<tr>
<td></td>
<td>Status: recruiting</td>
</tr>
<tr>
<td></td>
<td>Start date: November 2018</td>
</tr>
<tr>
<td></td>
<td>Estimated completion date: February 2021</td>
</tr>
</tbody>
</table>
### Trial name and registration number

<table>
<thead>
<tr>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Controlled Clinical Trial Evaluating Methotrexate + Biologic Versus Methotrexate, Salazopyrine and Hydroxychloroquine in Patients With Rheumatoid Arthritis and Insufficient Response to Methotrexate</td>
</tr>
<tr>
<td>NCT02714634; 6020 BIO 3</td>
</tr>
</tbody>
</table>

### Details

**Arms / interventions:**
- **Experimental:** Methotrexate + biologic group:
  - Methotrexate + biologic chosen by investigator (adalimumab or certolizumab or etanercept or golimumab or infliximab or abatacept or rituximab or tocilizumab)
- **Active Comparator:** Triple therapy
  - Triple therapy using 3 conventional disease modifying drugs (DMARDs):
    - Methotrexate + salazopyrine + hydroxychloroquine administration

**Phase:** IV

**Enrolment:** 286 participants

**Status:** not yet recruiting *(record last updated March 2016)*

**Start date:** March 2016

**Estimated completion date:** February 2020

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**Appendix D – References**


Cochrane Systematic Review and network meta-analysis (NMA). The Cochrane Library.

## Appendix E – Table of biosimilar medicines

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Original BNF list price</th>
<th>TA375 price</th>
<th>Current price</th>
<th>Percentage change in price since TA375</th>
<th>Currently used in NHS (Y/N)</th>
<th>&gt;50% drop</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infliximab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remicade (originator)</td>
<td>£419.62</td>
<td>£419.62</td>
<td>***</td>
<td>None</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td>Remsima (100mg)</td>
<td>£377.66</td>
<td>£377.66</td>
<td>***</td>
<td>None</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td>Inflectra (100mg)</td>
<td>£377.66</td>
<td>£377.66</td>
<td>***</td>
<td>None</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td>Flixabi (100mg)</td>
<td>N/A</td>
<td>£377.00</td>
<td>0.2%</td>
<td>Confidential</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MabThera (originator 500mg/50ml)</td>
<td>£873.15</td>
<td>£873.15</td>
<td>***</td>
<td>None</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td>Rixathon (500mg/50ml)</td>
<td>N/A</td>
<td>£785.84</td>
<td>10.00%</td>
<td>Confidential</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td>Truxima (500mg/50ml)</td>
<td>N/A</td>
<td>£785.84</td>
<td>10.00%</td>
<td>Confidential</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Humira (originator 40mg/0.8 pen/syringe)</td>
<td>£352.14</td>
<td>£352.14</td>
<td>***</td>
<td>None</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td>Hyrimoz (40mg/0.8ml)</td>
<td>N/A</td>
<td>£323.09</td>
<td>8.25%</td>
<td>Confidential</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td>Amgevita (40mg/0.8ml)</td>
<td>N/A</td>
<td>£316.80</td>
<td>10.04%</td>
<td>Confidential</td>
<td>Y</td>
<td>***</td>
</tr>
<tr>
<td>Medicine</td>
<td>BNF list price</td>
<td>Confidential price</td>
<td>Percentage change in price since TA375</td>
<td>Currently used in NHS (Y/N)</td>
<td>&gt;50% drop</td>
<td></td>
</tr>
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</tr>
<tr>
<td></td>
<td>TA375</td>
<td>Current</td>
<td>Current (2019)</td>
<td>List price</td>
<td>Confidential</td>
<td></td>
</tr>
<tr>
<td>Enbrel (originator 25mg/0.5ml)</td>
<td>£89.38</td>
<td>£89.38</td>
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<td></td>
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</tr>
<tr>
<td>Enbrel (originator 50mg/1ml)</td>
<td>£178.75</td>
<td>£178.75</td>
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<td></td>
<td></td>
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<tr>
<td>Benepali (25ml/0.5ml)</td>
<td>N/A</td>
<td>£89.38</td>
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<tr>
<td>Benepali (50ml/1ml)</td>
<td>N/A</td>
<td>£164.00</td>
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<td></td>
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<tr>
<td>Erelzi (25mg/0.5ml)</td>
<td>N/A</td>
<td>£89.38</td>
<td>None</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Erelzi (50mg/1ml)</td>
<td>N/A</td>
<td>£160.88</td>
<td>10.00%</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
</tbody>
</table>

*Denotes homecare inclusive price ** Humira 40mg/0.4mL is the contracted product