Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

golimumab 50mg solution for injections prefilled pen (auto-injector) or pre-filled syringe (Simponi®) SMC No. (721/11)

MSD

05 August 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

golimumab (Simponi®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

SMC restriction: golimumab is restricted to use in accordance with the British Society for Rheumatology (BSR) guidelines for anti-TNFα agents in adults with ankylosing spondylitis. Golimumab is restricted to use at a dose of 50mg only.

In a placebo controlled study golimumab 50mg and 100mg were superior to placebo given every four weeks in terms of the proportion of patients who achieved at least 20% improvement in the Assessment in AS International Working group Criteria at week 14. An indirect comparison indicates that golimumab has similar efficacy to two other anti-TNFα agents used in the treatment of ankylosing spondylitis.

The economic case was demonstrated for golimumab when used at a dose of 50mg. The economic case was not demonstrated for the 100mg dose of golimumab.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 September 2011

Indication

Treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Dosing Information

Golimumab 50mg subcutaneous injection given once a month, on the same date each month. Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after three to four doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

In patients weighing more than 100kg who do not achieve an adequate clinical response after three or four doses, increasing the dose of golimumab to 100mg once a month may be considered, taking into account the increased risk of certain serious adverse drug reactions with the 100mg dose compared with the 50mg dose. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving three to four additional doses of 100mg.

Golimumab treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis.

Product availability date

1 October 2009

Summary of evidence on comparative efficacy

Tumour necrosis factor α (TNFα) is a pro-inflammatory cytokine and when targeted can improve the signs and symptoms of ankylosing spondylitis (AS) in patients with moderate to severe disease. Golimumab is a human anti-TNFα monoclonal antibody, given as a subcutaneous injection once monthly, and is the fourth anti-TNFα agent licensed for the treatment of AS.

One phase III, multi-centre, randomised, placebo controlled study has been conducted to evaluate the efficacy and safety of golimumab in reducing signs and symptoms of AS. Adult patients with AS (diagnosed according to the modified New York Criteria) for at least three months, a Bath AS Disease Activity Index (BASDAI) score of at least 4 (on a 0 to 10 point scale) and a spinal pain assessment score of at least 4 (on a 0 to 10cm visual analogue scale [VAS]) were recruited. Patients were required to have an inadequate response to current or previous disease-modifying anti-rheumatic drugs (DMARDs) or non-steroidal anti-inflammatory drugs (NSAIDs) (taken continuously for at least three months at the highest recommended dose or unable to take due to intolerance, toxicity or contra-indications).

Patients were randomly assigned in a 1:1.8:1.8 randomisation schedule to placebo (n=78), golimumab 50mg (n=138) or golimumab 100mg (n=140), as subcutaneous injections every four weeks for 24 weeks. Patients were permitted to continue concurrent treatments with methotrexate, sulfasalazine, hydroxychloroquine, corticosteroids and NSAIDs at stable doses during the study.

Patients were assessed for the primary endpoint, proportion of patients who achieved at least 20% improvement in the Assessment in AS International Working group Criteria (ASAS20) at week 14. At week 16 the study protocol allowed an early escape for patients who achieved <20% improvement from baseline in total back pain and morning stiffness, in a double-blinded manner. Patients in the placebo group received golimumab 50mg, patients in the golimumab 50mg group received golimumab 100mg and patients in the golimumab 100mg group continued to receive golimumab 100mg, all administered every four weeks. Patients in the placebo and golimumab 50mg groups who met the criteria for early escape at week 16 were considered to be non-responders at week 24. At week 24 patients on placebo crossed over to blinded golimumab 50mg (every 4 weeks) and all others continued with the regimen taken at week 24. All patients entered the extension phase, continued treatment until week 100 and were evaluated at week 104.

The proportion of patients who achieved an ASAS20 response at week 14 was 22% (17/78), 59% (82/138) and 60% (84/140) in the placebo, golimumab 50mg and golimumab 100mg groups respectively ($p<0.001$ for both golimumab groups versus placebo). The proportion of patients who met the criteria for early escape at week 16 in the placebo group was 53% (41/78), and 50% went on to show an ASAS20 response at week 24. In the golimumab 50mg group 18% (25/138) of patients went on to receive golimumab 100mg and 16% of these patients showed an ASAS20 response at week 24.

Secondary endpoints included ASAS20 at week 24, change from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI) and in the Bath Ankylosing Spondylitis Metrology Index (BASMI) at week 14 and health related quality of life (HRQOL). The proportion of patients who achieved an ASAS20 response at week 24 was significantly higher for the combined golimumab group versus placebo (61% versus 23%). At baseline BASFI scores were 4.9, 5.0 and 5.4 for placebo, golimumab 50mg and golimumab 100mg groups respectively and the change in BASFI score was 0.1, -1.4 and -1.5 respectively. There were no significant differences in the median change in BASMI scores at week 14. The percentage of patients who achieved at least 50% reduction in BASDAI score was 15% for placebo versus 46% and 41% for golimumab 50mg and 100mg respectively. The Short Form 36 (SF-36) Health Survey was used to measure HRQOL; at week 14 both the SF-36 physical and mental summary scores were significantly superior for both doses of golimumab versus placebo.

In the extension phase at week 104 the proportion of patients who achieved an ASAS20 response was 60% and 76% in the golimumab 50mg and golimumab 100mg groups respectively.

Summary of evidence on comparative safety

There are no direct comparative safety data other than versus placebo for this indication. The European Medicines Agency (EMA) considered that “overall, the profile of golimumab is similar to that of other TNF-alpha blockers”.

In the pivotal study serious adverse events were reported in 5.2% (4/78), 3.6% (5/138) and 5.0% (7/140) patients respectively. Adverse events (≥ 5% frequency) that occurred more frequently in the combined golimumab group than placebo were; nasopharyngitis, upper respiratory tract infections, fatigue, headache, diarrhoea, injection site erythema and increases

in alanine aminotransferase (ALT) or aspartate aminotransferase (AST). One patient in the placebo group and four each in the golimumab groups discontinued from the study due to adverse events. There were no deaths in the study, including the extension phase.

Summary of clinical effectiveness issues

The efficacy of golimumab in AS has been established in the pivotal study, where there was a significant difference for both golimumab doses versus placebo for the primary endpoint, ASAS20 at week 14, which was maintained for up to two years. In addition, golimumab remained significantly superior to placebo in sensitivity analysis of the primary endpoint at week 14, including disease duration, which was longer in the placebo group at baseline. However there are no direct comparative studies of golimumab with other anti-TNFα agents. In their submission to SMC the company included a Bayesian mixed treatment comparison to indirectly compare golimumab, adalimumab and etanercept. Results suggest that golimumab has broadly similar efficacy to etanercept and adalimumab.

Patients were recruited to the pivotal study if they had a BASDAI and spinal pain assessment score ≥4 and had an inadequate response to current or previous NSAIDs or DMARDs. These are similar to criteria for TNF blocking agent use in the British Society for Rheumatology (BSR) guidance from 2004 and in the National Institute for Health and Clinical Excellence (NICE) technology appraisal, 'Ankylosing spondylitis - adalimumab, etanercept and infliximab', from 2008. Experts consulted by SMC report that these criteria are still valid. Concurrent treatment at stable doses with NSAIDs and DMARDs as well as corticosteroids whilst on study treatment was permitted. The percentages of patients on concurrent treatments were NSAIDs 90%, methotrexate 20%, sulphasalazine 26%, hydroxychloroquine 1.4% and corticosteroids 16%. Logistic regression of the primary endpoint showed that concurrent use of DMARDs was not significantly associated with an ASAS20 response. SMC experts consider that this level of conventional therapy use in the study population broadly reflects current Scottish practice for treatment of patients with AS.

The authors of the pivotal study publication commented that observational studies have shown that spondylarthritis responds well to treatment with a second anti-TNF agent, although these studies did not include golimumab. However, patients were excluded from the pivotal study if they had received previous treatments with an anti-TNF agent. Therefore the efficacy of golimumab following previous treatment with an anti-TNF agent is not known.

Golimumab, adalimumab and etanercept may be self administered by the patient after training in subcutaneous injection technique. Golimumab is administered monthly compared to twice weekly/weekly for etanercept or fortnightly for adalimumab, with all agents administered subcutaneously. The less frequent administration schedule for golimumab may offer advantages for the patient who is self-administering and for service delivery in situations where the patient is unable to self-administer.

The licensed dose of golimumab is 50mg given by subcutaneous injection given once a month, on the same date each month. In patients weighing more than 100kg who do not achieve an adequate clinical response after three or four doses, increasing the dose of golimumab to 100mg once a month may be considered, taking into account the increased risk of certain serious adverse drug reactions with the 100mg dose compared with the 50mg dose. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after

receiving three to four additional doses of 100mg. Clinical experts have advised that very few AS patients will weigh more than 100kg and suggested that in practice it is more likely that patients who do not respond to the 50mg dose would be switched to another anti-TNFα agent.

Summary of comparative health economic evidence

A cost-utility analysis was provided by the submitting company evaluating golimumab 50mg versus continuing conventional therapy (combination of NSAIDS and conventional DMARDs) for patients with severe AS who had an inadequate response to at least two NSAIDS. Anti-TNFα agents used in Scottish clinical practice, consisting of adalimumab and etanercept, were also compared with conventional therapy. A decision tree/Markov model was used to assess treatment effect at 12 week cycles (to correspond to BSR 3 monthly review timepoints), with a responder to anti-TNF α treatment defined according to BASDAI-50 criteria (at least a 50% reduction in BASDAI score). The model was run over a 20 year time horizon. Non-responders are assumed to be switched to conventional therapy.

Clinical effectiveness data for the model were derived from a mixed treatment comparison (MTC) of 12-24 week studies covering golimumab and the comparator anti-TNFα agents for responder efficacy, serious adverse events and injection site reactions. Conventional therapy outcomes were represented by the placebo arm of these studies, and used as a base to estimate a crude relative risk for the anti-TNFα agent outcomes. These relative risk estimates used as input parameters to the model indicated golimumab to have the same short term treatment effect as etanercept, but a slightly higher responder rate than adalimumab. Estimates for drug discontinuations were not derived from the MTC, but were assumed to be the same rate of 15% annually for all anti-TNFα agents, derived from a health technology assessment report produced for a prior NICE appraisal of anti-TNFα agents for AS. Regression equations were developed to predict long run outcomes for all the anti-TNFα agents based on BASDAI and BASFI scores from the pivotal golimumab study. Patients who respond to the anti-TNFα agents were assumed to have a period of 2-4 years during which BASDAI/BASFI disease progression is assumed to be lower than for conventional therapy, based on data in the pivotal golimumab study and evidence from published literature. A higher relative mortality for AS patients was included in the analysis.

Utility estimates associated with BASFI/BASDAI were derived from a previous mapping algorithm to EQ- 5D used in the NICE technology appraisal of AS. No costs were assumed for drug administration. Resource use data for the monitoring of treatment and management of AS associated with anti-TNFα agents or conventional therapy was derived from a UK expert survey questionnaire.

A patient access scheme (PAS) was proposed by the company. The PAS was not accepted by the Patient Access Scheme Assessment Group (PASAG) therefore the cost-effectiveness estimates based on the PAS were not considered by SMC as part of the economic case. The PAS was a simple scheme relating to the 100mg dose of golimumab only.

The results of the mixed treatment comparison suggested that the treatments were broadly similar in terms of outcomes, and using these data in the cost-utility analysis gave cost-effectiveness ratios that were very similar for all the treatment options compared to conventional therapy when golimumab was used at a dose of 50mg. Analysis was also provided to show the impact of use of the 100mg dose of golimumab in a proportion of patients. If 5% of patients were

assumed to require the 100mg dose of golimumab the cost per QALY versus conventional DMARDs was £32,546, which was less cost-effective than adalimumab and etanercept.

Given the similarity in treatment outcomes, SMC requested a simple cost-minimisation analysis from the company. This was subsequently provided and indicated that golimumab would be acceptable on cost-minimisation grounds compared to etanercept and comparable to adalimumab. It should be emphasised that these findings applied only to the 50mg dose of golimumab. The economic case was therefore considered demonstrated for golimumab when used at a dose of 50mg.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

BSR published the BSR guideline for prescribing TNFα Blockers in Adults with Ankylosing Spondylitis (report of a working party of the British Society for Rheumatology) in July 2004. The guideline was published when two anti-TNFα agents were licensed (infliximab and etanercept) and recommends that treatment with TNF blocking agents may be appropriate if:

- The patient's disease satisfies the modified New York criteria for diagnosis of ankylosing spondylitis.
- There is confirmation of sustained active spinal disease, demonstrated by:
    - a score of at least 4 units on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and
    - at least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (VAS). These should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment.
- Conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated or recommended dosage for 4 weeks has failed to control symptoms.

The BSR website does not include detail of any planned review of the guideline.

NICE published technology appraisal guidance number 143; adalimumab, etanercept and infliximab for ankylosing spondylitis in May 2008. It recommended adalimumab or etanercept as treatment options for adults with severe active ankylosing spondylitis only if all of the criteria [as in BSR guidance] are fulfilled. Response to treatment should be assessed every 12 weeks and treatment continued if there is an adequate response (reduction of the BASDAI score to 50% of the pre-treatment value or by 2 or more units and reduction of the spinal pain VAS by 2 cm or more). In patients who are intolerant of one of the treatments the other treatment may be tried. Infliximab was not recommended by NICE for the treatment of ankylosing spondylitis. The appraisal was due to be reviewed in October 2010. However NICE have proposed that a review of the guidance should be deferred until the ongoing single technology appraisal of golimumab for ankylosing spondylitis is considered for review.

The European League against Rheumatism (EULAR) and the Assessments in Ankylosing Spondylitis International Society (ASAS) published the 2010 update of the ASAS/EULAR

recommendations for the management of ankylosing spondylitis in 2011. Guidance on anti-TNF therapy is as follows:

- Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations.
- There is no evidence to support the obligatory use of DMARD before or concomitant with anti-TNF therapy in patients with axial disease.
- There is no evidence to support a difference in efficacy of the various TNF inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account.
- Switching to a second TNF blocker might be beneficial especially in patients with loss of response.
- There is no evidence to support the use of biological agents other than TNF inhibitors in AS.

The guidelines note that four anti-TNF agents are available but do not provide guidance on choice of anti-TNF agent.

Additional information: comparators

Adalimumab and etanercept may be used in the treatment of adults with severe AS who have had an inadequate response to conventional therapy. Infliximab is also indicated for the treatment of severe, active AS, however it has not been recommended by SMC and NICE MTA for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Golimumab	**50mg once monthly as a subcutaneous injection**	**9,156**
Adalimumab	40mg every two weeks as a subcutaneous injection	9,156
Etanercept	25mg twice weekly or 50mg weekly as a subcutaneous injection	9,295

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 24 May 2011 and MIMs (May 2011). Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment who have severe, active ankylosing spondylitis and have responded inadequately to conventional therapy to be 1,617 patients. This represents 20% of the estimated AS population in Scotland. Based on an estimated uptake of 5% in year 1 (69 patients), and 21% in year 5 (293 patients), the gross impact on the medicines budget was estimated at £660K in year 1 and £2.8 million in year 5. The net drug budget impact after displacement of adalimumab (estimated to be 3% displaced in year 1, up to 15% in year 5), and etanercept (estimated to be 9% displaced in year 1, up to 31% in year 5) was estimated as savings of £6K in year 1 rising to £21K in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

Inman R, Davis J, van der Heidje D, et al. Efficacy and Safety of Golimumab in Patients With Ankylosing Spondylitis. Arthrits and rheumatism 2008; 58(11): 3402–12.

Braun J, van der Heijde D, Deodhar A, Diekman L, Sieper J, Kim S, et al. Golimumab, a new, human, TNF- antibody administered subcutaneously every 4 weeks, in Ankylosing Spondylitis (AS): 104-week efficacy and safety results of the randomised, placebo-controlled GO-RAISE study. Arthritis and Rheumatism 2009;60 (Suppl 10):1259

European Medicines Agency. Assessment report for Simponi. EMEA/446762/2009. 20 October 2009. www.ema.europa.eu

This assessment is based on data submitted by the applicant company up to and including 15 July 2011**.**

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.