Briefing Paper for Surrey Heartlands Integrated Care System (ICS) Area Prescribing Committee (APC)

NICE Technology Appraisals: Local implementation

NICE TA Guidance name and number	Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed (partial review of TA375). Technology appraisal guidance 715		
Available at	www.nice.org.uk/guidance/ta715		
Date of issue	14 July 2021	**Implementation deadline**	14 October 2021

Medicine details[1]

Name, brand name and manufacturer

Name	Brand name®	Manufacturer
Adalimumab	Amgevita	Amgen Ltd
	Humira*	AbbVie Ltd
	Hyrimoz	Sandoz Limited
	Idacio	Fresenius Kabi Ltd
	Imraldi	Biogen Biosimilars
Etanercept	Benepali	Biogen Biosimilars
	Enbrel*	Pfizer Limited
	Erelzi	Sandoz Limited
Infliximab	Flixabi	Biogen Biosimilars
	Inflectra	Pfizer Limited
	Remicade*	Merck Sharp & Dohme (UK) Limited
	Remsima	Celltrion Healthcare UK Limited
	Zessly	Sandoz Limited
Abatacept	Orencia*	Bristol-Myers Squibb Pharmaceuticals limited

*originator product i.e., the medicine first authorised for use (the others are biosimilars).

Mode of action

Name	Mode of action
Adalimumab	Tumour necrosis factor (TNF)-alpha inhibitor
Etanercept	TNF-alpha inhibitor
Infliximab	TNF-alpha inhibitor
Abatacept	Selective modulator of the T-lymphocyte activation pathway. Inhibits activation of T lymphocytes

Licensed indication

See individual summary of products characteristics, available at: https://www.medicines.org.uk/emc

All four medicines are licensed for the treatment of moderate to severe rheumatoid arthritis in adults, when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate (unless contraindicated), has been inadequate'.

<table>
<tr><td></td><td>Adalimumab and etanercept can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.</td></tr>
<tr><td>Formulation</td><td>
<table>
<tr><th>Technology</th><th>Mode of action</th></tr>
<tr><td>Adalimumab</td><td>Pre-filled syringes and pre-filled pens for subcutaneous injection.
Solution for injection for paediatric use.</td></tr>
<tr><td>Etanercept</td><td>Powder and solvent, pre-filled syringes and pre-filled pens for subcutaneous injection</td></tr>
<tr><td>Infliximab</td><td>Powder for concentration for solution for infusion.
Pre-filled syringes and pre-filled pens for subcutaneous injection.</td></tr>
<tr><td>Abatacept</td><td>Powder for concentration for solution for infusion.
Pre-filled syringes and pre-filled pens for subcutaneous injection.</td></tr>
</table>
</td></tr>
<tr><td>Usual dosage</td><td>See individual summary of products characteristics.
Available at: https://www.medicines.org.uk/emc</td></tr>
<tr><td>Comparison with NICE TA use[2]</td><td>This appraisal is a partial review of NICE technology appraisal guidance 375, which recommended adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept as treatment options for people with severe rheumatoid arthritis only, assessed by having a disease activity score (DAS28) more than 5.1.

This partial review considers moderate disease, that is, with a DAS28 between 3.2 and 5.1.

A partial review has been done because biosimilar versions of adalimumab and etanercept are now available, and there have been changes in the prices for some of the other technologies.

Please note:
• Although certolizumab pegol, golimumab and tocilizumab were included in the original guidance, the manufacturers of these technologies decided not to participate in this partial review.

• The committee could therefore only consider adalimumab, etanercept, infliximab and abatacept when making recommendations for moderate disease.

• In addition, the subcutaneous formulation of Remsima® was not considered in this partial review because it was not included in the final scope for NICE technology appraisal guidance 375.

• The originator product for infliximab (Remicade) was also not considered because the manufacturer of this technology did not participate in this appraisal.</td></tr>
</table>

This TA therefore considers the following highlighted products:

Technology	Originator®	Biosimilar®	Method of administration
Adalimumab	**Humira**	**Amgevita** **Imraldi** **Idacio** **Hyrimoz**	Subcutaneous injection
Etanercept	**Enbrel**	**Benepali** **Erelzi**	Subcutaneous injection
Infliximab	**-**	**Flixabi** **Remsima** **Inflectra** **Zessly**	Intravenous injection
Abatacept	**Orencia**	**-**	Subcutaneous or intravenous injection

In addition, and importantly, the moderate treatment sequences modelled by the assessment group did not consider cycling of tumour necrosis factor (TNF)-alpha inhibitors (taking another TNF-alpha inhibitor after a first one).

This would happen if a person does not tolerate the first treatment, or if their disease either does not respond or responds inadequately after an initial response.

The clinical experts explained that because the technologies are protein-based drugs, there is a risk of developing antidrug antibodies, which reduces the treatment benefit over time. They noted that around 50% of people will stop treatment within 3 years because of loss of efficacy.

The clinical experts explained that the cycling of TNF-alpha inhibitors has a place in treating rheumatoid arthritis. They explained that, for this reason, having a variety of therapeutic choices for moderate disease would benefit people.

The committee noted that the scope for the appraisal includes only first-line use of biological DMARDs (after a person's disease has responded inadequately to 2 or more conventional DMARDs) as in NICE technology appraisal guidance 375. It agreed that it was appropriate to assume that after the first biological treatment has failed, if the disease progresses to severe, NICE technology appraisal guidance.

Please note:

- *There is no guidance given to patients who fail or are intolerant of the first biological treatment, but their disease is not yet classified as severe.*

Disease and potential patient group	
Brief description of disease[3]	Rheumatoid arthritis is a long-term condition that causes pain, swelling and stiffness in the joints. The condition usually affects the hands, feet, and wrists. There may be periods where symptoms become worse, known as flare-ups or flares. A flare can be difficult to predict, but with treatment, it is possible to decrease the number of flares and minimise or prevent long-term damage to the joints. Some people with rheumatoid arthritis also experience problems in other parts of the body, or more general symptoms such as tiredness and weight loss. Disease severity is assessed using the disease activity score (DAS28). DAS 28 Interpretation* DAS28 < 2.6: Remission DAS28 >= 2.6 and <= 3.2: Low Disease Activity DAS28 > 3.2 and <= 5.1: Moderate Disease Activity DAS28 > 5.1: High Disease Activity * https://www.msdmanuals.com/en-gb/medical-calculators/RheumatoidArthritisDAS28.htm
Potential patient numbers per 100,000[4]	Severe RA 85/100,000 Moderate RA 48/100,000

SUMMARY

Guidance[2]

1.1 **Adalimumab, etanercept and infliximab**, **all with methotrexate, <u>are</u> recommended** as options for treating active rheumatoid arthritis in adults, only if:

- intensive therapy with 2 or more conventional disease-modifying antirheumatic drugs (DMARDs) has not controlled the disease well enough and
- disease is moderate (a disease activity score [DAS28] of 3.2 to 5.1) and
- the companies provide adalimumab, etanercept and infliximab at the same or lower prices than those agreed with the Commercial Medicines Unit.

1.2 **Adalimumab and etanercept** can be used as **monotherapy** when methotrexate is contraindicated or not tolerated, when the criteria in 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. If this initial response is not maintained at 6 months, stop treatment.

1.4 If more than one treatment is suitable, start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may vary because of differences in how the drugs are used and treatment schedules.

1.5 Take into account any physical, psychological, sensory or learning disabilities, or

communication difficulties that could affect the responses to the DAS28 and make any appropriate adjustments.

1.6 **Abatacept with methotrexate is <u>not</u> recommended**, within its marketing authorisation, for treating moderate active rheumatoid arthritis in adults when 1 or more DMARDs has not controlled the disease well enough.

Why the committee made these recommendations

This appraisal reviews some of the treatments (adalimumab, etanercept, infliximab and abatacept) recommended for severe rheumatoid arthritis in NICE technology appraisal guidance 375 and considers them for moderate rheumatoid arthritis. The clinical evidence suggests that these treatments are likely to be similarly effective in both moderate and severe disease.

The most likely estimates suggest that adalimumab, etanercept and infliximab after 2 or more conventional DMARDs are a cost-effective use of NHS resources. So, they are recommended for treating moderate rheumatoid arthritis. The most likely cost-effectiveness estimates for abatacept are higher than what NICE normally considers cost effective, so it is not recommended for moderate disease.

Cost implications* [2,3,4]

Cost:

Technology	Product	List price (ex VAT) £
Adalimumab per 40mg pre-filled pen or pre-filled syringe	Humira	352.14
	Amgevita	316.80
	Imraldi	316.93
	Idacio	316.93
	Hyrimoz	323.09
Etanercept per 25mg pre-filled pen or pre-filled syringe	Enbrel	89.38
	Benepali	82.00
	Erelzi	80.44
Infliximab biosimilars per 100 mg vial	Flixabi	377.00
	Remsima	377.66
	Inflectra	377.66
	Zessly	377.66
Abatacept 125 mg pre-filled pen or pre-filled syringe and per 250 mg vial	Orencia*	302.40

*this is the originator product and there are no biosimilars available for abatacept yet.

The companies have each agreed either a regionally or nationally available price reduction with the Commercial Medicines Unit (CMU) where the prices agreed through the framework are commercial in confidence, or in the case of abatacept, the company has a commercial arrangement. This makes abatacept available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence.

Annual or monthly cost per patient:
Price reductions either through frameworks with the CMU or commercial arrangements are commercial in confidence.

These technologies are currently in extensive use and the implications of the TA relate to the increase in numbers of patients eligible for these technologies as use is extended to those patients with moderate disease.

Has dose escalation been considered as part of the NICE costing template?

No

Costing information per CCG:

Numbers of patients eligible for treatment:

Table 1: Number of people eligible for treatment in NHS Surrey Heartlands CCG

			Local assumption future practice (year 5) (local input)	Local assumption future practice (year 5) (local input)
	% of people	Number of people	% of people	Number of people
Total population for area selected (all ages)		1,049,170		1,049,170
Total adult population		815,884		815,884
Prevalence of rheumatoid arthritis	0.82%	6,730	0.82%	6,730
People with moderate RA	45%	3,028	45%	3,028
People who receive conventional disease modifying anti-rheumatic drugs (cDMARDs).	91%	2,756	91%	2,756
People who receive 2 or more cDMARDs	24%	661	24%	661
People in whom intensive therapy with 2 or more cDMARDs has not controlled the disease well enough	75%	496	75%	496
People in whom intensive therapy with 2 or more cDMARDs has not controlled the disease well enough who will receive bDMARDs or tsDMARDs with methotrexate	15%	**74**	30%	**149**

The estimates are that:

- 496 people with moderate rheumatoid arthritis who respond inadequately to, or are intolerant of, (two or more) conventional DMARDs are eligible for treatment. Of these, around 149 people are expected to receive bDMARDs or tsDMARDs once uptake has reached 30%.
- of the 149 people, 125 will receive adalimumab, etanercept or infliximab from year 2023/24
- this guidance will lead to the overall proportion of the eligible population receiving bDMARDs or tsDMARDs to increase from 15% to 30%.

Cost-effectiveness:
The assessment group's base-case ICERs for adalimumab and infliximab were both below the range NICE considers to be an acceptable use of NHS resources. Therefore, the committee recommended **adalimumab and infliximab as first-line biological treatments for moderate active rheumatoid arthritis** that has had an inadequate response to intensive therapy with 2 or more conventional DMARDs.

Although the assessment group's ICER for **etanercept** was higher than those for adalimumab and infliximab, it was below £30,000 per QALY gained. In response to consultation, it was highlighted that there are some people for whom etanercept would be a particularly useful treatment option. For example, etanercept has a much lower risk of reactivating latent tuberculosis, which has a higher prevalence in people with a South Asian family background. In addition, compared with some of the other biologicals, etanercept does not need to be stopped as far in advance by people wishing to conceive.

The committee recognised that these groups would likely only represent a small number of people with moderate rheumatoid arthritis. **The committee noted that the recommendations state that if more than 1 biological is an appropriate treatment option, treatment should start with the least expensive**. So, it also **recommended etanercept as an option.**

The assessment group's base-case ICER for abatacept was above the range NICE considers to be an acceptable use of NHS resources. The committee therefore **did not recommend abatacept** as a treatment option for moderate active rheumatoid arthritis.

Please note:

- *Clinical experts suggests that uptake of the technologies could be slower through 2021/22 or 2022/23 because of the sizeable backlog in rheumatology work following the pandemic and because it will take time for these new recommendations to be adopted into practice.*

Local modelling:
In the local geography, the resource impact template gives the following:

Table 1: Impact of change on cost per ICP (based on population figures, as ICP level data not available in resource impact template.

	Change in costs (£K)				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
East Surrey	£30	£44	£50	£59	£59
Guildford & Waverly	£33	£50	£66	£66	£66
North West Surrey	£55	£82	**£109**	**£109**	**£109**
Surrey Downs	£46	£69	£92	£92	£92

The change in cost exceeds £100,000 for North West Surrey ICP, starting at year 3.

However, the following may reduce this expected cost (for all geographies):

1. Accuracy of the resource impact template

The resource template gives a different number for the total adult population depending on whether the area selected is available as an option in the drop-down menus for organisation type or if the population is entered manually – please see below:

Table 2: variance in cost change depending on input method in the assumptions made on template.

Input	Population	Total adult population	Impact of change on cost (year 5)
Organisational type – England ICS and Surrey Health and Care Partnership	1,049,170	815,884	£323,991
Manual entry of population (1,049,170)	1,049,170	825,185	£327,685

2. The template predicts the split in the future use of adalimumab, etanercept and filgotinib in moderate RA as follows:

Drug	Current practice	Future use
People receiving adalimumab	0%	63%
People receiving etanercept	0%	21%
People receiving infliximab	0%	0%
People receiving filgotinib	**100%**	**16%**
Total	100%	100%

This reduction in filgotinib is based on clinical expert opinion but if the local pathway advised filgotinib as a cost-effective first line choice and increased the use of filgotinib to over 16%, then the cost impact would be reduced.

Availability of PAS and details (if appropriate):
The PAS price would be given to trusts which would reduce this cost.

The PAS price only applies to trusts and primary care services would not be able to prescribe and supply at this reduced price, in line with the NICE TA.

Availability of homecare service (if appropriate):
Yes – already in place but additional numbers of patients.
**NICE funding requirements are based on Quality Adjusted Life Years (QALY) threshold. If there is evidence that the incremental cost rises above this threshold in the future, the APC may reconsider the commissioning status.*

Alternative treatments and cost per patient per year

Other NICE recommended products:
Filgotinib for treating moderate to severe rheumatoid arthritis TA676

Cost:
The list price for filgotinib is £863.10 per bottle of 30-day pack (company submission).

Annual or monthly cost per patient:
The average cost for each patient per year is estimated at £10,508.00 based on the list price.

Availability of PAS and details (if appropriate):
The company has a commercial arrangement. This makes filgotinib available to the NHS with a discount. The size of the discount is commercial in confidence.

Impact to patients

- People with moderate rheumatoid arthritis would welcome another treatment option.
    - Although there are a range of advanced treatment options for severe rheumatoid arthritis, only filgotinib is recommended for treating moderate disease.
    - While medicines appraised are similarly beneficial for treating the articular features of rheumatoid arthritis, they differ in their effectiveness in preventing particular comorbidities.
    - earlier access to advanced treatments in moderate disease would reduce disease progression and increase the likelihood of remission.
- These technologies are currently already available under a homecare service so will be delivered directly to the patient.

Impact to primary care prescribers

- This is a PbRe drug and is commissioned by CCGs for use in secondary care. There should be no prescribing in primary care.
- Primary care prescribers should be aware that their patient is receiving this medicine and ensure that this is recorded in the patient's notes in order to be alert to potential side-

effects and interactions with other medicines prescribed in primary care. This will also ensure that GP records, which are accessed by other healthcare providers, are a true and accurate reflection of the patient's medication.

Impact to secondary care

- The initiation, administration and on-going treatment is managed by secondary care.
- Homecare arrangements already in place but additional numbers of patients would result in additional pressure.
- An additional treatment option would be valued by clinicians.
- Additional pressures for intravenous administration of infliximab if used – although modelling anticipates that use would only be for adalimumab and etanercept (and filgotinib).

Impact to CCGs

- The technology is commissioned by clinical commissioning groups (CCGs) and they are required to comply with the recommendations in a NICE TA within 3 months of its date of publication.
- Providers are NHS hospital trusts - additional referral costs associated with increased number of patients eligible for treatment.
- Additional cost pressures for intravenous administration of infliximab if used.
- Consider successive use of bDAMRDs for the cohort of patients who have had first line treatment and their DAS28 remains as moderate.

Implementation

- NICE TA implementation must be within 90 days of publication
- Blueteq forms to be developed
- Trusts to follow internal governance procedures to add to their formulary and initiate homecare
- Pathway to be discussed at Rheumatology Network to consider:
    - Review RA pathway to include use of bDMARDs in moderate use.
    - Consider choice of product for moderate use.
    - Discuss successive use of bDMARDs in patients who have had one line of therapy in moderate use as this is not included in this TA.

Recommendation to PCN

PbRe: Yes
Recommended traffic light status (see attached guidelines): Red

Please see proposed Blueteq forms on page 11.

References:

1 Specification of Product Characteristics. Adalimumab, etanercept, infliximab, abatacept. Available at: https://www.medicines.org.uk/emc/ Accessed <21.7.21>

2 NICE Technology Appraisal Guidance: Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed (partial review of TA375) (TA715). Available at: https://www.nice.org.uk/guidance/ta715 Accessed <21.7.21>

3 Rheumatoid Arthritis NHS. Available at: https://www.nhs.uk/conditions/rheumatoid-arthritis/ Accessed <2.3.21>

4 NICE Resource impact report: Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed. Available at: https://www.nice.org.uk/guidance/ta715/resources Accessed <21.7.21>

	Name	Role	Date	Declaration of interests (please give details below table)
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