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

AWMSG Secretariat Assessment Report – Limited submission

Adalimumab (Humira®) 40 mg solution for injection (pre-filled pen, pre-filled syringe and vial)

Company: AbbVie Ltd

Licensed indication under consideration:
Adalimumab (Humira®) for the treatment of moderately active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Date of licence extension: 11 May 2016 (licensed for the treatment of severely active Crohn's disease in the above population on 22 November 2012)

Comparator(s)

The comparator included in the company submission was off-label infliximab.

Limited submission details

The limited submission criteria were met based on:

- A minor licence extension (to include the treatment of moderately active Crohn's disease in paediatric patients from 6 years of age).
- Anticipated usage is considered to be of minimal budgetary impact.
- Estimated small difference in cost compared to comparator(s).

Clinical effectiveness

- Adalimumab (Humira®) was licensed for use in paediatric patients (from 6 years of age) with severely active Crohn's disease (CD) in 2012 and recommended as an option for this indication by AWMSG in 2013. At that time, the trials submitted to support marketing authorisation included both moderate and severe CD patients. However, adalimumab was not granted a licence for use in moderate CD because of the limited safety data available in paediatric patients and concerns about the long-term safety profile of adalimumab in these patients. Following the collection of additional long-term safety data, the licence has now been extended to include moderately active CD.
- As of August 2016, adalimumab is the only anti-TNF therapy licensed for this indication.
- The company submission included updated results from the trials used to support the licensing of adalimumab for severely active CD: a phase III multicentre, randomised, open-label induction followed by double-blind maintenance trial (IMAgINE 1) and a long-term, open-label extension study (IMAgINE 2). Eligible patients were 6–17 years old and had moderate to severe CD. IMAgINE 2 included patients who had successfully completed the IMAgINE 1 trial and demonstrated a clinical response to adalimumab. Due to the lack of licensed comparator and ethical concerns around the use of placebo, all patients in these trials received

adalimumab as either a high or low-dose regimen: dosage was dependant on patient weight and randomisation to either the low- or high-dose maintenance group.

- Across both IMAgINE 1 and 2, no new adverse drug reactions were identified in moderately active CD compared to severe disease. Treatment-emergent adverse events that were considered to be possibly drug related were seen in 63.4% (52/82) of patients in the moderate population. Serious adverse events considered as probably or possibly treatment-related were observed in 10 patients with either moderate or severe CD. Overall, the Committee for Medicinal Products for Human Use (CHMP) concluded that the pharmacology, efficacy and safety of adalimumab were comparable between moderate and severe CD in paediatric patients.

Budget impact

- The company estimated that 19 patients in Wales are eligible for adalimumab. This is based on the 0.025% NICE prevalence figure for CD in children applied to the Welsh population aged 6–17 years (416,054 in 2014 based on Welsh Government statistics), meaning 104 children are anticipated to have CD in Wales. It is assumed that 37% (38/104) of patients would have moderate disease and that of these patients, 50% would be deemed to have an inadequate response to conventional therapy.
- The recommended doses of adalimumab and infliximab are dependent on paediatric patients' weights. For infliximab, the company have calculated doses and costs based on the body weight distribution of UK paediatric CD patients from the UK Clinical Practice Research Datalink database. Adalimumab calculations have been based on all patients receiving the same adolescent dose (for patients weighing ≥ 40 kg) regardless of weight: an induction dose of 80 mg followed by 40 mg every other week. The recommended dose for patients weighing < 40 kg is an induction dose of 40 mg followed by 20 mg every other week. However, as each 40 mg vial/syringe/pen is single-use only, the impact of patient weight (and therefore adalimumab dose) on total medicine cost is negligible.
- The budget impact analysis is based on adalimumab displacing (off-label) infliximab. The company have assumed that all paediatric patients with moderate CD are currently receiving infliximab and anticipate 50% uptake (10/19 patients) of adalimumab in the first year, growing by 10% each year to reach 90% in year five (17/19 patients). Cost estimates for infliximab include medicine acquisition costs and infusion costs (£225.00 per infusion). The company anticipate that adalimumab would be administered at home, and therefore would have no associated infusion costs.
- The company have estimated the introduction of adalimumab will result in savings of £8,660 in year one, and will cost £6,403.36 in year two, rising to £9,172 in year five. This year-on-year cost variation is due largely to the infusion costs associated with infliximab, which are higher at the beginning of each patient's treatment.

Additional information

- 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 anticipate that adalimumab (Humira®) will be supplied by a home healthcare provider.

Evidence search

Date of evidence search: 4 August 2016
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Adalimumab (Humira®) 40 mg solution for injection (pre-filled pen, pre-filled syringe and vial). Reference number: 3118. August 2016.

Appendix: Previous AWMSG secretariat assessment report (published July 2013)

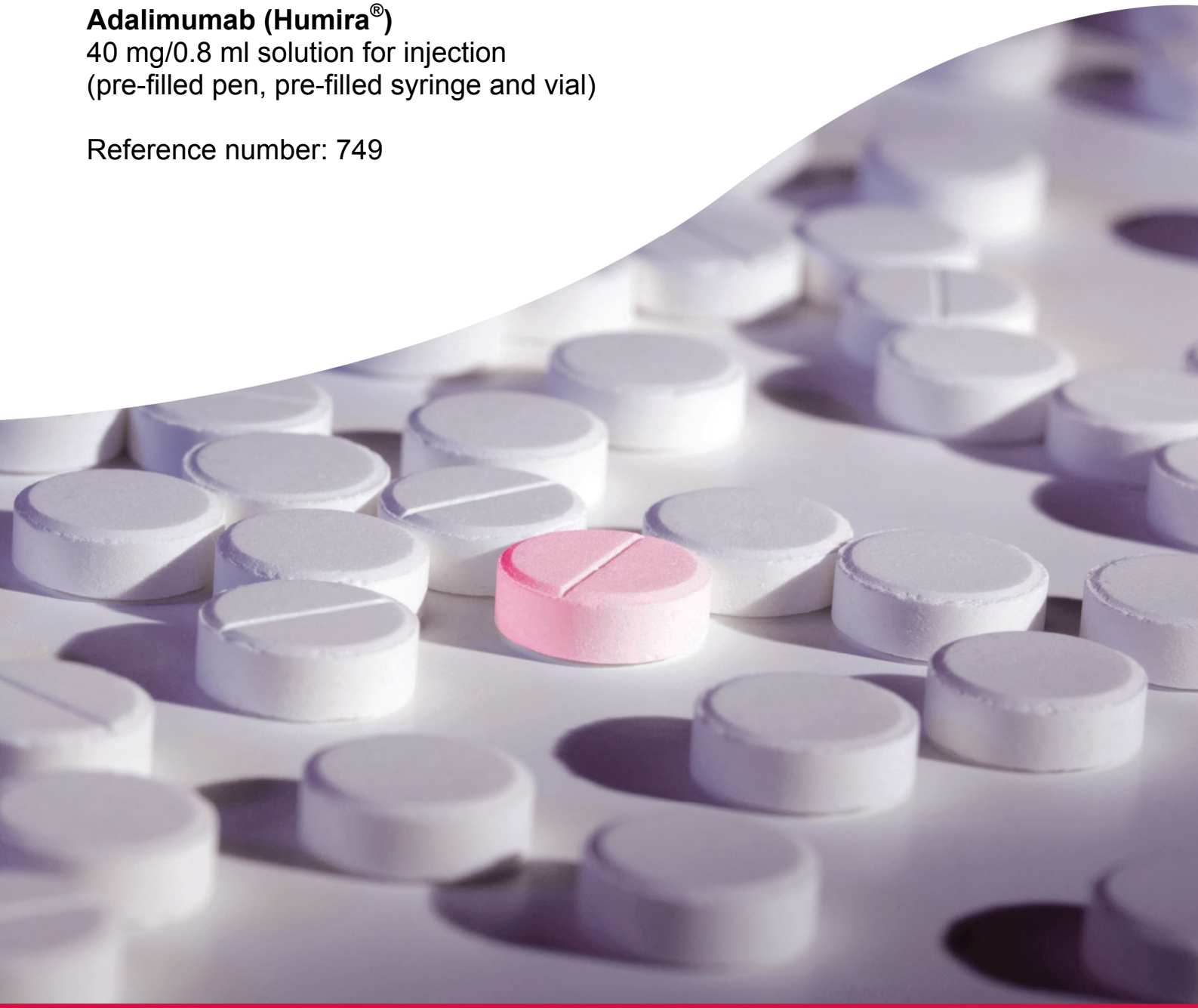
This report was published as part of a previous AWMSG appraisal of adalimumab (Humira®) (Advice number 2013). The advice from this appraisal has been superseded by advice number 3916. The original appraisal documentation is included here for completeness.

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

AWMSG SECRETARIAT ASSESSMENT REPORT

Adalimumab (Humira®)
40 mg/0.8 ml solution for injection
(pre-filled pen, pre-filled syringe and vial)

Reference number: 749



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Adalimumab (Humira®) 40 mg/0.8 ml solution for injection (pre-filled pen, pre-filled syringe and vial)

This assessment report is based on evidence from a limited submission by AbbVie Ltd on 30 January 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Adalimumab (Humira®) is indicated for the treatment of severe active Crohn's disease in paediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies[2].
Marketing authorisation date	22 November 2012 (previously licensed for the treatment of adult patients with moderately active Crohn's disease who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant on 23 August 2012)[3].
UK launch date	15 January 2013[1]
Comparators	The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was infliximab (Remicade®).
Limited submission details	Adalimumab (Humira®) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator(s).

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 IMAgINE 1

IMAgINE 1 (M06-806) was a randomised, multicentre, phase III trial that incorporated an open-label induction phase, followed by a double-blind maintenance phase of either high or low dose adalimumab[1,4]. Eligible patients (n = 192) were 6 to 17 years old with a diagnosis of moderate to severe Crohn's disease, defined as a paediatric Crohn's disease activity index (PCDAI)[5] score > 30, despite concurrent treatment with an oral corticosteroid and/or an immunomodulator, or who were intolerant to or had not responded to corticosteroid or immunomodulator therapy within the past two years. Patients that had previously received infliximab were eligible if they had experienced an initial response to infliximab (≥ 5 mg/kg), received at least two subsequent doses (≥ 5 mg/kg) and then discontinued due to loss of response or adverse event (AE). During the four-week induction phase of IMAgINE 1, patients ≥ 40 kg received 160 mg subcutaneous adalimumab at week 0 and 80 mg at week 2, whereas patients < 40 kg received 80 mg subcutaneous adalimumab at week 0 and 40 mg at week 2. At week 4, patients (n = 188) were randomised 1:1 to blinded high or low dose adalimumab and stratified according to their four-week clinical response (defined as a decrease in PCDAI score ≥ 15 from baseline) and prior exposure to infliximab. Patients randomised to high dose adalimumab (n = 93) were administered 40 mg or 20 mg every other week, depending on body weight (≥ 40 kg and < 40 kg, respectively); while the low dose group (n = 95) were administered 20 mg or 10 mg every other week, depending on body weight (≥ 40 kg and < 40 kg, respectively)[1,4].

The primary endpoint of clinical remission (defined as PCDAI score ≤ 10) at week 26 was met by 33.5% (63/188) patients overall, of which 38.7% (36/93) had received high dose adalimumab, compared with 28.4% (27/95) that had received low dose adalimumab; the difference between groups did not meet statistical significance (p = 0.075). Endpoints at week 26 and week 52, including subgroup analysis according to prior infliximab treatment, are reported in Table 1. Within the high dose group, which corresponds to the licensed dose of adalimumab for the indication under consideration, remission and response rates were significantly higher in the infliximab-naive patients compared with the infliximab-experienced patients (56.9% versus 16.7%; p = 0.001 for remission, and 68.6% versus 47.6%; p = 0.040 for response)[1,4].

Table 1. Results of IMAgINE 1 at week 26 and 52[1,4,6]

	Clinical remission (%)		Clinical response (%)	
	Week 26*	Week 52	Week 26	Week 52
Whole data set (n = 188)				
High dose (n = 93)	38.7	33.5	59.1	41.9
Low dose (n = 95)	28.4	23.2	48.4	28.4
p value	0.075	0.100	0.073	0.038
Infliximab-experienced patients (n = 83)				
High dose (n = 42)	16.7	19.0	47.6	26.2
Low dose (n = 41)	19.5	17.1	29.3	22.0
p value	0.736	0.815	0.086	0.652
Infliximab-naive patients (n = 105)				
High dose (n = 51)	56.9	45.1	68.6	54.9
Low dose (n = 54)	35.2	27.8	63.0	33.3
p value	0.026	0.065	0.541	0.026
* Primary endpoint				

Interim efficacy results from an ongoing open-label extension study (M06-807; n = 100) are supportive of those from IMAgINE 1[6].

2.2 Comparative safety

Safety results from IMAgINE 1 and the ongoing open-label extension study demonstrated that adalimumab is generally safe and well-tolerated for up to two years of treatment[4,6]. The most frequently reported AE deemed possibly or probably related to study drug was injection site reaction. The Committee for Medicinal Products for Human Use (CHMP) acknowledged that adalimumab has a well-characterised safety profile, and there were no new safety signals identified in the paediatric clinical development program submitted. No malignancies were observed in the studies presented[6]. In addition, no AEs related to demyelinating disease were reported from the studies[6]. Please refer to Section 2.3 for further safety information.

2.3 Points to note

- National Institute for Health and Care Excellence (NICE) technology appraisal (TA) 187 recommends infliximab, within its licensed indication, for the treatment of patients aged 6 to 17 years with severe active Crohn's disease[7,8]. Adalimumab was not licensed for this age group at the time TA187 was published.
- There are no head-to head studies that compare adalimumab and infliximab for the indication under consideration. Due to the heterogeneity in the study designs of the pivotal trials, an indirect comparison could not be performed. The inclusion of a placebo arm was deemed unethical for the IMAgINE1 study as infliximab is licensed for this severe condition[6,7]; therefore there are no common comparators between the trials to provide an estimate of the relative effectiveness[1].

- As there was no placebo arm in the IMAgINE 1 study, a primary external analysis was provided as part of the submission to the European Medicines Agency (EMA), which compared IMAgINE 1 with the pivotal adult study, M02-404. The results demonstrated that adalimumab was efficacious in the paediatric population. The proportion of paediatric patients in clinical remission at week 26 that had received high dose adalimumab in the IMAgINE 1 study exceeded that observed in adult patients in study M02-404 (46.77% versus 33.46%, respectively; difference: 13.31%; 95% confidence interval: 1.66–24.96)[6].
- Prior exposure to infliximab was high in the IMAgINE 1 study: overall, 44.1% of patients had received prior treatment with infliximab[1,4]. Although efficacy was attenuated in infliximab-experienced patients, CHMP stated that adalimumab offers an alternative for paediatric patients left with no other pharmacologic treatment options[6].
- The increased risk of some serious AEs with adalimumab (including infections, lymphoproliferative disorders or malignancies, and demyelination) are addressed in the Summary of Product Characteristics (SPC)[2]. The applicant company have committed to ongoing safety surveillance in children and adolescents, including those with malignancies, for up to five years, as specified in the current approved adalimumab Risk Management Plan[6]. Patients with moderate to severe disease were recruited to IMAgINE 1; however, due to the risk of malignancy and the expected longer treatment duration in paediatric patients, the licensed indication was restricted to those with severe active Crohn's disease[2,6].
- As part of the market authorisation, CHMP recommended that the induction dose used in IMAgINE 1 should be halved (80 mg and 40 mg at weeks 0 and 2 for patients ≥ 40 kg, and 40 mg and 20 mg at weeks 0 and 2 for those < 40 kg) as the exposure response is considered to be similar in adults and children. It was, however, acknowledged that patients with severe disease can in some situations benefit from a rapid response, and thus an option for a higher induction dose (160 mg and 80 mg at weeks 0 and 2 for patients ≥ 40 kg, or 80 mg and 40 mg at weeks 0 and 2 for those < 40 kg) was accepted. CHMP recognised that allowing for two options for induction provides the clinician with flexibility and allows for the optimisation of patient care. This approach is also consistent with the licensed dosing regimen for adult Crohn's disease[2,6].
- Adalimumab is administered via subcutaneous injection whereas infliximab is administered via intravenous infusion. After proper training in injection technique, patients may self-inject adalimumab, whereas infliximab infusions should be administered by qualified healthcare professionals[2,7].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

According to the company submission, based on data from NICE TA187 costing template, there are currently 17 patients in Wales with severe paediatric Crohn's disease that have had inadequate response to conventional therapy (primary nutrition therapy, corticosteroid and an immunomodulator) or are intolerant or have contraindications for such therapies, and may be considered for biologic therapy with either infliximab or adalimumab[1,8]. As infliximab is available for use in Wales for this patient group, the company expects most prevalent cases to be already treated with infliximab and a maximum of 50% of these patients could be treated with adalimumab.

The company estimates that the cost of adalimumab for patients ≥ 40 kg that require the high induction dose would be £10,564 in year one and £9,156 per year in subsequent years, while the costs for patients < 40 kg would be £9,508 and £9,156, respectively. No administration costs are assumed to be incurred.

Cost calculations for infliximab are based on a weighted average of the body weights of Crohns' disease patients aged 6-17 years, based on data from the General Practice Research Database (GPRD, now Clinical Practice Research Datalink [CPRD])[9]. Thus, infliximab acquisition cost is estimated to be £9,526 in year one and £7,740 in subsequent years. Taking into account the costs of administration by intravenous infusion, the total cost of using infliximab is estimated to be £11,326 in the first year and £9,540 in subsequent years.

3.2 AWTTC critique of the budget impact analysis

The incremental cost of using adalimumab is dependent on the distribution of patients' body weights. The company has provided cost estimates for infliximab based on the observed distribution of patient body weights taken from the GPRD, but has not provided the cost of adalimumab based on the same weights distribution. AWTTC analyses suggest a weighted average annual acquisition cost of adalimumab of £10,204 in year 1, and £9,156 in subsequent years, based on the GPRD-derived distributions.

The assumed doses of adalimumab relate to rapid induction and standard maintenance. The SPCs for adalimumab and infliximab, however, suggest alternative dose frequencies, or treatment discontinuation for patients who do not achieve sufficient response[2,7]. No data were provided to determine the proportion of patients requiring alternative dose frequencies.

The company assumed that adalimumab would incur no administration or monitoring costs as it would be provided via a homecare service for all patients.

The company's estimated uptake of adalimumab (50%) is based on supposition. However, based on the figures provided, the company does not anticipate that the use of adalimumab instead of infliximab would increase costs to NHS Wales.

3.3 Comparative unit costs

Table 2. Examples of acquisition costs for TNF-alpha inhibitors licensed for use in severe active paediatric Crohn's disease

Drug	Example dose (6–17 years)*		Example annual cost of treatment per patient†
Adalimumab (Humira®) 40 mg solution for injection (pre-filled pen, pre-filled syringe and vial)	≥ 40kg	Initially 80 mg by subcutaneous injection followed by 40 mg by subcutaneous injection every two weeks. Increase to max 40 mg by subcutaneous injection once weekly if necessary. Reassess if no response within 12 weeks. Rapid induction: see SPC[2].	First year: £9,860 Subsequent years: £9,156
	< 40kg	Initially 40 mg by subcutaneous injection followed by 20 mg by subcutaneous injection every two weeks. Increase to max 20 mg by subcutaneous injection once weekly if necessary.	First year: £9,508 Subsequent years: £9,156
Infliximab (Remicade®) 100 mg powder for concentrate for solution for infusion	5 mg/kg by intravenous infusion over two hours, repeated two weeks and six weeks after first infusion, then usually every eight weeks. Discontinue if no response after ten weeks.		First year: £6,714§ Subsequent year: £5,875

* Doses need to be individually tailored, based on patient body weight
† Costs are based on MIMS list prices as of 29 March 2013 and are calculated assuming the use of standard induction and standard maintenance regimens for both adalimumab and infliximab; costs will differ based on response[10].
§ Infliximab cost uses 40 kg as the average body weight of a paediatric Crohn's disease patient[8] . Note that costs of infliximab administration by IV infusion are excluded.
See SPCs for licensed indications and full dosing details[2,7]

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

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 anticipate that adalimumab (Humira®) will be supplied by a home healthcare provider.

4.2 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).

4.3 Evidence search

Date of evidence search: 5 April 2013
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

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