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

Re-Submission

golimumab, 50mg, solution for injection in pre-filled pen (auto-injector) or pre-filled syringe (Simponi®) SMC No. (674/11)

Merck Sharp & Dohme Limited

08 June 2012

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 re-submission

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

Indication under review: Alone or in combination with methotrexate, for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

SMC restriction: golimumab is restricted to use in patients whose disease has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination. It is also restricted to use at a dose of 50mg only.

Golimumab has demonstrated efficacy when compared with placebo in patients with active psoriatic arthritis who have had an inadequate response to DMARDs or non-steroidal anti-inflammatory drugs (NSAIDs).

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 09 July 2012

Indication

Alone or in combination with methotrexate, for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Golimumab has also been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and improve physical function.

Treatment should be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of psoriatic arthritis.

Dosing Information

Golimumab 50mg given once a month, on the same date each month [as a subcutaneous injection].

In patients weighing more than 100kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100mg once a month may be considered taking into account the increased risk of certain serious adverse 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 3 to 4 additional doses of 100mg.

This advice restricts use to the 50mg dose only.

Product availability date

27 October 2010

Summary of evidence on comparative efficacy

Golimumab is a human monoclonal antibody that binds to tumour necrosis factor alpha (TNFα), inhibiting its inflammatory effects. Over-expression of TNFα has been implicated in the pathophysiology of psoriatic arthritis. Evidence supporting the marketing authorisation is from one randomised controlled study.

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers only the 50mg dose on the basis that the 100mg dose is unlikely to be used in practice. This is supported by SMC clinical expert opinion and is consistent with previous SMC advice for golimumab in other indications.

The phase III double-blind, placebo-controlled GO-REVEAL study[1-4] recruited adults who had been diagnosed at least 6 months earlier with psoriatic arthritis that was active despite treatment with DMARDs or non-steroidal anti-inflammatory drugs (NSAIDs). Psoriatic arthritis was defined as active if there were ≥3 swollen and ≥3 tender joints, negative rheumatoid factor, at least one subset of psoriatic arthritis, and plaque psoriasis (lesion ≥2cm in diameter) present. Patients were excluded if they had previously received TNFα inhibitors, rituximab, natalizumab, or cytotoxic drugs. The use of concomitant stable doses of methotrexate, NSAIDs, and corticosteroids (prednisone ≤10mg/day) was permitted.

A total of 405 patients were randomised in a ratio of 1:1.3:1.3 with stratification for baseline use of methotrexate, to treatment with subcutaneous injections of placebo, golimumab 50mg or golimumab 100mg every 4 weeks for 24 weeks. At week 16 there was a pre-specified, blinded dose increase in patients receiving placebo or golimumab 50mg who achieved <10% improvement from baseline in swollen and tender joints counts. Forty five per cent (n=51) of patients in the placebo group changed to golimumab 50mg and 19% (n=28) of patients in the golimumab 50mg group changed to golimumab 100mg. All patients initially assigned to golimumab 100mg continued on this dose. Twelve (11%) of placebo treated patients and 13 (4%) of the combined group of golimumab treated patients discontinued treatment before the end of the study.

The co-primary outcomes were the proportion of patients meeting American College of Rheumatology 20% improvement criteria (ACR20) response at week 14 and change in psoriatic arthritis-modified Sharp/van der Heijde (PsA-modified SHS) score of the hands and feet from baseline to week 24. ACR20 was defined as ≥20% improvement in the swollen joint count (66 joints), the tender joint count (68 joints), and at least three of the following five assessments: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function using the Health Assessment Questionnaire (HAQ), and the C-reactive protein (CRP) level. The initial comparison was between the combined golimumab groups and the placebo group and this difference was required to be statistically significant before subsequent comparisons were made for individual golimumab dose groups versus placebo. Patients who crossed over at week 16 had their week 16 efficacy results carried forward to week 24.

The primary outcomes were met; 48% (140/292) of patients receiving golimumab achieved an ACR20 response after 14 weeks compared with 8.8% (10/113) receiving placebo. The individual golimumab groups also produced significantly more ACR20 responses than placebo: 51% (74/146) and 45% (66/146) for the 50mg and 100mg dose groups, respectively. Concomitant treatment with methotrexate was not a significant factor. The mean (standard deviation) change in PsA-modified SHS score of the hands and feet from baseline to week 24 was significantly less in the golimumab 50mg group than the placebo group, -0.16 (±1.31) versus 0.27 (±1.26), p=0.011.

The significant improvements in ACR20 response over placebo were maintained at week 24. This was supported by significant improvements in ACR50 and ACR70 responses (≥50% and ≥70% improvements) at weeks 14 and 24. The proportion of patients achieving a response according to the Psoriatic Arthritis Response Criteria (PsARC) was 73% (107/146), 72% (105/146) and 21% (24/113) for golimumab 50mg, golimumab 100mg and placebo treated patients respectively. Other outcomes that significantly improved from baseline to weeks 14 and 24 in each golimumab dose group compared with placebo were the European League Against Rheumatism (EULAR) response, change in Disease Activity Score in 28 joints using the C-reactive protein (CRP) level (DAS28-CRP), enthesitis and morning stiffness. Although significantly fewer patients receiving golimumab 100mg had dactylitis at weeks 14 and 24 compared with placebo, there was no significant difference for golimumab 50mg compared with placebo.

73% (296/405) of patients had ≥3% body surface area (BSA) psoriasis involvement at baseline so were evaluable for Psoriasis Area Severity Index (PASI). An improvement in the PASI of at least 75% at week 14 was achieved by 40% (44/109), 58% (63/108) and 2.5% (2/79) of patients in the golimumab 50mg, golimumab 100mg group and placebo group respectively. This improvement was irrespective of methotrexate use.

HAQ scores were significantly improved over placebo in patients receiving both doses of golimumab at week 24 with mean ± standard deviation (SD) change from baseline of 0.33 ±0.55 and 0.39 ±0.50 for golimumab 50mg and golimumab 100mg, respectively, compared with -0.01 ±0.49 for placebo. The physical component summary component of the Short Form 36 (SF-36) at week 14 was also significantly improved in patients receiving golimumab 50mg and 100mg, over placebo.

Two-year results from the open label extension of the study are available. All patients received golimumab 50mg or 100mg subcutaneously every 4 weeks from week 24 to week 104. The study was unblinded when all patients had received 1 year of study treatment, at which point the dose could be increased from 50mg to 100mg at the investigator's discretion. Response was maintained at 2 years although it was higher in those randomised to golimumab 50mg or 100mg who remained on the same dose than in those receiving golimumab 50mg who then switched to 100mg.

Summary of evidence on comparative safety

There is no comparative safety evidence in patients with psoriatic arthritis.

Data to week 24 in the pivotal study demonstrated comparable proportions of patients experiencing adverse events (AEs) between the combined golimumab group and the placebo group: 65% (222/343) and 59% (67/113) respectively. Nasopharyngitis and upper respiratory tract infection were the most frequently reported AEs in the golimumab groups. Fewer serious adverse events occurred in patients treated with golimumab compared with placebo (2.0% versus 6.2%). The proportions of patients who discontinued study drug because of AEs were 2.7% (8/292) of patients receiving golimumab and 4.4% (5/113) of patients receiving placebo.

Injection-site reactions were reported in 3.4% (10/292) of patients receiving golimumab and 2.7% (3/113) of patients receiving placebo and none were considered to be severe. In controlled phase III studies (to week 16) of golimumab in all licensed indications (rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis), 5.8% of golimumab-treated patients had injection site reactions compared with 2.2% in control patients.

After treatment for 2 years, golimumab was generally well-tolerated, with 8.6% (34/394) of patients experiencing SAEs. Injection site reactions were reported in 8.9% (35/394) of patients. There were few problems with infections or neoplasms and no reports of tuberculosis.

Summary of clinical effectiveness issues

The National Institute for Health and Clinical Excellence (NICE) has published a multiple technology appraisal of TNFα inhibitors (etanercept, infliximab and adalimumab) in psoriatic arthritis that is applicable to Scotland. It restricts the use of these drugs to patients whose disease has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination. This advice is supported by the Scottish Intercollegiate Guidelines Network (SIGN) publication 121: Diagnosis and management of psoriasis and psoriatic arthritis in adults. Golimumab would be expected to compete with the other currently available TNFα inhibitors.

There is no direct comparative evidence of the efficacy of golimumab in psoriatic arthritis. In addition, there is a lack of long-term safety data beyond 2 years. Furthermore, efficacy of golimumab in patients who have failed to respond to another TNFα inhibitor is unknown.

The primary endpoints were met in the pivotal placebo-controlled study; however, the study has a number of limitations. Firstly it assessed psoriatic arthritis outcomes in relatively few patients (n=146) receiving the licensed starting dose of golimumab and only 109 of these were evaluable for psoriasis outcomes. The use of the 100mg dose in the study was not related to weight unlike the marketing authorisation recommendations. Although the study duration was 24 weeks, for the 45% (n=51) of patients in the placebo group and 19% (n=28) of patients in the golimumab 50mg group who had the protocol specified dose increase for inadequate response, data at 16 weeks were carried forward.

Patients were included in the study if their psoriatic arthritis remained active despite treatment with DMARDs or NSAIDs. Twenty two per cent (22%) of patients in the combined golimumab group and 25% in the placebo group had received no prior treatment with DMARDs. This differs from the populations covered by the licensed indication (where patients are required to have an inadequate response to DMARD therapy) and NICE and SIGN guidance (where at least two standard DMARDs should have been tried). Finally, 73% of patients recruited to the study had a median psoriatic BSA involvement corresponding to mild psoriasis so the study results may have less relevance to patients with moderate to severe disease.

Golimumab's monthly treatment schedule may offer a potential advantage to patients compared with other TNFα inhibitors which are given more frequently. In addition, the submitting company claims the advantage of a lower incidence of injection site reactions over comparators, though there are no direct comparative data.

The standard dose of golimumab is 50mg subcutaneously once a month although the marketing authorisation allows for the dose to be increased to 100mg in patients weighing more than 100kg who do not achieve an adequate clinical response initially. The submitting company has asked SMC to consider the use of the 50mg dose only in active and progressive psoriatic arthritis on the basis that it is unlikely the higher dose will be used in clinical practice. This is supported by SMC clinical experts who have suggested that in practice patients who do not respond to the 50mg dose would be switched to another anti-TNFα agent.

A Bayesian mixed treatment comparison (MTC) with other TNFα inhibitors was presented. It included seven relevant placebo-controlled studies: the pivotal golimumab study and two each for adalimumab, etanercept and infliximab. PsARC, HAQ and PASI were analysed as the submitting company considered these secondary endpoints more relevant. ACR response, (the primary outcome in six of the studies), was not analysed. There were many assumptions and manipulations of data to facilitate comparisons among studies that used different methods of reporting endpoints. None of the study populations matched UK guidelines for use of the currently available TNFα inhibitors which specify failure of two DMARDs. The MTC results indicated that golimumab has comparable efficacy to etanercept, adalimumab and infliximab for PsARC, HAQ change from baseline and PASI outcomes.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing golimumab with adalimumab, etanercept and infliximab for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. The base case time horizon was 1 year.

The clinical evidence for the comparable efficacy of golimumab versus the other TNFα inhibitors was derived from a mixed treatment comparison.

The analysis compared the drug acquisition costs per annum, for treatment with golimumab and adalimumab, etanercept and infliximab, and included the drug costs only. The economic analysis focused only on the use of the 50mg dose of golimumab therefore the economic case for using the 100mg dose of golimumab has not been assessed.

The results showed the drug cost per annum is £9,156 for treatment with golimumab and adalimumab, £9,295 for treatment with etanercept and £10,910 for treatment with infliximab. Golimumab is therefore associated with cost savings compared with etanercept and infliximab and is cost-neutral relative to adalimumab.

Sensitivity analysis showed that the results were generally stable except when a low patient weight of 60kg was assumed, in which case golimumab was no longer cost-saving versus infliximab.

Given the results of the cost-minimisation analysis, the economic case has been demonstrated for the 50mg dose of golimumab.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Psoriasis Scotland Arthritis Link Volunteers (PSALV).

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) has published (October 2010) a national clinical guideline (SIGN 121) entitled Diagnosis and management of psoriasis and psoriatic arthritis in adults. It states that adalimumab, etanercept or infliximab are recommended for treatment of active psoriatic arthritis in patients who have failed to respond to, are intolerant of, or have had contraindications to, at least two disease-modifying therapies.

NICE published multiple technology appraisal (MTA) guidance 199 in August 2010: Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, which recommends these drugs for the treatment of adults with active and progressive psoriatic arthritis which has not responded to adequate trials of at least two standard DMARDs and where there is peripheral arthritis with at least three tender joints and at least three swollen joints. Treatment should only be continued after 12 weeks if there is an adequate response to PsARC or on a dermatologist's advice if there is a PASI 75 response. Treatment should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose).

Both guidelines predate the availability of golimumab.

Additional information: comparators

Comparators are the other TNFα inhibitors, adalimumab, etanercept and infliximab.

Cost of relative comparators

Drug	Dose Regimen	Cost per year (£)
Golimumab	**50mg subcutaneously once a (calendar) month**	**9,156**
Infliximab	5mg/kg as an intravenous infusion, repeated 2 and 6 weeks after the first infusion, then every 8 weeks thereafter	13,428 in year one then 10,071 thereafter
Adalimumab	40mg subcutaneously every 2 weeks	9,156
Etanercept	25mg subcutaneously twice weekly or 50mg subcutaneously once a week	9,295

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on.20 March 2012 and from MIMS (February 2012). Costs, where applicable, are based on a body weight of 70kg.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 248 in year 1 and 253 in year 5. Based on an estimated uptake of 2.32% in year 1 (8 patients) rising to 24.01% in year 5 (53 patients), the net impact on the medicines budget was estimated to be savings of £3.8k in year 1 and £10.4K in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Kavanaugh A, McInnes I, Mease P et al. Golimumab, a new human tumor necrosis factor α antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis. Arthritis and Rheumatism 2009; 60: 976-86

2. The European Medicines Agency (EMA) European Public Assessment Report golimumab (Simponi) EMEA/H/C/000992 2009

3. Kavanaugh A, McInnes I, Mease P et al. Golimumab, a human TNF-alpha antibody, administered every 4 weeks as a subcutaneous injection in psoriatic arthritis: clinical efficacy, radiographic, and safety findings through 1 year of the randomized, placebo-controlled, GO-REVEAL® study. Arthritis & Rheumatism 2012 accepted article doi: 10.1002/art.34436

4. Kavanaugh A, Mease P, Krueger GG, et al. Golimumab, a new, human, TNF-alpha antibody, administered subcutaneously every 4 weeks in psoriatic arthritis patients: 104-week efficacy and safety results of the randomized, placebo-controlled GO-REVEAL study. Presented at: EULAR 2009, Copenhagen, Denmark, June 12, 2009. Presentation no. OP-0195.

This assessment is based on data submitted by the applicant company up to and including 17 April 2012.

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.

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.