

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Adalimumab, etanercept and infliximab for Ankylosing Spondylitis

Comments on draft scope

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Source	Comment		Response
Department of Health	Scope	No Comment	NA
Welsh Assembly Government	Scope	We are content with the technical detail of the evidence supporting the provisional recommendations and have no further comments to make at this stage.	NA
Royal Pharmaceutical Society of Great Britain	Scope	No Comment	NA
Royal College of General Practitioners	Scope	No Comment	NA
Abbott Laboratories Ltd	Background	We believe this is sufficient.	NA

Source	Comment	Response
<p>Royal College of Physicians Edinburgh</p>	<p>Background</p> <ol style="list-style-type: none"> 1. There is little emphasis on the contribution of peripheral joint involvement, which may interfere significantly with the ability to work and pursue physical activities. Hip and knee replacement may be required. 2. Systemic involvement in addition to eye and cardiovascular disease may be significant. 3. It is difficult to be so precise (background, 2nd paragraph) about the average age of onset as opposed to presentation. 4. The section on treatment (background, 4th paragraph) could usefully include some more detail perhaps along these lines, "most patients derive benefit from Non-steroidal anti-inflammatory drugs. The disease modifying drugs used for ameliorating rheumatoid arthritis are ineffective in controlling spinal pain and stiffness but they may improve peripheral arthritis. By contrast, anti TNF alpha agents can have a beneficial impact on spinal pain and stiffness but may not be so effective in relieving or retarding peripheral joint involvement." 	<ol style="list-style-type: none"> 1. Last sentence of the first paragraph will be amended so that it reads "The large peripheral joints (hips, shoulders and knees) may also be involved, ...". Note: Sentence in third paragraph of the scope states: "Occasionally the disease is severe, which can cause spinal fusion with pronounced incapacity and significant deformities leading to joint replacement surgery for some patients." 2. Insert the following sentence at the end of paragraph 1: "Systemic involvement in addition to eye and cardiovascular disease may be significant." 3. Delete phrase indicate average age of onset. 4. The extra detail is not required since the appraisal aims to evaluate the cost-effectiveness of these interventions versus conventional therapies.

Source	Comment		Response
Wyeth Pharmaceuticals	Background	<p>Patients with AS often suffer for a number of years without gaining a formal diagnosis of disease. This leads to initial late diagnosis and inappropriate therapy. The scope needs to recognise this.</p> <p>Although DMARDs used in RA may be used to treat AS, the evidence for efficacy is limited. Additionally, DMARDs have not demonstrated an effect on spinal disease</p> <p>The prevalence of AS is quoted within the scope as 0.2 to 0.9%, which is substantially higher than the 0.1-0.2% quoted by the BSR. Could we please request the reference for this estimate of prevalence?</p>	<p>1. The appraisal will not consider initial patient diagnosis, but rather treatment with the anti-TNFs listed following diagnosis.</p> <p>2. No change necessary. The appraisal aims to evaluate the cost-effectiveness of adalimumab, etanercept and infliximab versus conventional therapies.</p> <p>3. Prevalence data from the Arthritis Research Campaign (2003). The scope will be amended however, and use BSR figures (0.05% to 0.23%) cited in its 2004 guideline.</p>
Chesterfield PCT	Background	It looks fine but it might be useful to add examples when you refer to 'drugs that modify the disease process in RA'.	Add "for example, sulfasalazine and methotrexate" to the relevant sentence.
British Society for Rheumatology	Background	<p>The disease begins in early adult life but persists lifelong. The course is usually persistent and progressive. Involvement of peripheral joints substantially increases disability. A third of people become medically unfit for work. This is not transient "at any one time". Conventional treatment is NSAID and physiotherapy. Other anti-rheumatoid drugs are ineffective for spinal disease.</p> <p>The background should include the drugs Sulfasalazine and Methotrexate as DMARDs used in the treatment of AS with peripheral joint disease.</p>	<p>Amend paragraph four of the background as follows:</p> <p>"Conventional therapy for AS includes drugs such as non-steroidal anti-inflammatory agents (NSAIDs) and drugs that modify the disease process in rheumatoid arthritis (for example sulfasalazine and methotrexate, and non-drug interventions (for example physiotherapy)."</p>

Source	Comment		Response
Abbott Laboratories Ltd	The technology/intervention	In answer to the question: <i>Is the description of the technology accurate?</i> For adalimumab, yes	NA
Royal College of Physicians of Edinburgh	The technology/intervention	This appears accurate and straightforward.	NA
British Society for Rheumatology	The technology/intervention	The technology is accurate.	NA
Chesterfield PCT	The technology/intervention	Is it possible to add the anticipated licence indication for adalimumab?	Anticipated licence indication is commercial-in-confidence. <u>(Confidential information removed)</u>
Abbott Laboratories Ltd	Licensing issues (only for manufacturers)	Adalimumab was recently approved and licensed by EMEA for both early rheumatoid arthritis and psoriatic arthritis in August 2005. <u>(Confidential information removed)</u>	Comments noted. No action for the scope.
Wyeth Pharmaceuticals	Licensing issues (only for manufacturers)	<u>(Confidential information removed)</u>	Comment noted. Appropriate action will be taken.
Liverpool Reviews and Implementation Group.	Licensing issues (only for manufacturers)	Regarding adalimumab we are currently not aware of the anticipated licence[d] indications and the assessment group would require this information, to determine appropriate comparators, prior to commencement of the review.	Assessment Group will be informed of the anticipated licensed indication for adalimumab.
Abbott Laboratories Ltd	Population	Yes, the population is defined appropriately.	NA

Source	Comment		Response
Royal College of Physicians of Edinburgh	Population	It is important to be clear about entry criteria, in particular whether patients with predominantly peripheral disease are to be included.	<p>Referring here to predominantly peripheral disease is unnecessary.</p> <p>Note that the interventions will be appraised in accordance with their licensed indications.</p> <p>The licensed indication for etanercept for example, states that it is to be used for the treatment of “adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy”. The licensed indication for infliximab explicitly restricts its use to patients with severe ‘axial symptoms, elevated serological markers of inflammatory activity’ and whose disease has responded inadequately to conventional treatment.</p>
British Society for Rheumatology	Population	Active uncontrolled spinal AS is an appropriate group. Treatment may also be appropriate for patients with AS but in whom uncontrolled peripheral joint disease is the main issue. Many people with AS are not currently within the hospital “system” because of the poor efficacy of conventional treatment: the prospect of effective treatment may increase referrals to hospital care. BSR guidelines for treatment of AS with TNF blockers exist and may be updated.	Comments noted. No amendment necessary to this section of the scope.

Source	Comment	Response
Liverpool Reviews and Implementation Group	Population	<p>The current treatments licensed for ankylosing spondylitis are etanercept and infliximab. Both are licensed for patients with severe disease that have had an inadequate response to conventional therapy. The current scope population: "active ankylosing spondylitis" needs clarification. It may be better to define the population as 'severe' as this is the patient population for which the two therapies are licensed. Furthermore, this lack of response to conventional therapy is not included in the current scope.</p> <p>This section will be amended to that it reads:</p> <p>Etanercept and Infliximab – Adults with active ankylosing spondylitis whose disease has responded inadequately to conventional treatment.</p> <p>Adalimumab – Adults with active ankylosing spondylitis</p>
Royal College of Nursing	Comparators/Economic analysis	<p>Comparators for the interventions - Standard treatment - NSAID with physiotherapy, cost of possible gastric side-effects should be included. Also annual inpatient 1 week courses for AS patients - cost implications should be used in comparator data.</p> <p>Comments noted. Comparators section now reads: "Conventional management without TNF inhibitors"</p>
Abbott Laboratories Ltd	Comparators	<p>Non-steroidal anti-inflammatory drugs (NSAIDs) can provide symptomatic relief in AS, but are not effective over the long term. Conventional therapy generally comprises of NSAIDs, Disease Modifying Anti-Rheumatic Drugs (DMARDs), corticosteroids and non-drug interventions such as physiotherapy and hydrotherapy. DMARDs such as sulfasalazine and methotrexate are ineffective on the axial disease of AS. Anti-TNF therapies are currently not standard of care.</p> <p>Comments noted. Section now reads: "Conventional management without TNF inhibitors"</p>
Schering-Plough	Comparators	<p>Make explicit – (Management without TNF inhibitors) "or DMARDs" (they have not been shown to be effective against AS)</p> <p>Section now reads: "Conventional management without TNF inhibitors"</p>
British Society for Rheumatology	Comparators	<p>NSAIDs are the treatments currently used in the NHS with which the technology should be compared.</p> <p>Section now reads: "Conventional management without TNF inhibitors"</p>

Source	Comment		Response
Royal College of Physicians of Edinburgh	Comparators	This is a difficult area because current treatment is unsatisfactory. Non-steroidal anti-inflammatory agents are probably most appropriate. The evidence base for the disease modifying drugs used in rheumatoid arthritis is poor.	Section now reads: "Conventional management without TNF inhibitors"
Chesterfield PCT	Comparators	Just add to this so it is clear ‘..but using other standard treatments.’	Section now reads: "Conventional management without TNF inhibitors"
Wyeth Pharmaceuticals	Comparators	The inadequacy of current therapy for AS (with the exception of TNF-targeted therapies) has resulted in a loss of confidence on the part of AS patients and a search for alternatives. The scope needs to recognise the inadequacy of current non-TNF-targeted therapy and incorporate an assessment of the broader set of therapies used to treat AS (e.g. hydrotherapy) which are a drain on the both the health service and the patients themselves.	Comment noted. Section now reads: "Conventional management without TNF inhibitors" The appraisal will take into account the components of therapy in the absence of TNF inhibitors.
Liverpool Reviews and Implementation Group	Comparators	The scope states the comparator as "management without TNF inhibitors". Conventional therapy includes biphosphonates, corticosteroids and DMARD's. However, these are not currently licensed for treatment of patients with ankylosing spondylitis. The assessment group would like clarification regarding the use of non-licensed comparators.	Comment noted. While NICE does not issue guidance on unlicensed therapies, it is important that all relevant comparators are identified, and these may include interventions not licensed for the disease under consideration.
Abbott Laboratories Ltd	Outcomes	In answer to the question: <i>Will these outcome measures capture the most important health related benefits of the technology?</i> Yes. It is important to assess reduction in signs and symptoms, improvement in function, adverse effects of treatment and health related quality of life. Suitable assessment measures may include the improvement in ASAS score or improvement in the BASDAI score.	Comments noted. Specific assessment measures will not be listed here.

Source	Comment		Response
Royal College of Nursing	Outcomes	Use of tools for assessing both disease activity, quality of life and functional impairment – BASDAI, BASFI, BASG-I and ASQoL.	Comments noted, but no amendment necessary. Specific assessment measures will not be listed here.
Wyeth Pharmaceuticals	Outcomes	<p>The following outcomes should be considered:</p> <ul style="list-style-type: none"> -Imaging including radiology and MRI -Halting/slowing disease progression 	<p>Imaging is not an outcome. Specific assessment measures will not be listed here.</p> <p>List of outcomes will be amended to include 'disease progression'</p>
Royal College of Physicians of Edinburgh	Outcomes	<p>The outcome measures need to be defined.</p> <ol style="list-style-type: none"> 1. For spinal disease the Bath Ankylosing Spondylitis Disease Activity Index would be appropriate. 2. Serum markers of inflammation should be included. 3. Measures of employment status and function are available. 	<p>Specific assessment measures will not be listed here.</p> <p>Function and health-related quality of life are included on the list of outcomes.</p> <p>Note: The perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on costs should be that of the NHS and PSS.</p> <p>If there is strong evidence that the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, additional sensitivity analyses can be presented.</p>

Source	Comment		Response
British Society for Rheumatology	Outcomes	Capacity for work and AS-related osteoporosis may also be considered The outcome measures should also include spinal inflammation as detected by MRI.	<p>The perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on costs should be that of the NHS and PSS.</p> <p>If there is strong evidence that the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, additional sensitivity analyses can be presented. (The 'Economic analysis' section of the scope has been amended to include the above statements).</p> <p>This section has been amended so it now reads: "Outcomes to be considered include:</p> <ul style="list-style-type: none"> • pain and other symptoms (e.g. muscle spasm and stiffness) • functional capacity • adverse effects of treatment • disease progression • health-related quality of life." <p>No further amendments necessary.</p>

Source	Comment		Response
Chesterfield PCT	Outcomes	<p>In answer to the question: <i>Will these outcome measures capture the most important health related benefits of the technology?</i></p> <p>Yes.</p>	NA
Abbott Laboratories Ltd	Economic analysis	<p>Because AS and AS treatments impose a substantial cost burden on patients in terms of unpaid self-care and informal caregiver burden, these costs should be considered in sensitivity analysis.</p>	<p>The perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on costs should be that of the NHS and PSS.</p> <p>If there is strong evidence that the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, additional sensitivity analyses can be presented. (This section of the scope has been amended to include the above statements).</p>
Royal College of Physicians of Edinburgh	Economic analysis	<p>It is worth noting that the costs of the condition are increased because the disease begins at an early age. The cost analysis should include the full long term impact of peripheral disease which may require joint replacement.</p>	<p>Comment noted. The sentences concerning time horizon for the economic analysis has been amended so that it now reads:</p> <p>“The time horizon for the economic evaluation should reflect the chronic nature of AS.”</p>

Source	Comment		Response
Royal College of Nursing	Economic analysis	It would be very unlikely for a patient to remain on these drugs indefinitely and this should be taken into consideration when looking at the economic analysis	<p>Comments noted and will be passed on to the Assessment Group.</p> <p>This does not have an impact on this section of the scope.</p>
National Ankylosing Spondylitis Society	Economic analysis	<p>Rheumatologists often remark that many of their older AS patients no longer return to clinic. Talking to many members of this society over the last 25 years, there is anecdotal evidence that many of them in their fifth & sixth decade of life, find that their AS goes into remission. They find it unnecessary to continue with their medication or only take it very occasionally or find it unnecessary to return to their rheumatologists. Obviously the ones I have spoken to are active in our branch network and conscientiously turn up for the weekly evening physiotherapy programme. We will later in the year be carrying out a survey among our members where this question will be dealt with and therefore we hope to have evidence. This can have very considerable cost implications for longterm use of anti-TNF. It therefore means that in many cases the treatment with anti-TNF will not be life-long in a high proportion of people.</p>	<p>Comments noted and will be passed on to the Assessment Group.</p> <p>This does not have an impact on this section of the scope.</p>
British Society for Rheumatology	Economic analysis	The time horizon will be similar to that of other joint diseases such as RA.	<p>Comment noted. The section concerning time horizon for the economic analysis has been amended so that it now reads: "The time horizon for the economic evaluation should reflect the chronic nature of AS."</p>

Source	Comment		Response
Liverpool Reviews and Implementation Group	Economic analysis	The perspective implied in the current scope is that of the NHS and Personal Social Services. However, the long term disabling effects of this disease means that the societal costs of ankylosing spondylitis are in fact quite critical. From the economic literature, it appears that the indirect costs of ankylosing spondylitis (AS) may account for between 55 – 73% of the total costs of AS (see attached Table 1). The large contribution of indirect costs to total costs in AS patients may in part be explained by the fact that AS predominantly affects men of working age, who are valued highly in terms of productivity. Omitting these productivity costs may mean a significant proportion of costs are overlooked.	<p>The perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on costs should be that of the NHS and PSS.</p> <p>If there is strong evidence that the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, additional sensitivity analyses can be presented.</p> <p>(This section of the scope has been amended to include the above statements).</p>
Abbott Laboratories Ltd	Other Considerations	None	NA
Royal College of Nursing	Other Considerations	Cost of surgery for this group of patients, both joint replacement and heart valve replacement with possible adverse events.	<p>Comment noted.</p> <p>The economic evaluation should take into account all relevant costs.</p> <p>No change necessary to this section of the scope.</p>
Schering-Plough	Other Considerations	<p><i>If the evidence allows, subgroups for whom the technology may be particularly cost-effective will be identified.</i></p> <p>Suggest adding the following subgroups: Those with co-morbid conditions</p>	Unnecessary to specify potential subgroups here. No amendment made.

Source	Comment		Response
Wyeth Pharmaceuticals	Other Considerations	There is no recognition of the potential co-morbid states associated with this disease which can have a significant impact on burden to the NHS.	The Background notes that for example the eye and cardiovascular system can also be affected. All changes in costs and outcomes directly related to the use of adalimumab, etanercept and infliximab are relevant. Consultees are encouraged to detail the full impact of these therapies in their economic analyses.
British Society for Rheumatology	Other Considerations	Because of the long-term slowly progressive nature of the disease and the insensitivity of currently available markers, it is likely that only limited data on disease modification will be available NICE may wish to consider the funding of a patient database to monitor patients and identify the of potential side-effects of treatment.	Comments noted. However, these will not lead to an amendment of this section of the scope. We would welcome relevant groups to fund a patient database. The Institute can not provide funding in such instances.
Liverpool Reviews and Implementation Group	Other Considerations	The addition of “the consecutive use of TNF inhibitors will be examined” to the scope will require further definition prior to being integrated within the review process.	If the evidence allows, the Institute would want information on the sequential use of the TNF inhibitors in the treatment of patients with AS. For example, are there benefits in switching to a different TNF inhibitor if the condition fails to respond to another?

Source	Comment		Response
British Society for Rheumatology	Additional Comments	<p>The assessment must recognise that no features of established spinal involvement of AS are reversible. Once ankylosis has occurred, surgery offers no benefit. This is in contrast to the potential for surgery to "rescue" patients with peripheral joint disease such as rheumatoid arthritis.</p> <p>The number of AS patients likely to be treated with these technologies will be considerably smaller than figures based on the prevalence of the disease. Many patients are undiagnosed in the community and therefore patients with active disease attending rheumatology clinics will be the target population.</p>	Comments noted.