

# 1 EXECUTIVE SUMMARY

In July 2006, NICE issued guidance for the use of etanercept and infliximab in adult patients with psoriatic arthritis (PsA). NICE recommended etanercept for PsA patients, who have peripheral arthritis with three or more tender joints and three or more swollen joints, and in whom the disease has not responded to adequate trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs), administered either individually or in combination.<sup>1</sup>

Since etanercept was granted a licence in 2004 for PsA, and the subsequent NICE recommendations for etanercept and other TNF- $\alpha$  inhibitors, these agents have become standard of care for the treatment of PsA. Data from additional randomised controlled trials and observational studies that have been made available since 2006, have further strengthened the evidence for the safety, efficacy and cost-effectiveness of TNF- $\alpha$  inhibitors in treating PsA.

We would request, therefore, that etanercept continues to be recommended for use in the NHS for appropriate patients with PsA.

## ***Clinical need in Psoriatic Arthritis***

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis. The prevalence is between 0.1% and 1% of the population and has an equal sex distribution.<sup>2</sup> It is a life long progressive disease, and, like rheumatoid arthritis (RA), can lead to chronic joint damage, disability and increased mortality.<sup>3</sup> Patients with PsA have significantly impaired quality of life similar to that seen in RA. There are differences, however, in that PsA patients may experience more pain and more role limitations due to emotional problems than do patients with RA.<sup>4-6</sup> Social and financial implications are also important to consider, both in terms of personal loss and the impact of direct (e.g. medical care) and indirect (e.g. productivity) costs to the state.

There are two goals of the medical management of PsA. The first is the relief of symptoms, with pain relief being the number one priority for patients. The second is modification of the disease process so that radiological progression, which is closely correlated with progressive functional impairment, can be retarded or stopped.

'Conventional' treatment of PsA relies heavily on DMARDs that have not been adequately evaluated in PsA. DMARDs are the recommended first line treatment for moderate to severe PsA,<sup>7</sup> however, none of the traditional DMARDs have been shown to prevent radiological progression nor to impact significantly on axial disease, dactylitis or enthesitis.<sup>8</sup>

MTX currently appears to be the most commonly used drug and may improve both PsA and psoriasis,<sup>9</sup> yet data on its effectiveness in PsA is limited, particularly with regard to its effectiveness in preventing long term joint damage

With their favourable impact on both therapeutic goals, the introduction of TNF- $\alpha$  inhibitors has revolutionised the treatment of PsA. There is a growing body of evidence from both randomised controlled trials (RCTs), and observational studies supporting the effectiveness of TNF- $\alpha$  inhibitors for the treatment of PsA. Unlike DMARDs, the TNF- $\alpha$  inhibitors have shown that not only do they address the symptoms of PsA, such as joint pain and tenderness, but they can also halt radiographic progression of joint damage.

Based on this evidence, international guidelines recommend the use of TNF- $\alpha$  inhibitors for the treatment of moderate to severe PsA.<sup>7</sup> Groups such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), state that there is no evidence to support the use of DMARDs ahead of TNF- $\alpha$  inhibitors, and the effect size for these agents is

larger than that for traditional DMARDs. They confirm that the TNF- $\alpha$  inhibitors are effective for the treatment of peripheral arthritis and for the inhibition of radiographic progression equally, something that has not been proven with DMARDs. Furthermore, GRAPPA recommends that patients with poor prognosis could be considered for TNF inhibitors even if they have not failed standard DMARD treatment.<sup>7</sup>

In addition, observational data from rheumatology registries have shown that not only is clinical improvement superior with TNF- $\alpha$  inhibitors compared to methotrexate in patients with PsA, when assessed in a setting of daily clinical practice,<sup>10</sup> but also that persistence with TNF- $\alpha$  inhibitors is better in patients with PsA than it is in patients with RA.<sup>10,11</sup>

### **Clinical effectiveness in joints**

Etanercept is a highly effective and well-tolerated treatment for PsA. Evidence from randomised clinical trials and open label extension studies support the use of etanercept in patients with PsA, demonstrating its effectiveness in improving joint pain/tenderness and swelling, as well as its ability to halt radiographic progression.<sup>12-13</sup> Etanercept is also effective in reducing the signs and symptoms of enthesitis and dactylitis,<sup>14-15</sup> and has a wealth of data evidencing its effectiveness in treating moderate to severe plaque psoriasis.<sup>16-19</sup> Furthermore, since the original NICE appraisal of etanercept for PsA, data from a large phase IV trial in patients with PsA with significant skin involvement has been completed, adding significantly to the evidence base available.<sup>14-15, 21-22</sup>

The effect of etanercept on functioning, as measured by HAQ and EQ-5D, as well as quality of life, measured by DLQI, is also significant, representing clinically meaningful improvements on all counts.

Patients consider a change of 0.3 as the HAQ Minimum Clinically Important Difference (MCID) in HAQ for PsA. In a Phase III study of etanercept in PsA, 50% of patients achieved a HAQ change greater or equal to the MCID at 24 weeks.<sup>12</sup> In a Phase IV study of patients with moderate to severe plaque psoriasis and psoriatic arthritis, standard treatment with etanercept reduced HAQ scores by a mean of 0.4, mean DLQI scores were reduced by 8.0, and EQ-5D scores improved over 24 weeks.<sup>20,22</sup>

Comparative data for the three TNF- $\alpha$  inhibitors is unavailable. However, data from Phase III clinical trials suggests that whilst all three agents are effective in treating both skin and joints, etanercept seems to have a higher effectiveness treating the arthropathic manifestations of the disease. At 24 and 48 weeks, etanercept shows higher PsARC, ACR20 and HAQ outcomes than those for infliximab and adalimumab.<sup>12,23-24</sup>

Executive summary Table 1: Comparative effectiveness overview

	Etanercept			Adalimumab		Infliximab	
	24 weeks <sup>14,22</sup>	24 weeks <sup>12</sup>	48 weeks <sup>12</sup>	24 weeks <sup>23</sup>	48 weeks <sup>23</sup>	24 weeks <sup>24</sup>	54 weeks <sup>24</sup>
PsARC (%pats)	80	70	80	60	58	70	74
ACR20	72	50	64	57	56	54	59
PASI75	62	23	33	59	58	60	50
HAQ change from baseline	-0.5	-0.6	-0.6	-0.4	-0.4	-0.4	-0.5

In addition, the percentage of patients achieving PsARC and ACR20 continues to increase from week 24 to 48 with etanercept treatment, unlike both adalimumab and infliximab. Furthermore, data from a Phase IV study shows etanercept is effective in both skin and joints.

Observational data also shows, that etanercept is associated with longer duration of treatment than the monoclonal antibody infliximab.<sup>11</sup> Further analysis of this data indicates

that over a long term period, persistence with etanercept treatment is better than both infliximab and adalimumab.

### **Clinical Effectiveness in Skin**

The etanercept PRESTA study directly evaluated the safety and efficacy of two licensed dosing regimens of etanercept in treating the skin and joint manifestations in patients with psoriasis and psoriatic arthritis.<sup>14-15,21-22</sup> In this study, patients had significant skin involvement with at least 10% body surface area and a PGA of moderate or worse, as well as active joint disease. Mean PASI score at baseline was 19, compared with mean PASI scores of between 7 and 11 in previous TNF- $\alpha$  inhibitor studies.

This study also demonstrated the efficacy of etanercept in treating moderate to severe skin disease, with 70% of patients achieving  $\geq 75\%$  improvement in PASI score at week 24 in the etanercept 50 mg BIW/QW group and 62% in the 50 mg QW group.<sup>16</sup>

Randomised controlled trials have demonstrated the safety and efficacy of etanercept in moderate to severe plaque psoriasis.<sup>16-19</sup> In a study of 50 mg once weekly etanercept, 71% of patients achieved a 75% improvement from baseline in their PASI scores after 24 weeks of treatment.<sup>18</sup> Long term studies of etanercept in psoriasis have shown that initial improvements in skin are maintained over a longer period. In the CRYSTEL study, continuous use of etanercept demonstrated sustained efficacy over 54 weeks.<sup>19</sup> Studies of infliximab and adalimumab in psoriasis patients have shown that whilst short term efficacy is good, over the longer term there is a significant loss of effect.<sup>25,26</sup> This is possibly due to the development of anti-drug antibodies that have a neutralising effect, thus reducing the efficacy of the monoclonal antibodies.<sup>25,27</sup> By contrast, there appears to be no correlation between antibody development and clinical response with etanercept.<sup>28</sup>

### **Safety**

Generally, the TNF- $\alpha$  inhibitors are well tolerated with adverse event profiles that would appear to be similar to that seen with DMARDs. Overall, the evidence suggests that treatment with TNF- $\alpha$  inhibitors is associated with a small increase in the risk of serious infections that occurs shortly after initiation of treatment. There is clear evidence of an increased risk of TB that can be significantly reduced by following screening guidelines. The risk of reactivation is higher with the monoclonal antibodies than with etanercept.<sup>29</sup> There is suggestive evidence that the risk of certain serious infections such as lower respiratory tract and herpes may be higher with infliximab and adalimumab than etanercept.<sup>30,31</sup>

### **Economic evaluation**

Treatments were compared using incremental analysis, that is, the least effective was compared to the next least effective treatment. The base-case costs and quality adjusted life years (QALYs) are shown in the executive summary Table 2.

Executive summary Table 2 - Cost-effectiveness results

ETN	6.90	£65,650	£12,480
Adalimumab	6.54	£61,381	Extendedly dominated by ETN
Infliximab	6.39	£66,867	Dominated by ADL
BSC	5.96	£53,860	

Probabilistic and univariate sensitivity analyses confirmed the robustness of these findings. The probabilistic sensitivity analysis demonstrated that one is 65% confident that etanercept is a cost-effective strategy when using a threshold of £20,000 per QALY. The univariate sensitivity analysis demonstrated that the vast majority of ICERs for etanercept are below £20,000/QALY.

We developed a comparative budget impact model which suggests that the use of etanercept results in a lower budgetary impact to the NHS than the use of adalimumab or infliximab.

### ***Conclusion***

This submission demonstrates that the use of etanercept is not only clinically appropriate but also represents a cost-effective approach to the management of PsA, thus being an appropriate use of NHS resources.

Wyeth therefore requests, that etanercept continues to be recommended for use in the NHS for the treatment of PsA.

## EXECUTIVE SUMMARY REFERENCES

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