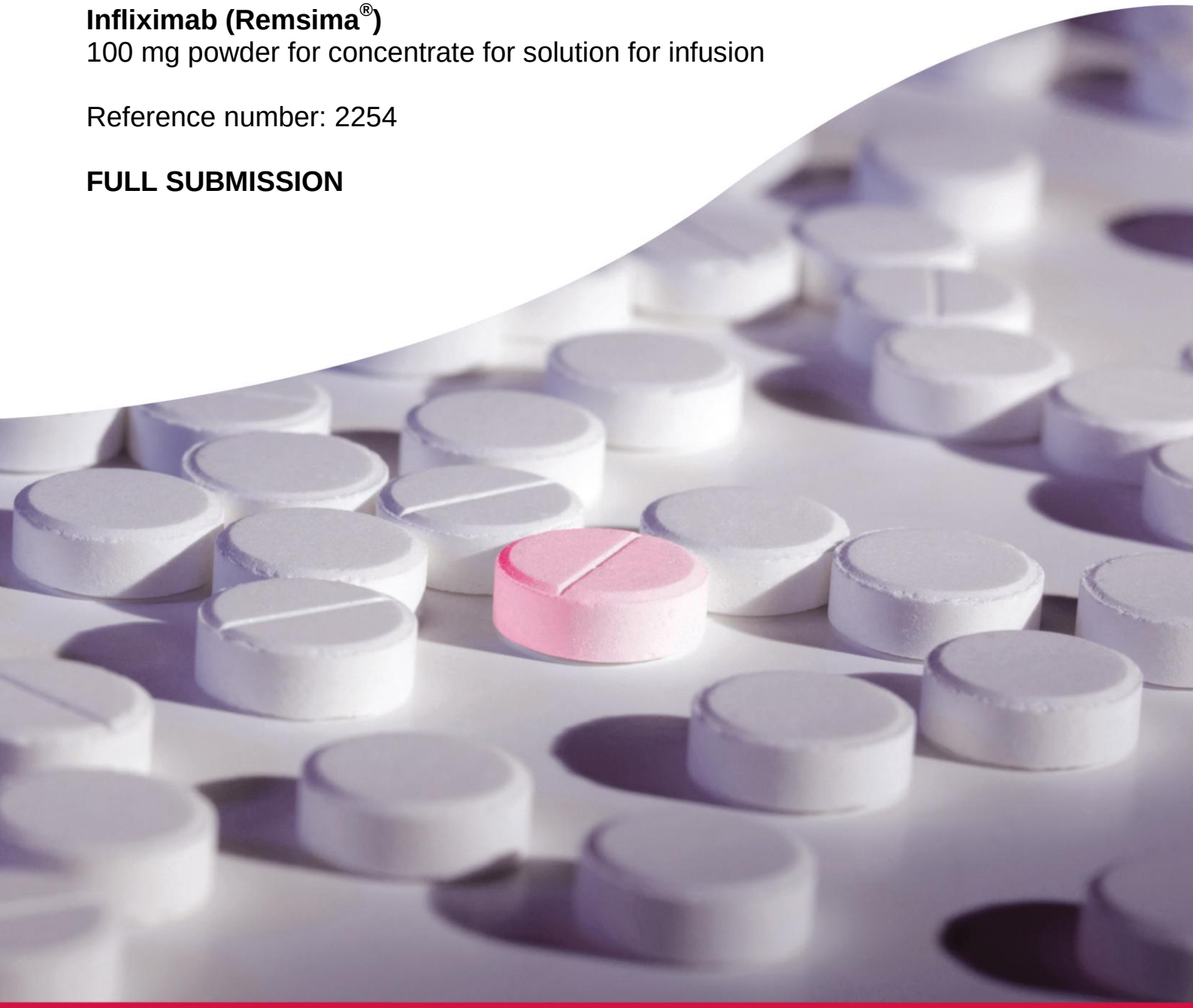
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Infliximab (Remsima®)
100 mg powder for concentrate for solution for infusion

Reference number: 2254

FULL SUBMISSION



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

This assessment report is based on evidence submitted by Napp Pharmaceuticals Ltd on 4 August 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Infliximab (Remsima®▼) 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 (Remsima®▼) 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[5,6]. 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[7]. Remsima®▼ is a European Medicines Agency (EMA) approved biosimilar medicine of infliximab (Remicade®)[1,5]. 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[8].

The licensed therapeutic indications, dosing regimen, pharmaceutical form and strength of Remsima®▼ are the same as those of Remicade®[5].

The company submission focuses on the licensed indications for which infliximab (Remicade®) is currently approved for NHS prescribing in Wales i.e. rheumatoid arthritis[9], severely active Crohn's disease[10], adult ulcerative colitis[11], psoriatic arthritis[12] and very severe psoriasis[13]. Infliximab (Remicade®) is not approved for prescribing in Wales for: the treatment of paediatric ulcerative colitis[14], AS[15], subacute manifestations of moderately to severely active ulcerative colitis[16], moderately active Crohn's disease[17], or moderate plaque psoriasis[13].

2.2 Comparator

The comparator included in the company submission is Remicade®, the reference medicine for Remsima®▼[1,5].

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)[18].
- NICE. CG 166. Ulcerative colitis: Management in adults, children and young people (2013)[19].
- NICE. Technology Appraisal (TA) 199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (2010)[12].
- NICE. TA 195. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (2010)[20].
- NICE. TA 187. Infliximab (review) and adalimumab for the treatment of Crohn's disease (2010)[10].
- NICE. TA 163. Infliximab for acute exacerbations of ulcerative colitis (2008)[11].
- NICE. TA 143. Adalimumab, etanercept and infliximab for ankylosing spondylitis (2008)[15].
- NICE. TA 140. Infliximab for subacute manifestations of ulcerative colitis (2008)[16].
- NICE. TA 134. Infliximab for the treatment of adults with psoriasis (2008)[13].
- NICE. TA 130. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (2007)[9].

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[14,17]. A further biosimilar version of infliximab (Inflectra®▼[21]) is being appraised by the All Wales Medicines Strategy Group (AWMSG) concurrently.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In their submission, the applicant company highlighted two trials that assessed and compared the pharmacokinetics, efficacy and tolerability of CT-P13 (subsequently marketed as Remsima®▼ by Napp Pharmaceuticals Ltd) with that of Remicade®. This included a comparative pharmacokinetic trial in patients with AS (PLANETAS) and a comparative efficacy and safety study in patients with active rheumatoid arthritis (PLANETRA)[1]. The PLANETAS study demonstrates that the pharmacokinetic profile of infliximab is equivalent after the administration of CT-P13 and Remicade®. The results

of the secondary pharmacokinetic analysis were supportive of the primary endpoints[22]. The applicant company consider the PLANETRA trial to be the more relevant to their submission[1].

3.1 PLANETRA (CT-P13 3.1)

This was a randomised, double-blind, multicentre, parallel-group phase III study to demonstrate the efficacy and safety of CT-P13 compared with Remicade® (both co-administered with methotrexate) in adult patients with active rheumatoid arthritis[1,5,23]. Patients were randomised to receive either CT-P13 (n = 302) 3 mg/kg or Remicade® (n = 304) 3 mg/kg at weeks 0, 2 and 6 and every eight weeks thereafter 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 pharmacokinetics and immunogenicity data[23].

Results of the primary efficacy analysis showed the proportion of ACR20 responders at week 30 were similar in the CT-P13 and Remicade® arms (60.9% and 58.6% of patients, respectively). The 95% confidence interval (CI) was contained within the range −0.15 to 0.15 (95% CI: −0.06 to 0.10), which indicated therapeutic equivalence between the treatment arms[5]. In accordance with the primary endpoint, secondary endpoints showed no significant difference in responses between the two treatment arms[23].

After week 54, a total of 302 of the 455 patients who completed scheduled visits in the PLANETRA study were entered into an open-label extension study for an additional 48 weeks. Of these patients, 158 continued to receive CT-P13 and 144 switched from Remicade® to CT-P13. Efficacy assessments included ACR20/50/70 response rates 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[24].

3.2 Safety

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) concluded that the treatment-emergent adverse events (TEAEs) pattern for CT-P13 observed in the clinical study were similar and appeared in line with the well-characterised safety profile of Remicade® as outlined in its Summary of Product Characteristics (SPC)[5,7].

In the PLANETRA study, the safety population included 301 patients in each treatment arm. Of these, 181 (60.1%) patients who received CT-P13 and 183 (60.8%) patients who received Remicade® reported TEAEs[1,23]. The most common TEAEs were infection (including latent or active tuberculosis and nasopharyngitis), increase in liver enzymes, infusion-related reactions, hypertension and headache[25].

3.3 AWTTC critique

- The PLANETAS trial was conducted in AS patients; use of infliximab in this indication is not recommended by NICE[15]. However, the CHMP guideline on biosimilar mAb 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[5,26]. CHMP concluded that, on the basis of the robust comparisons of the physicochemical and biological analyses, Remsima®▼ was considered biosimilar to the reference product, Remicade®[5].
- In the PLANETRA trial, a numerical imbalance in serious AEs was observed where there was a higher incidence of serious infections such as active

tuberculosis. After reviewing all the available data, CHMP concluded that the observed difference was most likely 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[5].

- Quality of life was measured as a secondary endpoint in both trials 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[5,22,23].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The applicant company submission presents cost minimisation analyses (CMAs) of Remsima®▼ within the licensed indications for which positive NICE/AWMSG guidance exists for the reference product Remicade®[1]. The analysis is based on 12 months of use in infliximab-naive patients who would otherwise receive Remicade®.

The applicant company has adopted a CMA approach on the basis that CHMP concluded Remsima®▼ is biosimilar to the reference product, and has demonstrated equivalence in clinical trials in patients with AS and rheumatoid arthritis. These data were considered sufficient to allow extrapolation to all other therapeutic indications approved for the reference product[5].

As the pharmaceutical form, strength and dosing regimen for each licensed indication are identical for Remsima®▼ and Remicade®, only the medicine acquisition costs are considered in the analyses, assuming average patient weight of 75 kg and vial sharing in the base case. The applicant company has stated that the price of Remsima®▼ agreed with the Department of Health is [commercial in confidence data removed]. The current British National Formulary (BNF) list price for Remicade® is £419.62 per 100 mg vial[27].

4.1.2 Results

The applicant company has provided estimates of cost savings from the use of Remsima®▼ instead of Remicade® in a range of licensed indications assuming Remicade® SPC-recommended doses[7] and vial sharing [commercial in confidence data removed] (Table 1).

Table 1. Company reported CMA results over 12 months[1]

Indication	Cost per patient per year: Remsima®▼*	Cost per patient per year: Remicade®*	Cost difference per patient per year*
Rheumatoid arthritis	-	£8,261.27	-
Psoriatic arthritis	-	£13,768.78	-
Psoriasis	-	£13,768.78	-
Crohn's disease	-	£13.768.78	-
Ulcerative colitis	-	£13,768.78	-
*Assuming 75 kg body weight and vial sharing occurs.			

4.1.3 AWTTC critique

The CMA approach assumes equivalence in all domains of health outcomes. The regulatory authority considered that pharmacokinetic and therapeutic equivalence had been demonstrated and that the claim for biosimilarity could be extrapolated to all licensed indications. As there are no differences in dose requirements or presentations, based on the lower list price of Remsima®▼ compared with Remicade®, Remsima®▼ would be cost saving in all indications compared with Remicade® at its current list price.

A further biosimilar biosimilar version of infliximab (Inflectra®▼[21]) is being appraised by AWMSG concurrently.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost effectiveness analyses of Remsima®▼ 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 and incidence rate estimates for rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriatic arthritis and psoriasis have been obtained from a range of sources and have been applied to Welsh population statistics. The applicant company assumes that only incident patients will be potentially eligible to receive Remsima®▼ and there will be no switching to Remsima®▼ in patients already treated with Remicade®. Based on the applicant company's market research data for prescribing of biologics in Wales 2012–14, and the estimates of patient numbers, the applicant company has estimated a total of 216 new patients receive biologics each year, of which, 29 will receive Remicade® across all relevant indications[1].

In its base case analysis, the applicant company anticipates the uptake of Remsima®▼ across all licensed indications to be 25% (approximately 8 patients) in year one, increasing to 71.4% (approximately 20 patients) in year five, assuming all market share will be taken from Remicade®.

Cost savings for each relevant indication have been estimated, reflecting the lower list price of Remsima®▼ compared with Remicade®. Vial sharing is assumed to occur in the base case analysis[1].

5.1.2 Results

The applicant company's net budget impact estimates for Wales in each of the next five years are presented in Table 2. Assuming vial sharing, the applicant company estimates cost savings, primarily due to use in Crohn's disease. [commercial in confidence data removed] The company suggests these are conservative estimates as cost savings would be greater if no vial sharing was assumed.

Table 2. [Removed due to commercial in confidence data]

5.1.3 AWTTC critique

- The applicant 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 several sources of prevalence and incidence estimates to the Welsh population and marrying these up with market research data on current prescribing. As such they are subject to uncertainty.
- As in all budget impact analyses, the applicant company's estimates of anticipated market share are subject to uncertainty. The applicant company's

anticipated uptake figures and associated cost savings do not account for entry to the market of another biosimilar infliximab, which is being appraised by AWMSG concurrently (Inflectra®▼[21]).

- The applicant company assumes use of Remsima®▼ only in incident cases, which may be a conservative assumption. Any switching to Remsima®▼ in patients currently treated with Remicade® could potentially increase cost savings (based on the current list price of Remicade®).
- Collectively, the applicant company's budget impact estimates are subject to uncertainty; however, irrespective of the actual number of patients estimated to receive infliximab and irrespective of assumptions on vial sharing, the use of Remsima®▼ would be anticipated to be cost saving compared with use of Remicade® at current list prices.

5.2 Comparative unit costs

[commercial in confidence data removed]

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, infliximab (Remsima®▼) 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 (Remsima®▼) will be supplied by a home healthcare provider.

6.2 AWMSG review

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

6.3 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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