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. (733/11)

MSD Ltd

07 October 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: In combination with methotrexate, for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease modifying anti-rheumatic drug therapy including methotrexate has been inadequate.

Golimumab, in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

SMC restriction: golimumab is restricted for use in accordance with British Society for Rheumatology guidance on prescribing TNFα blockers in adults with rheumatoid arthritis (2005). Golimumab is restricted to use at a dose of 50 mg only.

There are no head to head studies comparing golimumab with other TNFα inhibitors in the treatment of rheumatoid arthritis. Golimumab plus methotrexate was superior to methotrexate alone for the primary endpoint (ACR20 response and improvement in HAQ-DI) in patients with active rheumatoid arthritis despite methotrexate treatment.

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

Golimumab is also licensed for use in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. SMC cannot recommend the use of golimumab in this setting, however, as the company submission related only to its use in patients with an inadequate response to methotrexate.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

In combination with methotrexate, is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease modifying anti-rheumatic drug therapy including methotrexate has been inadequate.
Golimumab, in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Dosing Information

Golimumab 50mg subcutaneously given once a month, on the same date each month. Golimumab should be given concomitantly with methotrexate.

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 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 alpha (TNFα) is thought to play a pivotal role in joint inflammation. A number of TNFα inhibitors are licensed for the treatment of rheumatoid arthritis (RA). Golimumab is a human TNFα-inhibitor monoclonal antibody, given as a subcutaneous injection once monthly. Golimumab in combination with methotrexate is also indicated for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. The company have indicated that they do not intend making a submission to SMC for this indication at this time.

Evidence of efficacy comes from a phase III double-blind placebo-controlled study conducted in patients aged 18 years or older with RA according to the American College of Rheumatology (ACR) criteria for at least 3 months before screening and on a stable dose of methotrexate (15 to 25mg/week). Active RA was defined as ≥4 swollen joints and ≥4 tender joints and ≥2 of the following: C-reactive protein (CRP) ≥1.5mg/dL or erythrocyte sedimentation rate (ESR) ≥28mm/h; ≥30 minutes of morning stiffness; bone erosion determined by x-ray and or MRI; positive anti-cyclic citrullinated peptide antibody or rheumatoid factor test results. Patients could

continue with NSAIDs and corticosteroids provided the dose was stable for at least two weeks and remained stable whilst on study treatment. Patients were randomised to one of four groups: placebo plus methotrexate (group 1); golimumab 100mg plus placebo (group 2); golimumab 50mg plus methotrexate (group 3); or golimumab 100mg plus methotrexate (group 4). Injections were administered subcutaneously every 4 weeks. All patients (except for those in group 2) continued with their initial stable dose of methotrexate throughout the study without interruption. The dose regimens in group 3 (and group 4 in specific clinical situations) are the licensed doses of golimumab.

Patients with <20% improvement from baseline in tender and swollen joint counts in groups 1, 2 and 3 were permitted to receive early escape treatment (in a double-blind fashion) as follows. At week 16, 31% (41/133) of patients in group 1 began receiving golimumab 50mg every 4 weeks, 27% (36/133) in group 2 received methotrexate at same dose received at screening and 15% (15/89) in group 3 received golimumab 100mg every 4 weeks. Patients in group 4 had no adjustment made to their medication.

The co-primary endpoints were the proportion of patients achieving an ACR20 response at week 14 and the improvement from baseline in the health assessment questionnaire disability index (HAQ-DI) score at week 24. An ACR20 response was defined as a ≥20% improvement in swollen joint count (66 joints) and tender joint count (68 joints) and ≥20% improvement in three of the following five assessments: patient's assessment of pain; patient's global assessment of disease activity; evaluator's global assessment of disease activity; patient's assessment of physical function as measured by the HAQ and CRP. The HAQ-DI is a 20 question instrument which assesses the degree of difficulty the patient had in accomplishing tasks in eight functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the previous week. Responses in each functional area are scored from 0 (no difficulty) to 3 (inability to perform a task in that functional area) and a final score, with range 0 to 3, is calculated. Both golimumab plus methotrexate groups were superior to the methotrexate alone group for the co-primary endpoints; see table below (for groups 1, 3 and 4 only).

Table: primary endpoints for the pivotal study.

	Group 1 Methotrexate alone	**Group 3 Golimumab 50mg + methotrexate**	**Group 4 Golimumab 100mg + methotrexate**
n	133	89	89
ACR20 at week 14; n (%)	44 (33%)	49 (55%)	50 (56%)
P value	-	0.001	<0.001
Improvement in HAQ-DI at week 24 (interquartile range)	-0.13 (-0.38 to 0.13)	-0.38 (-0.75 to -0.13)	-0.50 (-0.75 to -0.13)
P Value	-	<0.001	<0.001

The golimumab 50mg and 100mg groups in combination with methotrexate were superior to the methotrexate alone group for the key secondary endpoints of disease activity score in 28 joints at week 14, ACR20 at week 24 and HAQ-DI at week 14. Radiographs of hands and feet were taken at baseline, week 24 (week 16 for patients who entered early escape) and week 52, and scored by two independent readers using the van der Heijde modification of the Sharp tool. There was minimal progression in all treatment groups and the changes in the modified Sharp scores from baseline to week 24 between golimumab plus methotrexate versus methotrexate

alone were not significant: 0.6 ±2.4 for the methotrexate alone group versus 0.6 ±2.7 for golimumab 50mg plus methotrexate and 0.2 ±1.3 for golimumab 100mg plus methotrexate groups. Short-form (SF-36) data were collected but are unpublished. At week 24 the mean change from baseline in the physical component summary score was superior for golimumab 50mg plus methotrexate versus methotrexate alone (8.28 versus 2.54), and this change from baseline was maintained at week 104. However, at week 24 there was no significant difference between golimumab plus methotrexate versus methotrexate alone groups in the mean change from baseline in the mental component summary score (1.83 versus 0.75).

At week 24, patients in group 1 who had been receiving placebo injections began receiving golimumab 50mg injections and patients in the other groups continued to receive the treatments they were receiving at week 24. All patients received treatment up to week 48; at week 52 the proportion of patients with an ACR20 response was 44% for group 1 versus 64% and 58% in groups 3 and 4 respectively.

Summary of evidence on comparative safety

In the pivotal study up to week 16, the proportion of patients with adverse events (AE) was 61% (81/133) in group 1 versus 69% (61/89) in group 3 and 69% (62/89) in group 4. Serious AE occurred in 2.3% (3/133), 5.6% (5/89) and 9.0% (8/89) of patients respectively. AE up to week 24 were presented as events per patient-year because of the fact that early escape was allowed at week 16. The event rate (95% CI) for any infection was 1.16 (0.89 to 1.48) for group 1 versus 0.36 (0.27 to 0.48) for group 3 and 0.79 (0.62 to 1.00) for group 4. The event rates for injection site reactions were 0.11 (0.04 to 0.24) for group 1 versus 0.08 (0.04 to 0.14) and 0.07 (0.03 to 0.15) for groups 3 and 4 respectively. No patients developed active tuberculosis during the study.

The European Medicines Agency (EMA) considered the AE profile of golimumab to be similar to other TNFα inhibitors.

Summary of clinical effectiveness issues

In the pivotal study, golimumab 50mg plus methotrexate and golimumab 100mg plus methotrexate were significantly superior to methotrexate alone for the primary endpoints of ACR20 response at week 14 and HAQ-DI at week 24 as well as for key secondary endpoints. The study included patients previously treated with methotrexate, approximately 75% of patients had also received treatment with another disease modifying anti-rheumatic drug and disease duration at enrolment was around 5 to 6 years. For the radiographic progression endpoint, there were no significant differences for golimumab plus methotrexate groups versus methotrexate alone. Limitations of the study design, including lack of statistical power for this endpoint and the early escape nature of the study, and the fact that only one-third of the patient population had a CRP ≥1.5mg/dL, may have contributed to this non-significant result. In January 2011 the EMA granted a type II variation for the joint damage progression indication based on data from a study in which patients were methotrexate-naïve at enrolment.

There are no direct comparative data other than versus methotrexate alone. The submitting company included a mixed treatment comparison (MTC) to indirectly compare golimumab with the TNFα inhibitors, adalimumab, certolizumab, etanercept and infliximab. Limitations of the

MTC include differences in patient populations and study designs, high drop-out rates in some studies and no measure of heterogeneity in the analysis. However results suggest that golimumab has comparable efficacy to etanercept, infliximab and adalimumab. A recent Cochrane review of golimumab efficacy in RA supports this conclusion. The authors of this review considered that golimumab had efficacy similar to the other biologics currently used for the treatment of RA.

Golimumab may be self-administered subcutaneously after training and when the physician considers it appropriate. This is also the case for adalimumab, etanercept and certolizumab. Golimumab is administered monthly compared to twice weekly or weekly for etanercept, and fortnightly for adalimumab and certolizumab pegol. Infliximab is administered as an intravenous (iv) infusion 8-weekly, and tocilizumab and abatacept as an iv infusion 4-weekly. The less frequent and subcutaneous administration schedule for golimumab may offer advantages for the patient and for service delivery. In addition, mean changes from baseline in all physical and some mental components of the health related quality of life tool used in the pivotal study were significantly superior for patients treated with golimumab plus methotrexate relative to methotrexate alone.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis comparing golimumab in combination with methotrexate to infliximab plus methotrexate, adalimumab plus methotrexate, etanercept plus methotrexate and certolizumab plus methotrexate in patients with moderate to severe RA who have had an inadequate response to DMARD therapy including methotrexate. The comparators used in the analysis were appropriate. A lifetime Markov model was used where response to treatment was categorised according to ACR criteria with non-responders progressing to subsequent treatments such as leflunomide or gold.

The clinical data for the golimumab arm were taken from the pivotal study. For the comparator treatments the MTC was the source of the efficacy data where the numerical differences in response rates were used in the model. The utility values were obtained by converting the HAQ scores to EQ-5D using a published equation which was also used by the National Institute for Health and Clinical Excellence (NICE) in the multiple technology appraisal of adalimumab, infliximab and etanercept. SF-36 quality of life data were collected in the study but were not used in the base case analysis. However, a sensitivity analysis was provided using the SF-36 data from the pivotal study. Resource use associated with hospitalisations was included but was assumed to be equivalent for all patients on TNFα inhibitors.

The company presented the results of the analysis based on the 50mg dose of golimumab showing the incremental cost effectiveness ratios (ICERs) for all the treatments versus methotrexate (baseline). This showed that golimumab has similar cost-effectiveness to the other TNFα inhibitors. It should be noted that the cost of certolizumab incorporated the certolizumab PAS.

	Incremental costs	Incremental QALYs	ICER versus methotrexate
Infliximab plus methotrexate	£27,898	1.059	£26,341
Adalimumab plus methotrexate	£29,399	1.171	£25,105
Etanercept plus methotrexate	£32,439	1.085	£29,892
Golimumab plus methotrexate	£33,355	1.26	£26,480
Certolizumab plus methotrexate	£37,234	1.678	£22,183

As the results of the MTC suggest that golimumab has comparable efficacy to the active comparator treatments, a cost-minimisation analysis was considered to be more appropriate. The submitting company subsequently provided this analysis which demonstrated that over a 1-year and 5-year time horizon golimumab would be considered a cost-effective treatment option relative to the other TNFα inhibitors. 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. The economic case for use of the 100mg dose was not submitted.

Summary of patient and public involvement

A Patient Interest Group Submission was received from National Rheumatoid Arthritis Society.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline number 79; Rheumatoid arthritis; the management of rheumatoid arthritis in adults in February 2009. It includes the following advice:

- The tumour necrosis factor alpha (TNF-α) inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics:
    - Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
    - Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.
- TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy.

NICE published technology appraisal 130; Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in October 2007. This advice was included in the clinical guideline 79 (as above).

An update on the British Society for Rheumatology guidelines for prescribing TNFα blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001) was published in January 2005. Eligibility criteria for treatment with biologics therapies are as follows.

Patients must:

1. Fulfil the 1987 criteria of the American College of Rheumatology classification criteria for a diagnosis of RA.
2. Have active RA (have a DAS28 score of >5.1). Measurements of disease activity should be made at two points, 1 month apart confirming on-going active disease.
3. Have failed standard therapy as defined by failure to respond or tolerate adequate therapeutic trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs) - intramuscular gold, hydroxychloroquine, sulphasalazine, penicillamine, azathioprine, methotrexate or leflunomide. One of the failed or not tolerated therapies must be methotrexate.

   Adequate therapeutic trial is defined as:

   (a) Treatment for at least 6 months, with at least 2 months at a standard target dose unless significant toxicity limited the dose tolerated.

   (b) Treatment for less than 6 months where treatment was withdrawn because of drug intolerance or toxicity, but normally after at least 2 months at therapeutic doses.

The Scottish Intercollegiate Guideline Network (SIGN) issued guideline number 123; Management of early rheumatoid arthritis in February 2011. Under "disease modifying anti-rheumatic drugs" the following is recommended;

- Methotrexate and sulfasalazine are the DMARDs of choice due to their more favourable efficacy and toxicity profiles.
- DMARD therapy should be sustained in patients with early RA to control the signs and symptoms of disease.

SIGN do not include any specific guidance under "biologic response modifiers" with the exception they note "Use of TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs is not recommended".

Additional information: comparators

Other TNFα inhibitors agents used in the treatment of RA when the response to disease modifying anti-rheumatic drug therapy including methotrexate has been inadequate include adalimumab, etanercept, infliximab, certolizumab pegol and tocilizumab. In addition abatacept may be used in patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs including methotrexate and a TNF-alpha inhibitor.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£) Cost per course (£)
Golimumab	**By subcutaneous injection, 50mg once every calendar month**	**9,156**
Infliximab	By intravenous infusion, 3mg/kg at weeks 0, 2 and 6 and then every eight weeks. If response is inadequate after week 12 dose can be increased to a maximum of 7.5mg/kg every eight weeks or 3mg/kg every four weeks	6,714 to 13,847 in first year then 5,875 to 17,624 in subsequent years
Certolizumab pegol	By subcutaneous injection, 400mg at weeks 0, 2 and 4, then 200mg every two weeks	10,368 in first year then 9,295 in subsequent years
Abatacept	By intravenous infusion 10mg/kg at weeks 0, 2 and 4 and then every four weeks	10,171 in first year then 9,445 in subsequent years
Tocilizumab	By intravenous infusion, 8mg/kg every four weeks	9,318
Etanercept	By subcutaneous injection, 25mg twice weekly	9,295
Adalimumab	By subcutaneous injection, 40mg every second week	9,156

Doses are for general comparison and do not imply therapeutic equivalence. Costs of golimumab, tocilizumab, and infliximab from MIMs July 2011, cost of abatacept from BNF61 and other costs from eVadis on 28 July 2011. Where applicable, doses based on body weight of 70kg. Lower limits of infliximab cost ranges round down dose from 210mg to 200mg. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated the population eligible for treatment to be 4,400 patients in year 1 and 4,471 in year 5. Based on an estimated uptake of 0.2% in year 1 and 17.5% in year 5 and a discontinuation rate of 6%, the impact on the medicines budget was estimated at £76K in year 1 rising to £6.7m in year 5. Assuming displacement of existing anti-TNF agents the net medicines budget impact was estimated at £1K in year 1 and £65K 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.

Keystone EC, Genovese MC, Klareskog L et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68:789-96.

Emery P, Fleischmann R, van der Heijde D. The effects of golimumab in radiographic progression in rheumatoid arthritis. Arthritis and Rheumatism. 2011: 63; 1200-10

Keystone EC, Genovese MC, Klareskog L et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis. 2010;69:1129-1135

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

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.