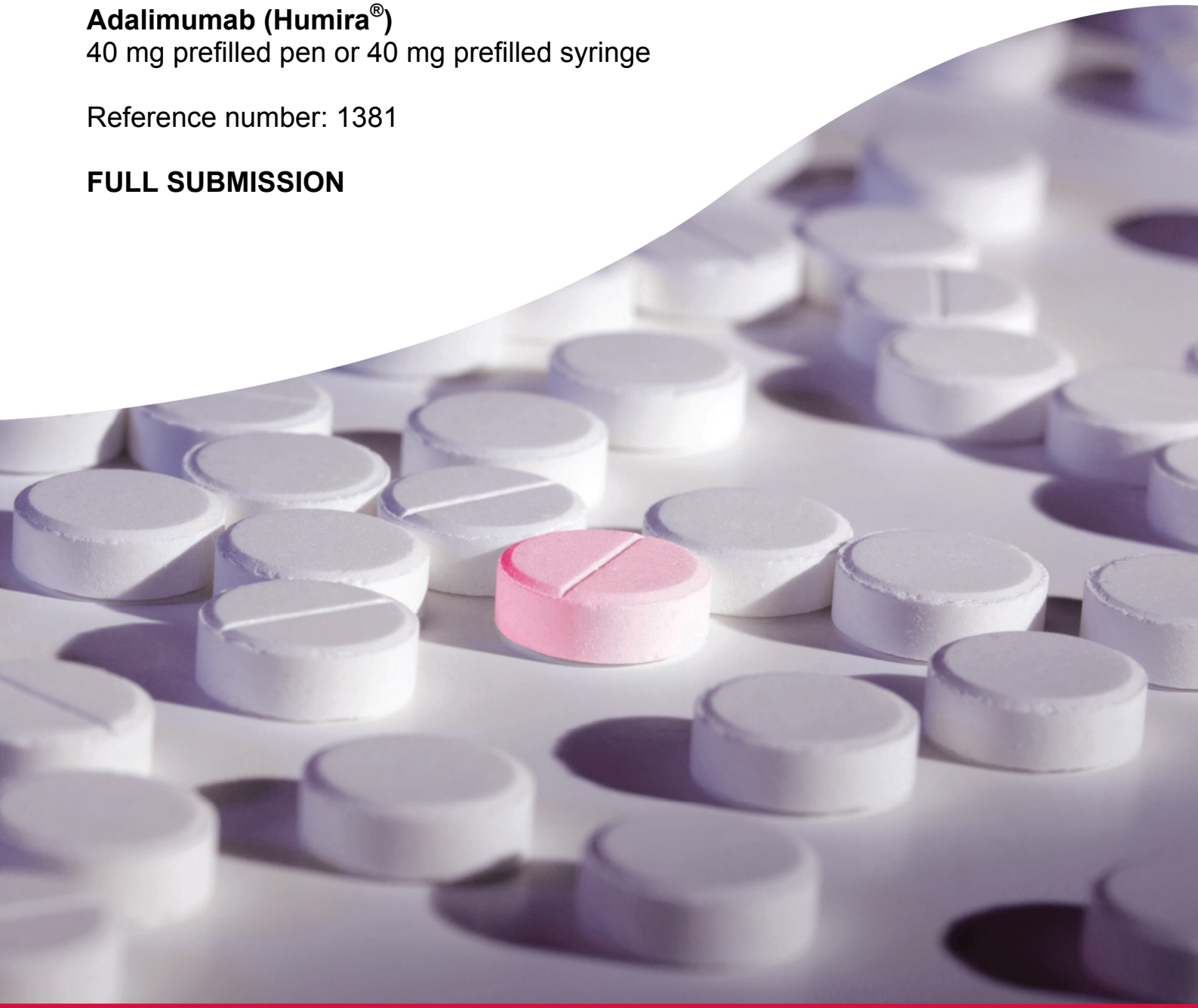
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Adalimumab (Humira®)
40 mg prefilled pen or 40 mg prefilled syringe

Reference number: 1381

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Adalimumab (Humira®) 40 mg prefilled pen or 40 mg prefilled syringe

This assessment report is based on evidence submitted by AbbVie Ltd on 20 December 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Adalimumab (Humira®) is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to non steroidal anti-inflammatory drugs (NSAIDs)[2].
Dosing	The recommended dose of adalimumab is 40 mg administered every other week as a single dose via subcutaneous injection[2].
Marketing authorisation date	25 July 2012 (licensed for the treatment of moderate to severe active rheumatoid arthritis in September 2003)[1].

2.0 DECISION CONTEXT

2.1 Background

Spondyloarthropathy is a term used to describe a number of conditions including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, enteropathic or inflammatory bowel disease (IBD)-related arthritis and undifferentiated spondyloarthritis (SpA)[3]. These conditions share common clinical, radiographic and genetic features, and can be classified into two broad categories based on their predominant clinical manifestations: axial or peripheral SpA[3]. Axial SpA (axSpA) is an inflammatory condition affecting the axial skeleton. It can be divided into two further categories: non-radiographic axial SpA (nr-axSpA; axial SpA without radiographic evidence of AS, a chronic, multifaceted disease of the joints and surrounding tissue) and AS (inflammation of the sacroiliac joint at the base of the spine [sacroiliitis] followed by inflammation rising along the spine, as diagnosed by the modified New York criteria)[1,4]. Patients with nr-axSpA can present with disease features and a level of disease activity similar to patients with AS[3]. The use of magnetic resonance imaging (MRI) can identify the presence of inflammation in the axial skeleton in the absence of radiographic changes[5].

Non-steroidal anti-inflammatory drugs (NSAIDs) are often an effective therapy for patients with axSpA; however, where NSAIDs have failed there has previously been no alternative treatment available[3]. Disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate or sulfasalazine are not recommended for the treatment of axSpA and the use of systemic corticosteroids is not supported by evidence[1,3]. Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody which acts as a tumour necrosis factor (TNF) antagonist. At the time of writing, adalimumab is the only therapy licensed for the indication under consideration[2].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was best supportive care.

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Adalimumab, etanercept and infliximab for ankylosing spondylitis. Technology Appraisal Guidance 143. (2008)[4].
- Sieper et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. (2009)[6].
- van der Heijde et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. (2011)[7].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of two studies, both contributing efficacy and safety evidence. ABILITY-1, the pivotal phase III trial, described the efficacy and safety of adalimumab 40 mg in patients with nr-axSpA[1,5]. This included a subgroup analysis investigating adalimumab 40 mg in the licensed population, i.e. patients with severe nr-axSpA but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs[1]. The company have also provided details of an investigator-initiated study, conducted by Haibel et al, which investigated the efficacy and safety of adalimumab in patients with nr-ax-SpA. Pooled efficacy data from the two trials were also presented[1].

3.1 ABILITY-1

ABILITY-1 was a multicentre, randomised, double-blind, placebo-controlled phase III study designed to evaluate the efficacy and safety of adalimumab 40 mg in patients (≥ 18 years) with nr-axSpA who fulfilled the ASAS criteria (see Glossary) for axial spondyloarthritis without meeting the modified New York criteria for AS. Eligible patients had an inadequate response, intolerance or contraindication to one or more NSAIDs. Patients (n = 192) were randomised 1:1 to receive adalimumab 40 mg (n = 95) or placebo (n = 97) administered subcutaneously every other week for 12 weeks. Seven patients were excluded from the efficacy analyses (four from the adalimumab arm and three from the placebo arm) due to investigator non-compliance identified at a single site[1,3,5]. To account for the excluded patients, efficacy was measured in the full analysis set (FAS); a sensitivity analysis was also carried out in the intention-to-treat population (ITT)[1,3]. Patients who completed the double-blind period were eligible to receive open-label adalimumab for up to an additional 144 weeks; results up to week 56 of this study are currently available[1,8].

The primary endpoint was the proportion of patients who achieved an ASAS40 response (see Glossary) at week 12. In the FAS group, a statistically significantly greater proportion of patients in the adalimumab arm (36.3%) achieved an ASAS40 response at week 12 compared to placebo (14.9%); $p = < 0.001$[5] (refer to Table 1). Similarly, in the ABILITY-1 subgroup analysis of the licensed population, i.e. in patients with nr-axSpA with objective signs of inflammation by elevated CRP and/or MRI, a statistically significant result was achieved in the adalimumab group (40.6%) compared to placebo (13.7%); $p < 0.001$[1] (refer to Table 2). Sensitivity analyses in the ITT population and secondary endpoints supported these findings.

All patients, regardless of their previous treatment arm, were switched to open-label adalimumab after the 12-week double-blind period. At week 68 (12 weeks of the double-blind period plus 56 weeks of open-label treatment), data from the open-label extension were available for 144 patients, of which 67% had an ASAS40 response and 47% were in a state of inactive disease according to the ankylosing spondylitis disease

activity score (ASDAS)[8]. A clinical response was maintained through to week 68 in patients who were previously randomised to adalimumab. In patients who were previously randomised to placebo, a clinical improvement was demonstrated as early as week 16, i.e. four weeks after switching to adalimumab[1].

Table 1. Efficacy results of the ABILITY-1 trial[1,5]

	Treatment regimen				
	Adalimumab		Placebo		p value
ABILITY-1					
Primary endpoint	**N**		**N**		
ASAS40 response at week 12 in the FAS, n (%)	91	33 (36.3)	94	14 (14.9)	< 0.001
ASAS40 response at week 12 in the ITT population, n (%)	95	33 (34.7)	97	14 (14.4)	0.001
Ranked secondary endpoints					
ASAS 20 response, n (%)	91	47 (51.6)	94	29 (30.9)	0.004
BASDAI 50 response, n (%)	91	32 (35.2)	94	14 (14.9)	0.001
SF-36v2 physical component score (mean change from baseline ± SD)	91	5.5 ± 8.98	93	2.0 ± 7.04	0.001
ASAS partial remission, n (%)	91	15 (16.5)	94	5 (5.3)	0.014
ASAS 5/6 response, n (%)	91	28 (30.8)	94	6 (6.4)	< 0.001
HAQ-S total score (mean change from baseline ± SD)	91	−0.3 ± 0.49	94	−0.1 ± 0.42	0.027
hs-CRP (mg/L) (mean change from baseline ± SD)	70	−4.7 ± 12.32	73	−0.3 ± 6.39	<0.001
SPARCC MRI score for sacroiliac joints (mean change from baseline ± SD)	84	−3.2 ± 8.34	84	−0.6 ± 6.19	0.003
SPARCC MRI score for the spine (mean change from baseline ± SD)	85	−1.8 ± 4.51	83	−0.2 ± 3.32	0.001

ASAS: assessment of spondyloarthritis international society; BASDAI: Bath ankylosing spondylitis disease activity index; FAS: full analysis set; ITT: intention-to-treat; HAQ-S: health assessment questionnaire modified for spondyloarthropathies; hs-CRP: high-sensitivity C-reactive protein; SD: standard deviation; SPARCC MRI: Spondyloarthritis Research Consortium of Canada magnetic resonance imaging

Table 2. Efficacy results of the ABILITY-1 subgroup analysis[1]
[Commercial in confidence data removed]

3.2 Investigator initiated study: Haibel et al[9]

This was a randomised, double-blind, placebo-controlled study conducted at two centres in Germany, designed to investigate the efficacy and safety of adalimumab in patients (≥ 18 years) with nr-axSpA. Patients (n = 46) were randomised 1:1 to receive either adalimumab 40 mg (n = 22) or placebo (n = 24) administered subcutaneously every other week for 12 weeks, followed by an open-label extension that continued up to week 52[1,9].

The primary endpoint was ASAS40; at week 12, a greater proportion of patients in the adalimumab group than in the placebo group achieved an ASAS40 response (54.5% versus 12.5%; p = 0.004). The clinical improvement achieved in patients treated with adalimumab was sustained up to week 52 (45.5% of patients with an ASAS40 response). Secondary endpoints supported these results[1,9].

3.3 Pooled efficacy data from ABILITY-1 and Haibel et al

In their submission, the applicant company provided a pooled analysis of the published data for the primary endpoint, ASAS40, for the ABILITY-1 trial (FAS) and the investigator-initiated study by Haibel et al. The pooled estimate for ASAS40 response from this analysis was 39.8% for adalimumab versus 14.4% for placebo[1].

3.4 Comparative safety

The safety of adalimumab 40 mg in patients with nr-axSpA was assessed in both the ABILITY-1 study and the investigator initiated trial by Haibel et al[1,5,8,9]. For both studies, the treatment-emergent adverse events (TEAEs) were found to be comparable between treatment and placebo groups (ABILITY-1: 57.9% adalimumab versus 58.8% placebo; Haibel et al: 51% adalimumab versus 49% placebo)[1,9]. However, in the ABILITY-1 trial, more patients in the adalimumab group reported AEs that the investigator considered possibly or probably related to the study treatment (32.6% adalimumab versus 21.6% placebo)[3,5]. During the 12-week double-blind period of the ABILITY-1 trial, the most frequently reported AEs in the adalimumab group were nasopharyngitis (11.6% adalimumab versus 3.1% placebo), nausea (7.4% versus 8.2%), headache (6.3% versus 3.1%) and injection site related infection (4.2% versus 0%)[1,3,5]. In the study by Haibel et al, the most frequently reported AEs were infection of the respiratory tract (15 patients in the adalimumab group versus 9 placebo-treated patients) and skin infections (12 adalimumab-treated patients versus 4 in the placebo group)[1,9]. Serious AEs (SAEs) were seen in 3.1% of adalimumab-treated patients during the 12-week double-blind period of the ABILITY-1 trial and in 6.8% of patients at any time point (including the open-label extension phase) during the ABILITY-1 trial[1,3,5,8]. In the study by Haibel et al, eight SAEs were reported during the open-label extension phase in five patients; none of which were thought to be related to the study treatment[1,9]. The safety profile for adalimumab 40 mg every other week is well established; no new safety concerns were identified from the studies for the indication under consideration[3].

3.5 AWTTC critique

- To support the clinical effectiveness and safety of adalimumab 40 mg in patients with severe nr-axSpA, the applicant company provided evidence from two placebo-controlled trials, which were carried out in a broader population of patient than specified by the licensed indication[1,5,9]. The ABILITY-1 trial demonstrated that there is a greater likelihood of a clinical response among patients with either elevated CRP or positive MRI, with no differences in safety compared to the overall study population[3,5]. At the time of writing, there are no alternative licensed active comparators for this condition in patients who have failed treatment with NSAIDs[1].

- Results from the ABILITY-1 trial demonstrated sustained efficacy outcomes from up to 68 weeks of treatment with adalimumab[5,8]. Patients were eligible to receive adalimumab for up to 144 weeks. The study is ongoing and is expected to be completed in July 2013[10].
- There are no validated outcome measures for spondyloarthritis. However, the Committee for Medicinal Products for Human Use (CHMP) considered it justified to use the ASAS response (an established measure for AS).
- Patients eligible for the ABILITY-1 trial must have responded inadequately or been intolerant to one or more NSAIDs; however the applicant company note that the majority of patients (69.2%) had been treated with ≥ two NSAIDs prior to the study[1]. The company state that the patient population in the ABILITY-1 study is therefore considered to be applicable to patients who would be eligible for adalimumab therapy for severe nr-axSpA in Wales[1,5,8].
- Adalimumab therapy resulted in improvements in pain, disease activity, health-related quality of life, and work outcomes in patients with severe nr-axSpA[1].
- Over time, patients with nr-axSpA may progress to AS[3]. There is no evidence available to confirm whether any treatment intervention for nr-axSpA can slow or prevent disease progression[1,3].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis of adalimumab (Humira®) 40 mg every other week versus conventional therapy (defined as a combination of physiotherapy and/or NSAIDs, or palliative care in patients with NSAID intolerance) in patients with severe nr-axSpA (Bath ankylosing spondylitis disease activity index [BASDAI] ≥ 4), who have failed treatment with NSAIDs and who have objective signs of inflammation by elevated CRP and/or MRI[1].

The analysis is based on a Markov model consisting of a short-term phase based on observed outcomes at 12 weeks in the ABILITY-1 trial, and a longer term phase that projects data from the ABILITY-1 trial over a 40 year period. Patients enter the model with nr-axSpA (BASDAI ≥ 4) and receive either adalimumab or conventional care. Non-responders to adalimumab at 12 weeks (defined as those who did not achieve a 40% improvement and an absolute change in score of 20 units for at least three out of four domains in the ASAS) discontinue therapy, while responders continue receiving adalimumab until subsequent discontinuation. This is modelled from the observed discontinuation rate of responders between weeks 12 and 68 in the open-label extension of the ABILITY-1 trial. Outcomes beyond 12 weeks are modelled by extrapolating BASDAI and Bath ankylosing spondylitis functional index (BASFI) scores observed between weeks 12 and 68 in the open-label extension. For responders, BASDAI and BASFI scores are assumed to improve while on treatment; upon discontinuation of adalimumab, BASDAI and BASFI scores are assumed to return immediately to the baseline levels. For patients receiving conventional care (both responders and non-responders), BASDAI and BASFI are assumed to return immediately to the baseline scores at week 12. The BASDAI scores remain constant from that point onward. However, BASFI scores for patients who are not on adalimumab after week 12 are assumed to worsen over time.

Utility values for the base case model are based on regression of both BASDAI and BASFI scores against trial-reported EQ-5D scores for the entire ABILITY-1 trial population. No administration costs were included as it was assumed that patients would be able to self-administer adalimumab via subcutaneous injections. Overall treatment costs, excluding medication, for SpA were derived from non-UK registry data

for ankylosing spondylitis, mapped to BASDAI scores[11]. The model assumes quarter-year cycles over the 40-year time horizon.

4.1.2 Results

Results of the base case analyses are summarised in Table 3. Adalimumab treatment was estimated to be more costly than conventional care by £8,349 and generated an additional 0.52 quality-adjusted life-years (QALYs). The difference in cost was mainly driven by adalimumab acquisition cost.

Table 3. Company-reported results of the base case analyses

Base case	Adalimumab	Conventional care	Difference	Plausibility?
Treatment acquisition	£12,228	£0	£12,228	Lack of long-term comparative data; Immediate loss of conventional therapy response observed at 12 weeks and continuous improvement in adalimumab responders?; Utilities were estimated using joint BASDAI and BASFI scores, and both instruments include elements for measuring physical functioning; Resource use data was derived from non-UK registry data[11] mapped to BASDAI scores
Initiation costs	£489	£0	£489	
Monitoring costs	£486	£0	£486	
AE costs	£59	£0	£59	
Other treatment costs	£105,962	£110,875	-£4,913	
Total cost	£119,224	£110,875	£8,349	
Total QALYs	9.58	9.06	0.52	
ICER	£16,154 per QALY gained			

AE: adverse event; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life-years

In probabilistic sensitivity analysis, adalimumab was more costly and more effective than conventional care in 100% of simulations. The probability of adalimumab having an incremental cost-effectiveness ratio (ICER) below £20,000 per QALY gained was 80% and below £30,000 per QALY gained was 100%.

The results of key one-way sensitivity and scenario analyses are summarised in Table 4. These indicate the model was most sensitive to the assumed treatment benefits over time, uncertainty in non-treatment cost estimates, the utility estimates and time-dependent discontinuation rate. In most cases the ICER remained below £20,000 per QALY gained. A scenario including both direct non-medical and indirect costs associated with SpA treatment (e.g. private household help, exercise sessions, physiotherapy and sick leave) showed adalimumab to be the dominant strategy compared to conventional care.

Table 4. Sensitivity and scenario analyses presented by the company

Scenarios	ICER (£/QALY gained)	Plausibility?
Equation used to estimate annual direct cost of treatment (base case: £835.68 × exp (0.2915 × BASDAI) Upper limit: £1095.65 × exp (0.3588×BASDAI) Lower limit: £637.40 × exp (0.2243×BASDAI)	 5,078 21,454	Goodness-of-fit data are not provided. Same limitations as in the base case.
Equation used to estimate utility using BASDAI & BASFI (base case: 0.992) Upper 95% limit Lower 95% limit	 22,488 12,604	Same limitations as in the base case.
Scenario: Utility equation based on trials-observed EQ-5D data	16,981	12-week EQ-5D utilities obtained from ABILITY-1 trial were not used directly in the base case analysis.
Scenario: Utility equation based on regression of BASDAI scores only against EQ-5D	18,398	Base case assumed worsening BASFI scores contribute to utility values; this analysis removes that assumption.
Scenario: Discontinuation rate based on week 12 to 68 data	17,839	No data on discontinuation beyond week 68. Same limitations as in the base case.
Scenario: Time horizon five years	20,755	The model is sensitive to assumed time horizon. Same limitations as in the base case.
Scenario: Conventional therapy responders keep response; discontinuation rate based on week 12–24 data; no BASFI progression for conventional therapy; no further improvement in BASDAI and BASFI for adalimumab recipients beyond 12 weeks	39,838	A conservative, worst case scenario
Scenario: No BASFI score increase over time for patients not on adalimumab	18,144	Still assumes BASFI score improvement continues over time for patients on adalimumab
Scenario: Indirect costs included	Adalimumab dominates	Resource use is based on non-UK data. Relevance for Wales unclear.
Supplementary scenario: 50% conventional therapy responders retain 12-week observed responses, and 50% lose response	27,996	Conventional therapy responders maintain some of the clinical response benefits over time, rather than all immediately losing response at 12 weeks as in base case.
BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index		

4.1.3 AWTTC critique

There is a lack of long-term efficacy and safety data of adalimumab for the potentially lifelong treatment of patients. The model projects results of the 12 week trial (plus 56 weeks of open-label study) over the 40 year time horizon, which is an inevitable source of uncertainty and presents potential for bias. The reliability of the estimates of discontinuation of adalimumab treatment over time, the BADSAI and BASFI-based utility estimates and the BASDAI based non-treatment costs is unclear. A range of

one-way sensitivity and scenario analyses suggest that the ICER remains less than £20,000 per QALY in most cases, based on these limited data, although these largely assume that conventional therapy responders immediately lose their observed 12 week benefit. A supplementary analysis provided by the company, in which some conventional therapy responders maintain over time the benefit observed at 12 weeks, generates an ICER mid-way between the base case and the worst case scenario.

Strengths of the economic evidence include:

- Cost-utility analysis is based on available direct comparative effectiveness data.
- The company conducted a range of sensitivity and scenario analyses to test key assumptions.

Limitations of the economic evidence include:

- The model relies on short term comparative data to model potentially life-long treatment outcomes, which is an inevitable source of uncertainty. The base case model assumes that continued adalimumab treatment continues to improve BASFI scores, whereas conventional therapy responders at 12 weeks immediately lose their response benefits at 12 weeks, with BASFI scores immediately deteriorating from baseline values. Scenario analyses demonstrate the model is sensitive to these assumptions.
- There are no data available to inform on whether adalimumab treatment impacts on progression of nr-axSpA to ankylosing spondylitis. The cost-effectiveness of the early use of adalimumab in nr-axSpA that progresses to ankylosing spondylitis compared with use only in ankylosing spondylitis is therefore not reflected.
- The model is reliant on associations between BASDAI/BASFI scores and costs and utility weights; however, the company acknowledges that BASDAI may not capture the extra-articular effects and costs of nr-axSpA.
- Utility values used in the base case analysis were estimated by using joint BASDAI and BASFI scores, although both instruments include domains measuring elements of physical functioning, and progression of BASFI may contribute to the BASDAI scores. Limiting the utility estimates to a function of only BASDAI increases the ICER marginally to £18,398 per QALY. EQ-5D data collected in the trial were not used in the base case analysis directly, as they were collected only in the 12-week randomised phase.
- Resource use data were derived from non-UK registry data for ankylosing spondylitis, mapped to BASDAI scores. It is not clear whether this reflects expected resource use associated with current treatment of spondyloarthritis in Wales.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of adalimumab in patients with severe nr-axSpA who have failed treatment with conventional therapy.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on published studies and Welsh population statistics, the company estimated that there are 692,949 (28.5%) adults with lower back pain in Wales[1]. Of these, 391,516 (56.5%) are expected to consult their GP and 26,427 (7%) to have inflammatory back pain and be referred to a rheumatologist. It is anticipated that 3,832 (29%) of these patients will meet ASAS criteria for axial SpA. The number of people who meet the ASAS criteria for axial SpA without radiographic evidence of SpA is

expected to be 1,150 (30%). The number of nr-axSpA patients who are likely to have a positive MRI scan result and/or raised CRP is assumed to be 885. Of these, 35% are likely to have severe active disease (BASDAI score ≥ 4) and have failed with or been intolerant to NSAIDs. Combining these assumptions, the company estimated 310 patients with nr-axSpA in Wales to be eligible for adalimumab treatment within the licensed indication covered by this submission. Given the lack of data on the incidence of nr-axSpA in Wales, the company assumed a 10% incidence rate, which results in 31 new cases each year. The mortality rate was assumed to be the same as in the general population. In the absence of alternative licensed treatments for this patient group, the company anticipates market uptake for adalimumab to be 100% starting from year one upon introduction.

5.1.2 Results of company budget impact analysis

The analysis assumes that patients who receive adalimumab would be assessed for treatment response after 12 weeks and 59.4% of them will not achieve ASAS40 criteria (and therefore discontinue). The estimated numbers of patients and the associated costs are summarised in Table 5.

Table 5. Company-reported costs associated with use of adalimumab

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	340	371	401	432	462
Uptake (%)	100%	100%	100%	100%	100%
Treated patients (minus non responders who discontinue at week 12)	340	170	183	196	209
Initiation, administration and monitoring costs	£261,921	£47,916	£100,218	£106,741	£113,264
Drug costs	£1,734,994	£1,478,636	£1,551,881	£1,670,904	£1,789,928
Staffing, Infrastructure, Personal social services costs	-£159,245	-£153,345	-£114,560	-£91,608	-£77,148
Overall net cost	£1,837,670	£1,373,207	£1,537,538	£1,686,037	£1,826,043

The company conducted a scenario analysis based on an alternative source of the estimated prevalence of nr-axSpA among people with inflammatory back pain. Assuming that the number of patients who meet the ASAS criteria for axial SpA to be 67% (base case 29%), of which 41% are assumed to meet the ASAS criteria for axial SpA without radiographic evidence (base case 30%), the estimated number of patients eligible for treatment with adalimumab in Wales would be 1,075 in year one rising to 1,459 in year five. The estimated overall net cost of treatment in this case would be £5,779,191; £4,295,146; £4,794,605; £5,243,725 and £5,665,933 in years one to five, respectively.

5.1.3 AWTTC critique of the budget impact analysis

- Due to the lack of epidemiological data for nr-axSpA in Wales, the estimation of the number of patients eligible for treatment with adalimumab is based on assumptions and data drawn from published studies. The scenario analysis

provided by the company estimates significantly greater numbers of eligible patients and, hence, significantly greater budget impact estimates.
- Since estimations of treatment costs are based on the cost-effectiveness model, the limitations of this model equally apply to the budget impact analysis (e.g. resource use, administration costs).
- A 100% uptake rate was assumed starting from year one, which may overestimate initial uptake.
- Collectively, the company's estimates of budget impact appear subject to considerable uncertainty.

5.2. Comparative unit costs

Currently adalimumab is the only licensed treatment of patients with severe SpA who have failed treatment with conventional therapy. Adalimumab 40 mg/0.8 ml solution for injection in pre-filled syringe or pre-filled pen, administered on alternate weeks, costs £9,156 per patient per year[2,12].

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, adalimumab (Humira®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration. The company have indicated that this medicine may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 11 and 15 January 2013
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Assessment of SpondyloArthritis international Society (ASAS) criteria for classification of axial spondyloarthritis (SpA)
The ASAS classification criteria for axial SpA apply to patients with ≥ three months chronic back pain and who, at age of onset, are aged < 45 years. Patients either have sacroiliitis on imaging plus one or more SpA feature, or alternatively, patients may present with HLA-B27 plus ≥ two SpA features[6].

ASAS40
This is defined as a ≥ 40% improvement and an absolute improvement from baseline of ≥ 20 units (range 0–100) in ≥ three of the following four domains: Patient Global Assessment of Disease activity (0–10 cm visual analogue scale [VAS]), pain (total back pain, 0–10 cm VAS, function (Bath Ankylosing Spondylitis Functional Index [BASFI], 0–10 cm VAS) and inflammation/morning stiffness (mean score of items five and six of the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], 0–10 cm VAS)[3].

ASAS20
This is defined as an improvement of ≥ 20% and absolute improvement of ≥ 10 units from baseline in ≥ three of the four domains identified in ASAS40, with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 10 units)[3].

BASDAI 50
This is defined as a 50% improvement from baseline in BASDAI using six VAS-scales, which score fatigue, spinal pain, peripheral arthritis, enthesitis, intensity and duration of morning stiffness. The mean of the two last items is calculated, and added to the mean of questions 1-4. The result is divided by five[3].

Short Form-36 questionnaire version 2 (SF-36v2)
An instrument designed to assess health status consisting of eight sub-domains: physical function, role-physical, bodily pain, general health, energy/fatigue, social function, role-emotional and mental health[1].

ASAS partial remission
This is defined as an absolute score of < 20 units for each of the four domains identified in ASAS40[3].

ASAS5/6 response
This is defined as a 20% improvement in five out of the following six domains: BASFI, total back pain, PTGA-Disease Activity, inflammation (represented by questions five and six of the BASDAI), lateral lumbar flexion from Bath Ankylosing Spondylitis Metrology Index (BASMI), and acute phase reactant (pooled CRP)[3].

Health Assessment Questionnaire modified for spondyloarthropathies (HAQ-S)
This is a questionnaire designed to assess the physical functional status using items from the Disability Index of the Health Assessment Questionnaire (HAQ). An additional five questions specific to those persons with spondylitis were added and addressed dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores[13]. A mean change in HAQ-S was reported as a secondary endpoint in the ABILITY-1 study[1,3,5].

Spondyloarthritis research consortium of canada (SPARCC) MRI score
This MRI method scores 6 images, which are divided into quadrants. Additional scores are given for depth and intensity[14]. A mean change in SPARCC MRI score for sacrolitic joints and the spine were reported as secondary endpoints in the ABILITY-1 study[1,3,5].

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