Etanercept (Enbrel) for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

SUMMARY

Etanercept (Enbrel) is intended to be used for the treatment of axial spondyloarthritis in adults without radiographic evidence of ankylosing spondylitis. Etanercept is currently licensed for a range of indications including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis and paediatric plaque psoriasis.

A recent study published in the US reported an estimated AS prevalence of 0.52-0.55%, and the prevalence of axial SpA as approximately 1.0-1.4%. The proportion of non-radiographic axial SpA among patients with axial SpA is estimated to be between 20-80%. Symptoms of axial SpA include pain and stiffness in the joints, as well as bone destruction causing deformities of the spine.

Short-term and long-term treatment goals for axial SpA include minimising pain and stiffness, maintaining function and posture, and arresting radiographic progression. Treatment should be individualised according to a patient’s clinical manifestations and presentation. Current treatment options including NSAIDs, analgesics, corticosteroid injections, DMARDs, TNFα inhibitors and other non-pharmacological treatments.
TARGET GROUP

• Axial spondyloarthritis (SpA): adults without radiographic evidence of ankylosing spondylitis.

TECHNOLOGY

DESCRIPTION

Etanercept (Enbrel) is a human tumour necrosis factor-α (TNFα) receptor p75 Fc fusion protein. It binds to, and neutralises, the biological activity of TNFα and lymphotoxin, competitively inhibiting the binding of both soluble and membrane bound TNFα to cell surface receptors. This prevents the TNFα-mediated signal transduction, which requires the cross-linking of cell surface receptors. Etanercept is administered via subcutaneous (SC) injection at 25mg twice weekly or 50mg once weekly.

Etanercept is currently licensed in the EU for:

• Rheumatoid arthritis: moderate to severe, active – second line, after failure of disease-modifying antirheumatic drugs (DMARDs) in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX, or when continued treatment with MTX is inappropriate.
• Rheumatoid arthritis: severe, active and progressive – first line in combination with MTX or as monotherapy in case of intolerance to MTX, or when continued treatment with MTX is inappropriate.
• Juvenile idiopathic arthritis: polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis – second line, in children and adolescents from the age of 2 years who have had an inadequate response to, or have proved intolerant to, MTX.
• Juvenile idiopathic arthritis: psoriatic arthritis – second line, in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant to, MTX.
• Juvenile idiopathic arthritis: enthesitis-related arthritis – second line, in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.
• Psoriatic arthritis: active and progressive – second line, in adults when the response to previous DMARD therapy has been inadequate.
• Ankylosing spondylitis: severe, active – second line, in adults who have had an inadequate response to conventional therapy.
• Plaque psoriasis: moderate to severe – second line, in adults who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies.
• Paediatric plaque psoriasis: severe, chronic – second line, in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Common recognised adverse events (>10%) include infections (upper respiratory tract infections, bronchitis, cystitis, skin infections) and injection site reactions (bleeding, bruising, erythema, itching, pain, swelling).

Etanercept is also in phase II clinical trials for graft-versus-host disease and metabolic syndrome.
INNOVATION and/or ADVANTAGES

If licensed etanercept will offer an additional treatment option for this patient group who currently have limited therapeutic options.

DEVELOPER

Pfizer Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Spondyloarthritis (SpA) is the name for a heterogenous family of inflammatory rheumatic diseases which include ankylosing spondylitis, psoriatic arthritis, reactive arthritis (formerly known as Reiter’s syndrome), enteropathic arthritis associated with inflammatory bowel diseases, undifferentiated SpA and juvenile SpA. The diseases all share common genetic, histologic and clinical characteristics such as a high prevalence of HLA-B27, synovitis, and involvement of the axial and peripheral skeleton. Axial SpA describes a spectrum of chronic inflammatory arthritis which may be diagnosed as either non-radiographic axial SpA or ankylosing spondylitis (AS) according to Assessment of SpondyloArthritis international Society (ASAS) criteria. Patients with established radiographic sacroiliitis can be diagnosed as having AS, whilst patients without radiographic sacroiliitis can be classified as non-radiographic axial SpA. Symptoms of SpA include pain and stiffness in the joints, as well as bone destruction causing deformities of the spine.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to: The Musculoskeletal Services Framework (2006).

CLINICAL NEED and BURDEN OF DISEASE

An estimated 2% of patients present to General Practice in the UK with back pain each year, and up to 5% of these will show features of ankylosing spondylitis. Spondyloarthritis as a group are one of the most common rheumatic diseases with a prevalence of 0.5-1.9%, roughly as common as rheumatoid arthritis. A recent study published in the US reported an estimated AS prevalence of 0.52-0.55%, and the prevalence of axial SpA as approximately 1.0-1.4%. The proportion of non-radiographic axial SpA among patients with axial SpA is estimated to be between 20-80%.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance
• NICE technology appraisal in development. Ankylosing spondylitis and axial spondyloarthritis (non-radiographic) – adalimumab, etanercept, infliximab and golimumab (including reviews TA143 and TA233). Expected January 2015\(^{10}\).
• NICE technology appraisal. Golimumab for the treatment of ankylosing spondylitis. August 2011\(^{11}\).
• NICE technology appraisal. Golimumab for the treatment of psoriatic arthritis. April 2011\(^{12}\).
• NICE technology appraisal. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. August 2010\(^{13}\).
• NICE technology appraisal. Adalimumab, etanercept and infliximab for ankylosing spondylitis. May 2008\(^{14}\).
• NICE technology appraisal. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. October 2007\(^{15}\).
• NICE technology appraisal. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. March 2002\(^{16}\).

**Other Guidance**

• Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. 2011\(^{17}\).
• 2010 update of the ASAS/EULAR recommendation for the management of ankylosing spondylitis. 2010\(^{18}\).
• Assessment of SpondyloArthritis International Society. ASAS Handbook: a guide to assess spondyloarthritis. 2009\(^{19}\).
• Assessment of SpondyloArthritis International Society and European League Against Rheumatism (ASAS/EULAR) recommendations for the management of ankylosing spondylitis. 2006\(^{20}\).
• British Society for Rheumatology. Guidelines for prescribing TNFα blockers in adults with rheumatoid arthritis. 2004\(^{21}\).

**EXISTING COMPARATORS and TREATMENTS**

Short-term and long-term treatment goals for axial SpA include minimising pain and stiffness, maintaining function and posture, and arresting radiographic progression\(^{3}\). Treatment should be individualised according to a patient’s clinical manifestations and presentation\(^{22}\). Management of axial SpA includes\(^{4,20,22}\):

- NSAIDs – first line.
- Analgesics – for patients in whom NSAIDs are insufficient, contraindicated and/or poorly tolerated.
- Intra-articular corticosteroid injections in sacroiliac joints.
- DMARDs – shown efficacy only in treating peripheral arthritis.
- TNFα inhibitors – infliximab and adalimumab in patients with ankylosing spondylitis that have persistently high disease activity. Adalimumab is currently the only licensed biologic for non-radiographic axial SpA.
- Non-pharmacological treatments – education, physical therapy and exercise.

**Efficacy and Safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
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<tbody>
<tr>
<td>NCT01258738, B1801031, 0881A3-4725; etanercept vs placebo; phase III.</td>
<td>Pfizer Ltd.</td>
<td>Published in abstract.</td>
</tr>
<tr>
<td>ESTHER, NCT00844142, M01; etanercept vs sulfasalazine; phase II.</td>
<td>Charite University, Berlin.</td>
<td>Complete.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{23} and abstract\textsuperscript{24}.</td>
<td>Trial registry\textsuperscript{23} and publication\textsuperscript{26}.</td>
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<td>Location</td>
<td>EU (incl UK) and other countries.</td>
<td>Germany.</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, open-label, active-controlled.</td>
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<td>Participants</td>
<td>n=200 (planned); aged 18-49 years; axial SpA defined by Assessments in Ankylosing Spondylitis (ASAS) criteria; axial symptoms of back pain with less than favourable response to NSAIDs; patients with sacroiliitis grade 3-4 unilaterally or grade 2 bilaterally as defined by NY criteria were excluded.</td>
<td>n=76; aged 18-50 years; axial SpA with a symptom duration of less than 5 years; chronic low back pain with a duration of at least 3 months and onset at less than 45 years.</td>
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<td>Schedule</td>
<td>Randomised to SC etanercept 50mg once weekly or placebo, in addition to background NSAID treatment. During extension period, all patients receive etanercept 50mg once daily and background NSAID treatment.</td>
<td>Randomised to SC etanercept 25mg twice weekly or oral sulfasalazine 2,000-3,000mg daily.</td>
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<td>Follow-up</td>
<td>Active treatment period 12 weeks; 92 week extension thereafter.</td>
<td>Active treatment period 1 year followed by 1 year open label extension.</td>
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<td>Primary outcome/s</td>
<td>ASAS 40\textsuperscript{a} at week 12.</td>
<td>Reduction of active inflammatory lesions in MRI at 12 months.</td>
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<td>Secondary outcome/s</td>
<td>ASAS 40; ASAS 20; ASAS 5/6; ASAS change from baseline; ASAS partial remission; time to ASAS partial remission; Visual Analogue Scale (VAS) subject global assessment; VAS physician global assessment; VAS nocturnal and total back pain; Bath Ankylosing Spondylitis Functional Index (BASFI); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); BASDAI 20 &amp; BASDAI 50; Bath Ankylosing Spondylitis Global Index (BAS-G); spinal mobility measured by Bath Ankylosing Spondylitis Metrology Index (BASMI), occiput-to-wall distance and chest expansion; inflammation measured by MRI; tender and swollen joint counts (44 counts); dactylitis and enthesitis score (MASES); acute phase reactants C-reactive Protein (CRP) and erythrocyte sedimentation rate (ESR); safety; health related quality of life (using various instruments).</td>
<td>ASAS 20; ASAS 40; ASAS 70; ASAS partial remission; BASDAI 20, BASDAI 50, BASDAI 70, BASFI; BASMI; enthesitis index (Maastricht scale); swollen joints count; EQ-5D; CRP; patient and physician global assessments of disease activity.</td>
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<td>Key results</td>
<td>Patients achieving endpoint at 12 weeks for etanercept vs placebo groups respectively (p-value): ASAS 40 (modified intention-to-treat), 32.4% vs 15.7% (p=0.006); ASAS 40 (MRI+ and/or CRP+), 34.0% vs 18.1% (p=0.018); ASAS 40 (CRP+), 45.8% vs 18.6% (p=0.008); ASAS 20, 50.5% vs 38.0% (p=0.073); ASAS partial remission, 25.7% vs 11.9% (p=0.014); ASAS 5/6, 24.3% vs 4.7% (p&lt;0.0001); BDAI 50, 43.8% vs 23.9%.</td>
<td>Etanercept group, baseline vs 48 week score respectively, mean (SD): BASDAI, 5.5 (1.3) vs 2.5 (2.0); BASFI, 4.3 (2.3) vs 2.0 (2.1); patient global, 6.7 (2.1) vs 2.6 (2.2); physician global, 6.4 (1.2) vs 1.8 (1.8); joint count, 2.3 (5.8) vs 0.2 (0.7); enthesitis score, 4.4 (4.6) vs 1.8 (4.2); BASMI, 1.9 (1.7) vs 1.6 (1.8); EQ-5D, 0.6 (0.3) vs 0.8 (0.2); AS-QoL, 9.7 (4.5) vs 4.4 (4.8); CRP, 11.9 (13.2) vs 4.3 (3.7).</td>
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\textsuperscript{a} ASAS 40 represents a 40% response according to the improvement criteria of the Assessment of SpondyloArthritis international Society.
Mean change from baseline (SE) for etanercept vs placebo respectively (p-value):
ASDAS-CRP, -1.1 (0.1) vs -0.5 (0.1) (p<0.001); BASDAI, -2.0 (0.3) vs -1.3 (0.3) (p=0.019); BASFI, -1.4 (0.2) vs -0.8 (0.2) (p=0.016); SPARCCb (0-108), -2.2 (0.5) vs -1.2 (0.5) (p=0.040); SPARCC SI joint score (0-72), -4.0 (0.7) vs -0.8 (0.6) (p<0.001).

Sulfasalazine group, baseline vs 48 week score respectively, mean (SD):
BASDAI, 6.0 (1.2) vs 4.4 (2.4); BASFI, 4.3 (1.8) vs 3.3 (2.2); patient global, 7.1 (1.6) vs 4.9 (3.0); physician global, 6.1 (1.5) vs 4.1 (2.9); joint count, 1.3 (1.7) vs 0.3 (1.5); 3.4 (3.4) vs 1.4 (2.9); BASMI, 1.7 (1.4) vs 1.9 (1.7); EQ-5D, 0.6 (0.3) vs 0.7 (0.3); AS-QoL, 9.3 (3.6) vs 7.5 (5.4); CRP, 10.6 (14.9) vs 8.7 (12.5).

### Adverse effects (AEs)

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<tr>
<th>Adverse effects (AEs)</th>
<th>Estimated study completion date October 2014.</th>
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<tbody>
<tr>
<td>None reported.</td>
<td>Infecteds of the respiratory tract were the most frequently reported AEs. There were three serious AEs in the etanercept group and seven in the sulfasalazine group, with only three regarded as treatment related.</td>
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</tbody>
</table>

### ESTIMATED COST and IMPACT

#### COST

The cost of etanercept for non-radiographic axial SpA is not yet known. However, etanercept is already marketed in the UK, and for its other licensed indications, costs £89.38 for 25mg

The annual cost of etanercept at a dosage of 25 mg twice weekly is £9,295.52.

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: *may allow earlier successful treatment of patients who would otherwise have to wait for plain radiographic evidence of sacroiliitis before being allowed anti-TNFα drugs*.
- No impact identified

**Impact on Services**

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

**Impact on Costs**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other
- None identified

**Other Issues**

- Spondyloarthritis Research Consortium of Canada – scoring system where the 6 most affected vertebrae are assessed.
- Expert personal communication.
Clinical uncertainty or other research question identified: may result in patients with minimal sacroiliac disease receiving treatment when disease may settle spontaneously. May be seen as an equal alternative to other anti-TNFα drugs.

REFERENCES

1 eMC. Etanercept – summary of product characteristics
2 Arthritis Research UK. Spondyloarthritis.
http://www.arthritisresearchuk.org/health-professionals-and-students/reports/hands-on/hands-on-spring-2010.aspx

d Expert personal communication.
23 ClinicalTrials.gov. Study comparing etanercept (ETN) against a placebo for etanercept on a background nonsteroidal anti-inflammatory drug (NSAIDs) in the treatment of early spondyloarthritis (SpA) patients who do not have X-ray structural changes (AS EARLY) http://clinicaltrials.gov/ct2/show/NCT01258738 Accessed 8 August 2013.
26 Song IH, Hermann KG, H Haibel et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48 week randomised trial. Annals of the Rheumatic Diseases 2011;70:590-596.