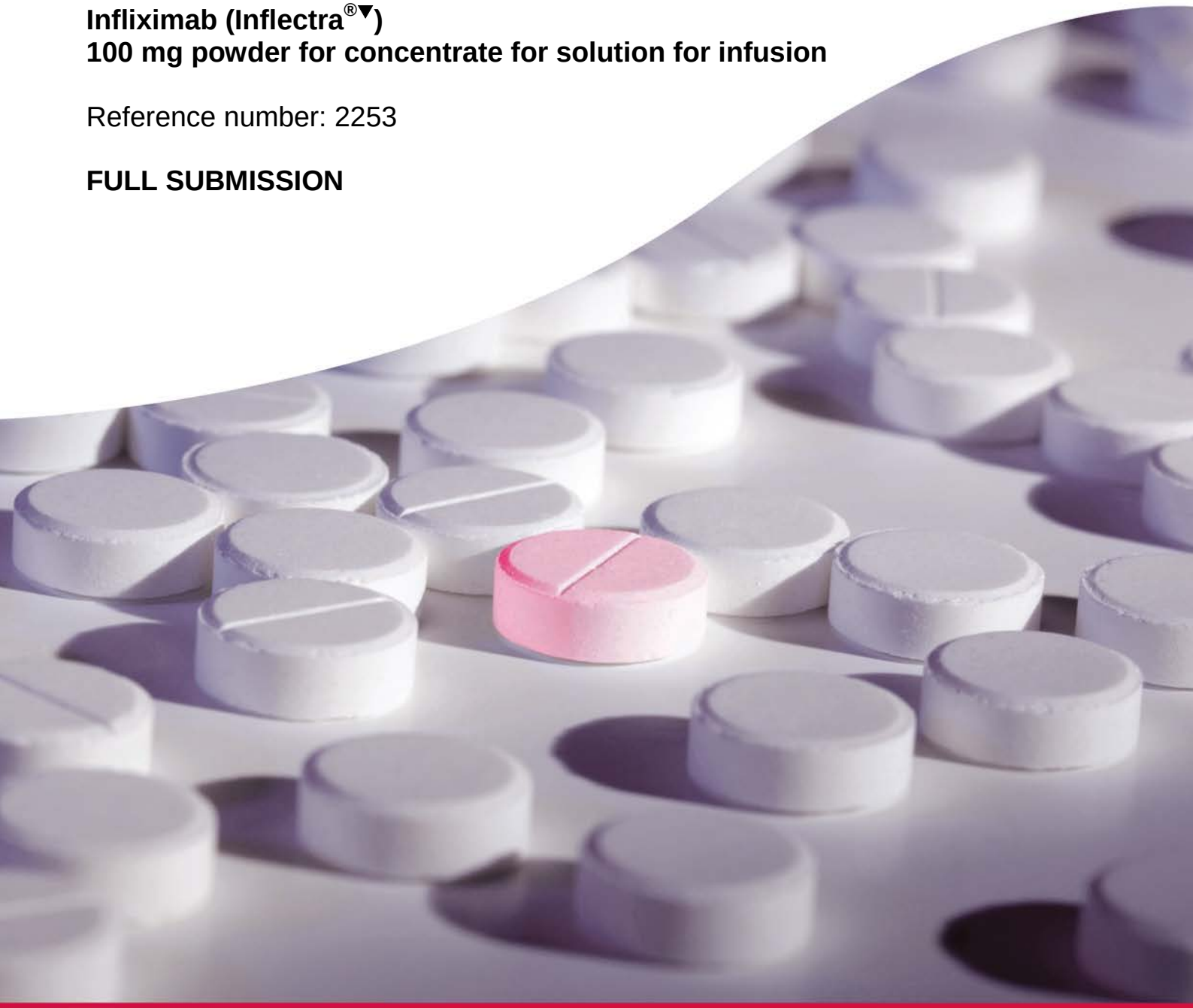
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Infliximab (Inflectra®▼)
100 mg powder for concentrate for solution for infusion

Reference number: 2253

FULL SUBMISSION



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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Infliximab (Inflectra®▼) 100 mg powder for concentrate for solution for infusion Reference number: 2253. November 2014.

AWMSG Secretariat Assessment Report
Infliximab (Inflectra®▼) 100 mg powder for concentrate for solution for infusion

This assessment report is based on evidence submitted by Hospira UK Ltd on 22 July 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Infliximab (Inflectra®▼) is indicated for the treatment of: • Rheumatoid arthritis • Adult Crohn's disease • Paediatric Crohn's disease • Ulcerative colitis • Paediatric ulcerative colitis • Ankylosing spondylitis • Psoriatic arthritis • Psoriasis Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2].
Dosing	For dosing of infliximab (Inflectra®▼) refer to the SPC[2].
Marketing authorisation date	10 September 2013[3]
Anticipated UK launch date	February 2015[1]

2.0 DECISION CONTEXT

2.1 Background

Autoimmune disorders cover a broad group of disorders in which the host immune system is activated and driven by endogenous components. Autoimmune disorders can affect patients of all ages but generally begin from the age of 20 with a peak at 30 to 60 years old. Many instances of autoimmune disorder are more common in females but this does vary between diseases[4].

Clinical problems associated with chronic inflammatory autoimmune disorders can be mediated by the activity of the cytokine tumour necrosis factor alpha (TNFα). Although TNFα activity promotes beneficial inflammation response and protective immune response against injury or infectious pathogens, sustained or excessive activity has been identified in several chronic inflammatory autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis (AS), psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis[3,5]. Inflammatory response is coordinated by the action of TNFα binding to receptors; medicines that inhibit this process are used for the treatment of such disorders[4].

The biological medicine infliximab (Remicade®) is a chimeric human-murine monoclonal antibody (mAb) that binds with both soluble and transmembrane forms of TNFα, preventing TNFα receptor activation[6]. Inflectra®▼ is a European Medicines

Agency (EMA) approved biosimilar medicine of infliximab (Remicade®)[1,3]. A biosimilar medicine is a biological medicine developed to be similar to an existing biological medicine (the reference medicine). The active substance of the biosimilar and its reference medicine is essentially the same substance, though due to the complex nature and production of the product there may be minor differences[7].

The licensed therapeutic indications, dosing regimen, pharmaceutical form and strength of Inflectra®▼ are the same as those of Remicade®[3].

The company submission focuses on the licensed indications for which infliximab (Remicade®) is currently approved for NHS prescribing in Wales i.e. rheumatoid arthritis[8], severely active Crohn's disease[9], adult ulcerative colitis[10], psoriatic arthritis[11] and very severe psoriasis[12]. Infliximab (Remicade®) is not approved for prescribing in Wales for: the treatment of paediatric ulcerative colitis[13], AS[14], subacute manifestations of moderately to severely active ulcerative colitis[15], moderately active Crohn's disease.[16] or moderate plaque psoriasis[12].

2.2 Comparator

The comparator included in the company submission is (Remicade®), the reference medicine for Inflectra®▼ [1,3].

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Clinical Guideline (CG) 79. Rheumatoid arthritis: The management of rheumatoid arthritis in adults (2013)[17].
- National Institute for Health and Care Excellence (NICE). CG 166. Ulcerative colitis: Management in adults, children and young people (2013)[18]
- NICE Technology Appraisal (TA) 199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (2010)[11].
- NICE. TA 195. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (2010)[19].
- NICE TA 187. Infliximab (review) and adalimumab for the treatment of Crohn's disease (2010)[9].
- NICE TA 163. Infliximab for acute exacerbations of ulcerative colitis (2008)[10].
- NICE TA 143. Adalimumab, etanercept and infliximab for ankylosing spondylitis (2008)[14].
- NICE TA 140. Infliximab for subacute manifestations of ulcerative colitis (2008)[15].
- NICE TA 134. Infliximab for the treatment of adults with psoriasis (2008)[12].
- NICE TA 130. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (2007)[8].

The All Wales Medicines Strategy Group (AWMSG) has previously issued Statements of Advice for the use of infliximab (Remicade®), not endorsing use within NHS Wales for the treatment of moderately active Crohn's disease and the treatment of severely active ulcerative colitis in children and adolescents[16,20]. A further biosimilar version of infliximab (Remsima®▼) is being appraised by the All Wales Medicines Strategy Group (AWMSG) concurrently[21].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included two pivotal studies to demonstrate biosimilarity between CT-P13 (subsequently marketed as Inflectra®▼ by Hospira UK Ltd) and Remicade®: a comparative pharmacokinetic (PK) study in patients with AS (CT-P13 1.1) and a comparative efficacy and safety study in patients with active rheumatoid arthritis (CT-P13 3.1)[1]. The pivotal studies are described in more detail below.

Supportive evidence was also provided by a small randomised, double-blind, parallel-group phase I pilot study. Nineteen patients with active rheumatoid arthritis were randomised; results showed that values of C_{max} were comparable between the CT-P13 and Remicade® arms[3].

An independent systematic review and meta-analysis was provided by the company comparing the efficacy and safety of CT-P13 with other biological medications including Remicade® in the treatment of rheumatoid arthritis. The results of the review and analysis showed no significant difference in efficacy or safety between CT-P13 and Remicade®[22].

3.1 Pivotal pharmacokinetic study CT-P13 1.1 (PLANETAS)

This was a randomised, double-blind, multicentre, parallel-group phase I study comparing the PK, safety and efficacy of CT-P13 and Remicade® in patients with active AS[23]. Patients were randomised to receive 5 mg/kg of CT-P13 (n = 125) or 5 mg/kg Remicade® (n = 125) at weeks 0, 2, 6 and then every 8 weeks up to week 54. Clinical assessment and blood sampling was undertaken at baseline, weeks 14 and 30. The primary endpoint was to demonstrate PK equivalence at steady state (ss) assessing area under the concentration curve [AUC] and $C_{max,ss}$ between weeks 22 and 30 (doses five and six). Secondary endpoints included additional PK, efficacy, immunogenicity and safety parameters[23].

Results of the primary PK analysis showed that the 90% confidence intervals (CIs) of the ratios of geometric means for both AUC (104.10 [90% CI 93.93–115.36]) and $C_{max,ss}$ (101.47 [90% CI 94.57–108.86]) were within the reference range of 80–125%. This indicates that the PK profile of infliximab is equivalent after administration of CT-P13 and Remicade®. The results of the secondary PK analysis were supportive of the primary endpoints[1]. The secondary endpoints for efficacy showed no significant difference in clinical response between treatment groups at weeks 14 and 30[23].

After week 54, a total of 174 patients who had completed CT-P13 1.1 continued on an open-label, 48 week extension to the study[24]. Eighty-eight patients were continuously treated on CT-P13 and 86 patients were switched from Remicade® to CT-P13. Results showed that comparable efficacy was maintained up to 102 weeks in both the maintained group and in patients switched from Remicade® to CT-P13[24].

3.2 Pivotal efficacy and safety study CT-P13 3.1 (PLANETRA)

This was a randomised, double-blind, multicentre, parallel-group phase III study which was designed to demonstrate the efficacy and safety of CT-P13 compared with Remicade® (both co-administered with methotrexate) in patients with active rheumatoid arthritis[25]. Patients were randomised to receive either CT-P13 (n = 302) 3 mg/kg or Remicade® (n = 304) 3 mg/kg at weeks 0, 2, 6 and thereafter every 8 weeks up to 54 weeks. The primary endpoint was the proportion of patients achieving clinical response in accordance to the American College of Rheumatology definition of a 20% improvement (ACR20) at week 30. Secondary endpoints included additional efficacy and safety parameters and PK and immunogenicity data[25].

Results of the primary efficacy analysis showed the proportion of ACR20 responders at 30 weeks were similar in the CT-P13 and Remicade® arms (60.9% and 58.6% of patients, respectively [95% CI −0.06 to 0.10]). The 95% CI was contained within the range −0.15 to +0.15, which indicated therapeutic equivalence between the treatment arms[3]. In accordance with the primary endpoint, secondary efficacy endpoints showed no significant difference in responses between the treatment arms[25].

After week 54, a total of 302 of 455 patients who completed scheduled visits in study CT-P13 3.1 were entered into an open-label extension study for an additional 48 weeks. Of these patients, 158 were maintained on CT-P13 and 144 switched from

Remicade® to CT-P13. Efficacy assessments included ACR20/50/70 response rates and were monitored at weeks 54, 78 and 102. Results demonstrated efficacy of CT-P13 in patients with active rheumatoid arthritis over two years, and showed comparable efficacy between the maintenance group and the switch group for the duration of the extension study[26].

3.3 Safety

Safety data were pooled from studies CT-P13 1.1, CT-P13 1.2 and CT-P13 3.1 to include a total of 871 patients, 455 in the rheumatoid arthritis trial and 210 patients in the AS trial. Safety data at week 54 of each study were included on request to the Committee for Medicinal Products for Human Use (CHMP); consequently all patients had completed the comparative treatment phase of the studies and received treatment for one year[3].

From the pooled data the type and incidence of treatment-emergent adverse events (TEAEs) of CT-P13 and Remicade® reported in the studies appeared similar and were in line with those expected on the basis of the Remicade® SPC. The most common TEAEs were infections (including latent or active tuberculosis and nasopharyngitis), increase in liver enzymes, infusion-related reactions, hypertension and headache[3].

3.2 AWTTC critique

- The pivotal study CT-P13 1.1 (PLANETAS) was conducted in AS patients; use of infliximab in this indication is not recommended by NICE[14]. However, the CHMP guideline on biosimilar mAbs states that extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of pharmacokinetic and therapeutic equivalence[27]. CHMP concluded that, on the basis of the comparisons of physicochemical and biological analyses, Inflectra®▼ was considered biosimilar to Remicade®[3].
- An imbalance in numbers of patients with serious infections, including tuberculosis reported in study CT-P13 3.1 (PLANETRA), was considered to be a chance finding. Serious infections will be monitored in the longer term and in a larger patient population as part of the risk management plan[3].
- Quality of life was measured as a secondary end point in both pivotal studies using the Medical Outcomes Study Short Term Health Survey Questionnaire (SF-36). In both studies the mean increases in SF-36 scores from baseline to week 30 were similar in the CT-P13 and Remicade® treatment arms[1,23,25].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission presents cost minimisation analyses (CMAs) of Inflectra®▼ within the licensed indications for which positive NICE/AWMSG guidance exists for the reference product Remicade®[1].

The company has adopted a CMA approach on the basis that CHMP concluded Inflectra®▼ is biosimilar to the reference product, and has demonstrated pharmacokinetic and therapeutic equivalence in patients with AS and rheumatoid arthritis, respectively. These data were considered sufficient to allow extrapolation to all other therapeutic indications approved for the reference product[3].

As the pharmaceutical form, strength and dosing regimen for each licensed indication are identical for Inflectra®▼ and Remicade®, only the drug acquisition costs are considered in the analyses.

The company has stated it will provide Inflectra®▼ at a cost of £377.66 per 100 mg vial, which is 10% lower than the current British National Formulary list price for Remicade® (£419.62 per 100 mg vial)[28].

4.1.2 Results

The company estimates cost savings from the use of Inflectra®▼ instead of Remicade® in all licensed indications, as exemplified in Table 1.

Table 1. Company reported CMA results[1]

Indication	Example dose regimens[6]	Inflectra®▼ cost/patient*	Remicade® cost/patient*	Cost saving/ patient
Rheumatoid arthritis	3 mg/kg at 0, 2 and 6 weeks then every 8 weeks. 8 doses in year 1 and 6.5 doses per year thereafter	Yr 1: £9,064 Yr 2+: £7,364	Yr 1: £10,071 Yr 2+: £8,183	Yr 1: £1,007 Yr 2+: £818
Crohn's disease (Adult)	5 mg/kg at 0, 2 and 6 weeks then every 8 weeks. 8 doses in year 1 and 6.5 doses per year thereafter	Yr 1: £12,085 Yr 2+: £9,819	Yr 1: £13,428 Yr 2+: £10,910	Yr 1: £1,343 Yr 2+: £1,091
Crohn's disease (Paediatric)		Yr 1: £6,043 Yr 2+ £4,910	Yr 1: £6,714 Yr 2+: £5,455	Yr 1: £671 Yr 2+: £546
Ulcerative colitis (Adult)		Yr 1: £12,085 Yr 2+: £9,819	Yr 1: £13,428 Yr 2+: £10,910	Yr 1: £1,343 Yr 2+: £1,091
Psoriatic arthritis		Yr 1: £12,085 Yr 2+: £9,819	Yr 1: £13,428 Yr 2+: £10,910	Yr 1: £1,343 Yr 2+: £1,091
Plaque psoriasis		Yr 1: £12,085 Yr 2+: £9,819	Yr 1: £13,428 Yr 2+: £10,910	Yr 1: £1,343 Yr 2+: £1,091
*Assuming 70 kg adults and 40 kg paediatric patients, vial wastage occurs				

4.1.3 AWTTC critique

The CMA approach assumes equivalence in all domains of health outcomes. As there are no differences in dose requirements or presentations, Inflectra®▼ based on the company provided price, would be cost saving in all indications compared with Remicade® at its current list price.

Actual costs of infliximab may differ from list prices in different settings due to locally negotiated procurement discounts.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost-effectiveness analyses of Inflectra®▼ of relevance to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Prevalence estimates for rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriatic arthritis and plaque psoriasis have been obtained from a NICE biologic drugs commissioning guide for England, 2012[29].

Their incidence rates have been obtained from a range of sources. These estimates have been applied to Welsh population statistics, with the net number of patients incorporating simple weighted average population mortality rates[1,30]. The proportions of patients estimated to be eligible for biologic treatment is based on those reported in the NICE commissioning guide for England[29]. The company reports it has estimated current use of Remicade® based on interviews with UK clinicians, and anticipates that Inflectra®▼ will initially replace 10% of Remicade® use across the relevant indications, increasing to 50% over the following four years[1]. Cost estimates are based on the CMA discussed in Section 4.

5.1.2 Results

The company's net budget impact estimates for Wales in each of the next 5 years are presented in Table 2.

The company estimates cost savings of around £96,000 in year 1, rising to around £553,000 in year 5 following the introduction of Inflectra®▼.

The company has provided two alternative budget impact estimates. In the first, it is assumed that Inflectra®▼ will instead replace 20% of Remicade® prescribing in year 1, rising to 100% in year 5. As would be expected, the estimated costs savings are double those reported in the base case analysis.

In the second alternative estimate, the company notes that the total spend on infliximab in Wales in Q1/Q2 of 2012/13 was reported by the Welsh Analytical Prescribing Support Unit as £3,299,814[31]. Therefore, for the whole year it is assumed to have been £6,599,628. Assuming a 3% annual increase in infliximab prescribing and that Inflectra®▼ will replace 10% of Remicade® in year 1, rising to 50% in year 5, the company estimates cost savings of around £70,000 in year 1, rising to £394,000 in year 5[1].

Table 2. Company estimates of net cost implications[1]

	Year 1	Year 2	Year 3	Year 4	Year 5
Rheumatoid arthritis					
Patients eligible for biologic treatment	2,139	2,177	2,214	2,250	2,287
Number receiving Remicade® (13%)	278	283	288	293	297
Number prescribed Inflectra®▼ (10% rising to 50%)	28	57	86	117	149
Net costs	−£22,907	−£46,613	−£71,104	−£96,365	−£122,383
Adult Crohn's disease					
Patients eligible for biologic treatment	658	680	702	724	745
Number receiving Remicade® (51%)	335	347	358	369	380
Number prescribed Inflectra®▼ (10% rising to 50%)	34	69	107	148	190
Net costs	−£36,980	−£76,437	−£118,325	−£162,602	−£209,226
Paediatric Crohn's disease					
Patients eligible for biologic treatment	18	23	28	33	38
Number receiving Remicade® (51%)	9	12	14	17	20
Number prescribed Inflectra®▼ (10% rising to 50%)	1	2	4	7	10
Net costs	−£523	−£1,334	−£2,433	−£3,819	−£5,492
Adult ulcerative colitis					
Patients eligible for biologic treatment	30	32	35	38	41
Number receiving Remicade® (87%)	26	28	31	33	36
Number prescribed Inflectra®▼ (10% rising to 50%)	3	6	9	13	18
Net costs	−£2,876	−£6,305	−£10,276	−£14,781	−£19,810
Psoriatic arthritis					
Patients eligible for biologic treatment	380	380	379	378	378
Number receiving Remicade® (20%)	76	76	76	76	76
Number prescribed Inflectra®▼ (10% rising to 50%)	8	15	23	30	38
Net costs	−£8,321	−£16,612	−£24,875	−£33,111	−£41,319
Plaque psoriasis					
Patients eligible for biologic treatment	1,087	1,167	1,246	1,324	1,401
Number receiving Remicade® (20%)	217	233	249	265	280
Number prescribed Inflectra®▼ (10% rising to 50%)	22	47	75	106	140
Net costs	−£24,182	−£51,853	−£82,953	−£117,419	−£155,192
All relevant indications					
Number receiving Remicade®	942	979	1,016	1,052	1,088
Number prescribed Inflectra®▼ (10% rising to 50%)	94	196	305	421	544
Total Net costs	−£95,789	−£199,154	−£309,965	−£428,096	−£553,422

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of patients eligible for treatment in Wales; however, these estimates are based on extrapolation of estimates of eligible patient numbers in England and expert opinion on infliximab use. As such they are subject to uncertainty.
- The alternative budget impact estimate, based on actual use of Remicade® in Wales in 2012/13, may therefore be more plausible. This indicates that cost savings from the use of Inflectra®▼ may be lower than those estimated in the company's base case budget impact analysis.

- As in all budget impact analyses, estimates of uptake are subject to uncertainty. The company's anticipated uptake figures and associated cost savings do not account for entry to the market of another biosimilar infliximab (Remsima®▼[21]), which is being appraised by AWMSG concurrently.
- Collectively, the company's budget impact estimates are subject to uncertainty and may overestimate cost savings as a result of the introduction of Inflectra®▼; however, irrespective of the actual number of patients estimated to receive infliximab, the use of Inflectra®▼ would be anticipated to be cost saving compared with use of Remicade® at its current list price.

5.2 Comparative unit costs

Table 3 includes comparative acquisition costs for Remicade® and the biosimilar Inflectra®▼, based on BNF list price[32] and company information. Only the acquisition costs for the available presentations are provided (example dose regimens and cost differences are provided in Table 1, above).

Table 3. Comparative acquisition costs for Inflectra®▼and its reference product

Medicine	Dose	List price*
Inflectra®▼	100 mg vial	£377.66
Remicade®	100 mg vial	£419.62
*Price of Remicade® based on BNF list price as of 08/09/2014[33]. Inflectra®▼ price based on company information[1]		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, infliximab (Inflectra®▼) may be appropriate for prescribing within NHS Wales in line with Remicade® prescribing arrangements that health boards currently have in place.

The company do not anticipate that infliximab (Inflectra®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted one ongoing study that is likely to be available within 6–12 months[1]:

- CT-P13 3.2: An open-label, single-arm, extension study to demonstrate long-term efficacy and safety of Inflectra®▼ when co-administered with methotrexate in patients with rheumatoid arthritis who were treated with infliximab (Remicade® or CT-P13) in Study CT-P13 3.1[1,34].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 22 September 2014
Date range of evidence search: No date limits were applied to database searches.

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