

## 6.1 ADALIMUMAB

**20 mg/0.4 ml injection, 2 x 0.4 ml syringes,  
40 mg/0.8 ml injection, 2 x 0.8 ml cartridges,  
40 mg/0.8 ml injection, 2 x 0.8 ml syringes,  
40 mg/0.8 ml injection, 6 x 0.8 ml cartridges,  
40 mg/0.8 ml injection, 6 x 0.8 ml syringes;  
Humira®; AbbVie Pty Ltd.**

### 1 Purpose of Application

- 1.1 The submission proposed the inclusion on the Pharmaceutical Benefits Scheme (Section 85, Authority Required) of adalimumab for treatment of severe refractory Crohn's disease in paediatric patients aged 6 to 17 years.

### 2 Requested listing

- 2.1 Presented below is the abridged proposed restriction. The restriction will need to be finalised in consultation with the sponsor, the Department of Human Services and the Restrictions Working Group.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer			
ADALIMUMAB, INITIAL TREATMENT, BODY WEIGHT < 40 KG 40 MG IN 0.8 ML INJECTION, 2 X 0.8 ML SYRINGE 40 MG IN 0.8 ML INJECTION, 2 X 0.8 ML CARTRIDGE 20 MG IN 0.4 ML INJECTION, 2 X 0.4 ML SYRINGE	1 1 1	0 0 3	Humira®	AbbVie Pty Ltd		
ADALIMUMAB, INITIAL TREATMENT, BODY WEIGHT ≥ 40 KG 40 MG IN 0.8 ML INJECTION, 6 X 0.8 ML SYRINGE 40 MG IN 0.8 ML INJECTION, 6 X 0.8 ML CARTRIDGE 40 MG IN 0.8 ML INJECTION, 2 X 0.8 ML SYRINGE 40 MG IN 0.8 ML INJECTION, 2 X 0.8 ML CARTRIDGE	1 1 1 1	0 0 2 2				
Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts			Proprietary Name and Manufacturer	
ADALIMUMAB, CONTINUING TREATMENT, BODY WEIGHT < 40 KG 20 mg in 0.4 mL injection, 2 x 0.4 mL syringe	1	5			Humira®	AbbVie Pty Ltd
ADALIMUMAB, CONTINUING TREATMENT, BODY WEIGHT ≥ 40 KG 40 mg in 0.8 mL injection, 2 x 0.8 mL syringe 40 mg in 0.8 mL injection, 2 x 0.8 mL cartridge	1 1	5 5				

- 2.2 The use of Paediatric Crohn's Disease Activity Index (PCDAI) for determining an inadequate response to conventional therapies or losing response to infliximab seems appropriate and was used by the PBAC for determining the eligibility of infliximab Crohn's disease treatment in the paediatric population. The definition used

in the clinical trial is slightly different and less stringent (at least a 15 point reduction in PCDAI) than that in the proposed listing. Further the response criteria defined in the PBS listing for infliximab is a 15 point reduction and a total score of no more than 30 points (PCDAI score). This may result in higher continuation rates for adalimumab compared with infliximab, due to the higher total score of no more than 40 points in the response definition for adalimumab.

- 2.3 The submission considered that the requested restriction is similar to that of infliximab in moderate to severe paediatric Crohn's disease, except for the following differences:
- The requested adalimumab listing is for severe patients only (PCDAI >40), while infliximab has a listing for moderate to severe Crohn's disease (PCDAI >30);
  - The 40 mg formulation is to be used as maintenance therapy in patients weighing 40 kg or more, while 20 mg is to be used as maintenance therapy in patients weighing less than 40 kg; and
  - General Schedule rather than Section 100 listing;
  - Second and subsequent continuing treatment authorities to be telephone authority items.
- 2.4 The Secretariat comments in the commentary suggested one written-only continuing restriction (as opposed to an initial continuing and a second and subsequent telephone authority continuing restriction) for consistency with the Crohn's disease in adults listing and on the basis that there does not appear to be any difference between the criteria.
- 2.5 Under its proposed indication, adalimumab can be used as a treatment alternative to infliximab or as a next line of treatment following treatment failure or intolerance to infliximab. While patients who failed an infliximab therapy are currently required to wait 12 months before retrying the therapy, it is assumed that they would be immediately eligible for adalimumab therapy, as is the case in the current listing for adult Crohn's disease. In addition, the submission proposes that patients should be allowed to switch between adalimumab and infliximab, without having treatment failure, up to two times per treatment cycle, parallel to the adult listing. This may create circumstances conducive to unauthorised use, given that adalimumab is not proposed for the treatment of patients with moderate Crohn's disease. Additionally, subgroup analyses presented in the submission indicate that adalimumab is less effective in patients who have failed infliximab. The submission also assumes that patients would have to cease therapy having failed three courses of treatment for adalimumab and infliximab individually. Combined with the possibility to alternate treatments, this would enable patients to fail five treatment cycles before ceasing TNF- $\alpha$  treatment.
- 2.6 The Pre-Sub-Committee Response (PSCR) stated that the submission is not requesting patients to be able to fail five treatment cycles before ceasing TNF- $\alpha$  therapy but requests that patients can switch between adalimumab and infliximab without failing treatment, up to two times per treatment cycle parallel to the adult Crohn's disease listing (i.e. up to two courses of either adalimumab or infliximab per cycle). The ESC noted that the swapping criteria between adalimumab and infliximab in the adult Crohn's disease indication would require clarification.

- 2.7 The requested basis for listing is a cost minimisation analysis against infliximab. The submission suggested that it is [REDACTED], however all calculations (economic evaluation and financial estimates) are performed using the proposed DPMQ. [REDACTED].
- 2.8 The PSCR proposed the addition of a grandfathering clause to the proposed restrictions in line with infliximab in paediatric Crohn's disease (but limited to patients with severe disease).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **3 Background**

- 3.1 TGA status: Adalimumab was TGA registered on 2 June 2014 for paediatric Crohn's disease.
- 3.2 Adalimumab is currently listed on the PBS for adult Crohn's disease, rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and psoriatic arthritis. In July 2014 the PBAC rejected a submission for adalimumab for use in adult patients with moderate to severe ulcerative colitis.

### **4 Clinical place for the proposed therapy**

- 4.1 Crohn's disease is a chronic and debilitating type of inflammatory bowel disease. The symptoms include diarrhoea, constipation, abdominal pain and rectal bleeding, and may lead to fatigue, fever, weight loss, and menstrual cycle disruptions. The disease may occur at any age and is not curable. Existing treatment options include the alleviation of symptoms, maintenance of remission and prevention of relapse. The current first-line treatment of paediatric Crohn's disease comprises exclusive enteral nutrition and/or corticosteroids, the second-line therapy is based on immunosuppressants, and the third line relies on an anti-rheumatic drug therapy (i.e. infliximab) with the possibility of a surgical intervention.
- 4.2 The submission proposed that (1) adalimumab will become an alternative to infliximab in the third line therapy, (2) adalimumab will become an additional line of treatment for patients who have lost their response or are intolerant to infliximab, and (3) patients will be able to alternate between infliximab and adalimumab without failing the therapy.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **5 Comparator**

- 5.1 Infliximab is the appropriate comparator. It is the only biological agent currently listed on the PBS for Crohn's disease in paediatric patients who fail conventional therapies (exclusive enteral nutrition and/or corticosteroids and immunosuppressant therapy).

- 5.2 Additionally, the submission provided limited evidence in support of the claim that adalimumab efficacy and safety is similar in paediatric and adult patients with severe Crohn's disease. This comparison was not used in a cost-minimisation analysis.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **6 Consideration of the evidence**

### **Sponsor hearing**

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (30), health care professionals (12) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with adalimumab including the following:

- significant benefit to the paediatric community as they are often severely affected by Crohn's disease and it may affect their adolescent growth and puberty;
- the large unmet need for this condition as currently children who fail infliximab or who are intolerant have to continue with active disease and be treated with long term steroids or have surgery; and
- enables paediatric patients with the condition to lead a normal life.

- 6.3 In addition, the consumer comments highlight current issues of equity of access to third-line treatment for paediatric patients with Crohn's disease. In particular, infliximab requires infusion in a hospital setting, which requires patients living in regional and remote areas to travel significant distances, whereas adalimumab can be self-administered. Accordingly, the comments note that the availability of adalimumab will translate into reduced disruption to education, work and family life for both the patient and carers.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Clinical trials**

- 6.4 The submission was based on a naïve indirect comparison of single arms from an adalimumab trial (IMAGINE-1, n=93) and an infliximab trial (REACH, n=52).
- 6.5 Details of the trials presented in the submission are provided in the following table.

Public Summary Document – November 2014 PBAC Meeting

**Trials and associated reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Trial including adalimumab treatment</b>		
IMAGINE-1	<p>A Multicentre, Double-blind Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Paediatric Patients with Moderate to Severe Crohn's Disease, Protocol: M06-806.</p> <p>A Multi-centre, Open-label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Efficacy and the Long-term Safety and Tolerability of Repeated Administration of Adalimumab in Paediatric Patients with Crohn's Disease Who Have Demonstrated a Clinical Response in the M06-806 Study, Protocol: M06-807</p> <p>Hyams, J. S., A. Griffiths, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children.</p>	<p>Date of report: 21st April 2011, NCT00409682.</p> <p>Date of report: 28th June 2011, NCT00686374.</p> <p>2012 Gastroenterology 143(2): 365-374 e362.</p>
<b>Trial including infliximab treatment</b>		
REACH	<p>A Randomized, Multicentre, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF a Chimeric Monoclonal Antibody (infliximab) in Paediatric Subjects With Moderate to Severe Crohn's Disease,</p> <p>Hyams, J., W. Crandall, et al. Induction and Maintenance Infliximab Therapy for the Treatment of Moderate-to-Severe Crohn's Disease in Children.</p> <p>Hyams, J., T. D. Walters, et al. Safety and efficacy of maintenance infliximab therapy for moderate-to-severe Crohn's disease in children: REACH open-label extension.</p>	<p>Protocol: CR004786, NCT00207675.</p> <p>2007 Gastroenterology 132(3): 863-873.</p> <p>2011 Curr Med Res Opin 27(3): 651-662.</p>
<b>Supplementary trial with adalimumab treatment</b>		
CHARM	<p>A multi-centre, randomized, double-blind, placebo-controlled study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with Crohn's disease. 2006.</p> <p>Colombel J-F, Sandborn-William J, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial.</p>	<p>Protocol: M02-404 NCT00195715</p> <p>2007 Gastroenterology; 132(1): 52-65.</p>

Source: Table B.2.2 p.54 of the submission.

6.6 The key features of the direct randomised trials are summarised in the following table.

**Key features of the included evidence**

Trial	N <sup>a</sup>	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Adalimumab in paediatric patients</b>						
IMAGINE-1	93	R, MC, DB, 52 weeks	Low	Infliximab naïve or experienced	Response, remission	Yes
<b>Infliximab in paediatric patients</b>						
REACH	52	R, MC, OL, 54 weeks	Unclear	Infliximab-naïve <sup>b</sup>	Response, remission	Yes
<b>Adalimumab in adult patients</b>						
CHARM	260	R, MC, DB, PBO, 56 weeks	Low	Infliximab naïve or experienced <sup>b</sup>	Response, remission	No

Source: compiled during the evaluation;

DB=double blind; MC=multi-centre; OL=open label; R=randomised, PBO=placebo controlled;

<sup>a</sup> number of patients in the relevant single arms in Section B of the submission;

<sup>b</sup> infliximab or other tumour necrosis factor inhibitor;

- 6.7 The key difference between the IMAGINE-1 and REACH trial populations was the inclusion of infliximab-experienced patients in IMAGINE-1. For the naïve indirect comparison between adalimumab and infliximab, infliximab experienced patients in the adalimumab trial were excluded. Additionally, IMAGINE-1 randomised all patients to low or high dose adalimumab maintenance treatment after adalimumab induction treatment (week 4), while in REACH patients who responded to infliximab induction treatment at week 10, were randomised to a low or high infliximab maintenance dose (5 mg/kg every 8 or 12 weeks). The submission uses a post-hoc subgroup of the IMAGINE-1 trial which included patients receiving high dose adalimumab, were infliximab-naïve and responded after four weeks of treatment for the naïve indirect comparison. This post-hoc subgroup may still not be comparable because patients were included based on response criteria measured at differing time points.
- 6.8 The main differences between the IMAGINE-1 and CHARM trials were (1) the enrolment of paediatric or adult patients, respectively, and (2) efficacy measured using different outcome tools, i.e. PCDAI or Crohn's Disease Activity Index (CDAI).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**Comparative effectiveness**

- 6.9 The following table presents the efficacy from the IMAGINE-1 (adalimumab) trial, for the ITT population and subgroups of patients who were infliximab naïve or experienced.

**Results of response and remission rates for the high dose adalimumab group and selected sub-groups of the IMAGINE-1 trial**

Outcome n (%)	ITT paediatric population		Post-hoc subgroup of high dose adalimumab group		
	High dose	Low dose	Prior infliximab	Infliximab-naïve	Infliximab-naïve + week 4 response
<b>N</b>	93	95			
<b>Week 26</b>					
Remission	36 (38.7%)	27 (28.4%)			
Response	55 (59.1%)	46 (48.4%)			
<b>Week 52</b>					
Remission	31 (33.3%)	22 (23.2%)			
Response	39 (41.9%)	27 (28.4%)			

Source: Table B.6.1 pp.89-90 of the submission and extracted during evaluation from Clinical Study Report attached with the submission;

ITT = intent-to-treat;

- 6.10 In IMAGINE-1, high dose patients had better response than the low dose group. Remission and response rates were considerably higher in infliximab-naïve patients than in those with prior infliximab experience. The sub-group of infliximab-naïve, week 4 responders achieved the highest rates for both outcomes. The naïve indirect comparison against infliximab uses the adalimumab high dose subgroup of infliximab naïve, week 4 responders (n=█), rather than all patients randomised to the adalimumab high dose treatment arm (n=93).
- 6.11 The table below presents the results from the relevant arm of the infliximab trial (REACH) and the naïve indirect comparison of adalimumab and infliximab in paediatric Crohn's disease.

**Naïve indirect comparison of response and remission rates in IMAGINE-1 and REACH**

	Post-hoc subgroup IMAGINE-1 high dose ADA Infliximab naïve + week 4 response	ITT - REACH IFX 5 mg/kg every 8 weeks TNF $\alpha$ naïve week 10 responders	RD (95% CI)
<b>N</b>		52	
<b>Weeks 26-30</b>			
Remission		31 (59.6%)	
Response		38 (73.1%)	
<b>Weeks 52-54</b>			
Remission		29 (55.8%)	
Response		33 (63.5%)	

Source: Tables B.6.7 and B.6.8 p.97-98 of the submission; Attachment 4 to the submission (excel spreadsheet);

RD = risk difference; CI = confidence interval; IFX = infliximab; ADA = adalimumab; TNF $\alpha$  = tumour necrosis factor alpha; ITT = intent-to-treat;

- 6.12 The submission considered that adalimumab has a similar efficacy as infliximab, based on a naïve indirect comparison, with no common comparator. The submission considered that the analysis meets the non-inferior criteria as the lower confidence interval for the primary analysis (remission at week 26) was █% in favour of infliximab, which does not meet the minimal clinically important difference (MCID) of 20%. There are concerns with this methodology and with the conclusion that adalimumab has non-inferior efficacy compared to infliximab:
- The patient characteristics were different in the adalimumab and infliximab trials as IMAGINE-1 included patients regardless of prior infliximab experience,

whereas REACH only recruited infliximab-naïve patients. The PSCR agreed that the patient populations in these two trials seem comparable, except for the inclusion of infliximab-experienced patients in IMAGINE-1. Such an approach is likely to bias the results. It is unclear whether this would favour adalimumab.

- The analyses were performed using a post-hoc subgroup from the adalimumab trial.
- The proposed restriction is for patients with severe Crohn's disease. Both trials included patients with moderate to severe Crohn's disease.

- 6.13 Adalimumab resulted in similar efficacy in paediatric and adult patients with Crohn's disease, based on the limited naïve indirect comparison using the CDAI score in paediatric patients aged 13 or over compared to adult patients.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Comparative harms**

- 6.14 The sources of safety data are the clinical trials and extension studies. The comparison involved an analysis of aggregate categories of adverse events. No statistically significant differences were detected in the rates of adverse events, serious adverse events, adverse events leading to discontinuation, infectious and serious infectious adverse events, or adverse events related to injection site reactions.

- 6.15 The submission provided no evidence or discussion regarding the comparative safety of adalimumab in paediatric vs. adult patients.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Benefits/harms**

- 6.16 A summary of the comparative benefits and harms for adalimumab versus infliximab is presented in the following table.

Public Summary Document – November 2014 PBAC Meeting

Summary of comparative benefits and harms for adalimumab and infliximab

Outcome	Adalimumab <sup>a</sup> n/N	Infliximab <sup>b</sup> n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Adalimumab <sup>a</sup>	Infliximab <sup>b</sup>	
<b>BENEFITS</b>						
<b>Remission</b>						
Weeks 26-30	████	31/52	██████████	████	59.6	██████████
Weeks 52-54	████	29/52	██████████	████	55.8	██████████
<b>Response</b>						
Weeks 26-30	████	38/52	██████████	████	73.1	██████████
Weeks 52-54	████	33/52	██████████	████	63.5	██████████
<b>HARMS</b>						
Serious AEs	████	8/53	██████████	████	15	██████████
Infectious AEs	████	39/53	██████████	████	74	██████████
Injection-site related AEs	████	9/53	██████████	████	17	██████████

Source: Tables B.6.7, B.6.8, B.6.12 pp.97-98, 102 of the submission; Attachment 4 to the submission (excel spreadsheet);

RD = risk difference; RR = relative risk; CI = confidence interval; ITT = intent-to-treat; AE = adverse event;

\* maximum treatment duration 52 weeks for adalimumab and 54 weeks for infliximab.

<sup>a</sup> Post hoc subgroup of the high dose adalimumab arm of IMAGINE-1, which included infliximab naïve patients who responded at four weeks

<sup>b</sup> ITT, 5 mg/kg every 8 weeks arm of REACH trial, patients were randomised at 10 weeks if they responded to infliximab induction therapy (week 0, 2 and 6)

- 6.17 Based on a naïve indirect comparison, with no common comparator arm, it is not clear whether adalimumab is worse or better than infliximab in the treatment of paediatric Crohn's disease.

For more detail on PBAC's view, see section 7 "PBAC outcome"

**Clinical claim**

- 6.18 The submission claimed that adalimumab is non-inferior to infliximab in paediatric Crohn's disease. The ESC advised that this claim is unclear:
- The evidence is from a naïve indirect comparison of single arms of two trials. The PSCR acknowledged the limitation of the naïve indirect comparison, but considered the approach of the post-hoc subgroup of the adalimumab study to be reasonable.
  - The evidence for adalimumab is from a post-hoc subgroup of infliximab-naïve patients who responded at week 4 to adalimumab induction treatment, which is different from the requested PBS-listing: 1) response at week 12; and 2) infliximab naïve and experienced patients.
  - The evidence is for moderate and severe Crohn's disease, which is different from the requested PBS-listing of patients with severe Crohn's disease.
  - Patients were randomised based on response measured at different points in time (week 4 for adalimumab and week 10 for infliximab).

- The assumed MCID (risk difference of 20% for the lower confidence interval) is not sufficiently justified, and the secondary outcomes (remission and response at week 52-54) may not meet the non-inferiority criteria. The PSCR (p2) disagreed with the commentary that the 20% MCID is not sufficiently justified. The submission claims that this value was based on the IMAGINE-1 trial which was powered to detect a difference in remission rate of 20% between the high and low dose arms. The ESC disagreed and noted there is an apparent lower efficacy at 52-54 weeks that may meet inferiority limits.

6.19 Additionally, the submission suggested that adalimumab has comparable efficacy and safety in paediatric and adult populations. As with the comparison to infliximab, there are concerns with using a naive indirect comparison approach. Numerically, adalimumab appears to result in more adverse events in paediatric patients, however it is unclear whether in clinical practice adalimumab would result in higher rates of adverse events in the paediatric population compared to the adult population.

6.20 The PSCR argued it did not consider it appropriate to compare the adverse event profile in adults (CHARM) to children and adolescents (IMAGINE-1). The ESC considered that the submission's claim of similar safety with infliximab was reasonable.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### Economic analysis

6.21 The submission presented a cost-minimisation analysis of adalimumab vs. infliximab.

6.22 The equi-effective doses are presented in the table below. Equi-effective doses are based on the trial dosage as well as on the consideration of current PBS listings of infliximab in paediatric Crohn's disease and adalimumab for adult patients with Crohn's disease. The ESC agreed that the equi-effective doses are reasonable.

**Equi-effective doses of adalimumab and infliximab in paediatric Crohn's disease**

	<b>Adalimumab</b>	<b>Infliximab</b>
Mode of administration	SC injection	IV infusion
Induction	BW <40 kg: 80 mg at week 0, 40 mg at week 2 BW ≥40 kg: 160 mg at week 0, 80 mg at week 2	5 mg/kg at weeks 0, 2 and 6
Maintenance	BW <40 kg: 20 mg every other week BW ≥40 kg: 40 mg every other week	5 mg/kg every 8 weeks

Source: text pp.133-134 of the submission;  
SC = subcutaneous; IV = intravenous; BW = body weight;

6.23 The following table summarises the results of the cost-minimisation analysis presented in the submission.



**Cost-minimisation analysis and additional sensitivity analyses**

Cost	Week 12	Week 52	Year 2+
<b>Base model</b>			
Adalimumab treatment			
Infliximab treatment			
Incremental cost at DPMQ			
<b>Incremental cost with adalimumab price rebate <sup>a</sup></b>			
<b>Sensitivity analyses (incremental cost including adalimumab price rebate)</b>			
Infusion cost MBS item only (base case MBS + hospital cost \$ )			
Number of infliximab vials 2.9 <sup>b</sup> (base case 3)			
Adalimumab induction packs for BW<40kg <sup>c</sup>			
Infusion cost MBS only + 2.9 infliximab vials + adalimumab 2 packs			

Source: Calculated during evaluation;

MBS = Medicare Benefits Schedule; DPMQ = Dispensed Price for Maximum Quantity; BW = body weight;

<sup>a</sup> The proposed price rebate is % for the two-pack and % for the six-pack;

<sup>b</sup> For the base case the submission estimates that 34.4% of patients are below 40 kg and 65.6% above (average 46.3 kg), resulting in an average of 2.32 vials per infusion, which is rounded to 3 vials. For the sensitivity analysis, 2.9 vials per infusion were considered, similar to the value for the financial estimates, based on the percentage of patients receiving 2, 3, or 4 vials.

<sup>c</sup> The induction dose for patients under 40 kg is 80 mg in week 0, 40 mg in week 2, 20 mg in week 4, 6, 8 and 10. For the base case the submission includes 1.5 packs of 2 x 40 mg and 2 packs of 2 x 20 mg. For this sensitivity analysis the proposed maximum quantities are used, i.e. 1 pack of 2 x 40 mg and 3 packs of 2 x 20 mg, whereby it is assumed that at week 2 a patient will receive two 20 mg injections.

- 6.24 Adalimumab is administered as a subcutaneous injection whereas infliximab is administered as an intravenous injection. In the submission the cost of infliximab treatment is likely to be overestimated due to the infliximab administration cost per infusion calculated at \$ (MBS cost + inpatient hospital cost of \$ ), and due to the assumption of 0.7 vials of wastage per infliximab infusion, which is inconsistent with the approach for the financial estimates. These two assumptions favour adalimumab. The sensitivity analyses indicate that adalimumab treatment ( ) may be more costly than infliximab treatment in some scenarios. The PSCR considered that the MBS item fee of \$97.95 (for infliximab administration cost) is inappropriate to estimate the cost of in-patient infliximab infusion. The Sponsor considers data from the which reports a cost estimate of \$ , to be more appropriate. This data could not be verified. Additionally, the infusion would be as an out-patient, not as an in-patient. This favours adalimumab.
- 6.25 The ESC agreed with the commentary that the infliximab in-patient costs are questionable and this is a major problem with the cost estimates.
- 6.26 The PSCR provided an updated cost minimisation analysis (see following table) which incorporated the proposed effective price of adalimumab and corrected the inconsistency between the proposed maximum quantity and the dosing schedule in the strength and number of adalimumab injections used on day 14 of the initial treatment for patients weighing less than 40 kg.

**Comparison of adalimumab (effective price) and infliximab treatment costs**

Time horizon	Adalimumab	Infliximab	Difference
<b>Week 12 total</b>			
Drug			
IV administration			
<b>Week 52 total</b>			
Drug			
IV administration			
<b>Subsequent years total</b>			
Drug			
IV administration			

Source: Compiled based on Table 4, p7 of the PSCR;

Italics calculated during evaluation; The values for infliximab were slightly different, using the average number of vials ( ) from the Section E spreadsheet.

DPMQ = dispensed price, maximum quantity; IV = intravenous

- 6.27 The table above includes the cost of in-patient infliximab administration. A further sensitivity analysis was performed excluding these costs (see table below). The updated sensitivity analysis indicates that adalimumab may be even more costly than infliximab with the in-patient cost removed than previously estimated.

**Sensitivity analyses of adalimumab and infliximab treatment costs**

	Incremental cost		
	Week 12	Week 52	Subsequent years
Revised base case ( infliximab vials)			
Infusion cost MBS item only (base case MBS + hospital cost \$ )			

Source: Calculated during evaluation

MBS = Medical Benefits Schedule; PSCR = Pre-Sub-Committee Response

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Drug cost/patient/year**

- 6.28 The drug cost/patient/year was estimated to be \$ in Year 1 and \$ in subsequent years ( ), based on 100% continuation rates (see Table 8).

- 6.29 Crohn’s disease is chronic and incurable therefore the adalimumab treatment is likely to be ongoing. The typical treatment would comprise an induction therapy and continued maintenance therapy for those who respond to induction therapy. The drug cost of infliximab treatment is \$ in year 1 and \$ in subsequent years, assuming infusions in year 1 and in subsequent years and infliximab vials per infusion.

**Estimated PBS usage & financial implications**

- 6.30 This submission was not considered by DUSC. The submission took a market share approach and relies on the Highly Specialised Drugs Program, the 10% PBS sample and the Australian Bureau of Statistics as primary data sources.

**Estimated use and financial implications**

	2015-16	2016-17	2017-18	2018-19	2019-20
<b>Estimated extent of use <sup>a</sup></b>					
Infliximab vials total in severe disease					
Substitution rate					
Market growth					
Adalimumab packs <sup>a</sup>					
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS					
Net cost to MBS					
<b>Estimated total net cost</b>					
<b>Net cost to government</b>					
<b>Including rebate <sup>b</sup></b>					

Source: Table E.4.1 p.161 of the submission and Section E electronic attachment to the submission.

<sup>a</sup> Assuming infliximab vials per year as estimated by the submission, a 4/3 adalimumab to infliximab pack relativity, and severe disease accounting for █% of infliximab use;

<sup>b</sup> the proposed price rebate is █% for the two-pack and █% for the six-pack;

The redacted table above shows that in Year 5, the estimated number of adalimumab packs supplied would be less than 10,000 and the net cost to Government would be less than \$10 million.

6.31 The submission estimated a net cost to the PBS/MBS over five years of \$ █ and \$ █.

The increase in PBS/MBS cost is due to an additional line of treatment after infliximab treatment failure or intolerance and cost-offsets for inpatient infusions which are not included in the PBS/MBS cost. The estimates may be higher or lower depending on:

- The substitution rate of adalimumab in severe patients currently treated with infliximab is estimated to be █% in year 5, which may be an overestimate. The PSCR acknowledged that the substitution rate is conservative and may be overestimated.
- The submission did not estimate uptake for induction and maintenance therapy separately. This may not be appropriate if the continuation rate at 12 weeks is low.
- The analysis implicitly assumed that continuation rates and compliance in adalimumab and infliximab are equal, which may or may not be true.
- Leakage of use to patients with moderate disease, as clinicians may prefer to use PBS prescribing than the proposed compassionate program (see paragraph 6.32). The PSCR disagreed and argued that the compassionate supply process is both straight forward and efficient. The ESC nonetheless considered that there may be some leakage of use to patients with moderate disease.

6.32 As requested in the commentary, the PSCR provided details of the 10% PBS sample data for adult Crohn’s disease on the number of scripts for adalimumab and infliximab per year. The PSCR noted that timing differences in PBS-listing of both drugs for adult and paediatric patients which may affect the applicability of substitution and market growth assumptions across both populations.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Quality Use of Medicines**

- 6.33 myHEALTHguide and OnTrack are the Sponsor's programs that aim at improving patient education, support, quality of life and enhancing the quality use of medicines. myHEALTHguide offers the possibility of home injections assisted by a nurse. OnTrack includes a possibility of compassionate supply enabled through patient enrolment by a clinician for patients:
- with moderate disease, or
  - who require dose escalation to weekly dosing, after initial response at 12 weeks.
- Details of the programs were not provided.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Financial Management – Risk Sharing Arrangements**

- 6.34 The PBAC noted the submission did not propose a risk sharing arrangement (RSA).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended extending the current Section 85 listing of adalimumab to include listing for the treatment of severe refractory Crohn's disease in paediatric patients aged 6 to 17 years. The PBAC recommended an Authority required (written-only) restriction for both initial and continuing treatment.
- 7.2 The PBAC recommended the listing of adalimumab on a cost-minimisation basis with infliximab. The PBAC considered the equi-effective doses are:
- adalimumab – patients weighing less than 40 kg: 80 mg at week 0, 40 mg at week 2, then 20 mg every other week thereafter; patients weighing more than or equal to 40 kg: 160 mg at week 0, 80 mg at week 2, then 40 mg every other week thereafter; and
  - infliximab – 5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter.
- 7.3 The PBAC noted the differences between the proposed restriction for adalimumab and current restrictions for infliximab (i.e. severe Crohn's disease for adalimumab versus moderate to severe Crohn's disease for infliximab, PCDAI definition and clinical response criteria). The PBAC recommended to keep the adalimumab restriction as proposed when finalising the restriction wording, however, the PBAC requested the Secretariat to work with the Restrictions Working Group and sponsor

in clarifying the interchangeability criteria between adalimumab and infliximab as for the adult Crohn's disease indication.

- 7.4 The PBAC noted that the sponsor, in its PSCR, proposed the addition of a grandfathering clause in line with infliximab in paediatric Crohn's disease but limited to patients with severe disease. The PBAC agreed to the inclusion of a grandfather restriction to enable continuing PBS-subsidised adalimumab treatment for patients with severe disease that are currently being treated under the compassionate access program.
- 7.5 The PBAC agreed that the clinical place for adalimumab would be as an alternative treatment to infliximab in the third line therapy and will become an additional line of treatment for patients who fail treatment or are intolerant to infliximab. The PBAC considered that patients can alternate between adalimumab and infliximab without failing the therapy. The PBAC acknowledged that there is a high clinical need for this treatment in the paediatric population. The PBAC agreed that the administration of adalimumab as a subcutaneous injection, as opposed to infusion for infliximab, will result in significant benefits for patients with this condition.
- 7.6 The PBAC accepted infliximab as the appropriate comparator.
- 7.7 The PBAC noted the results of the naïve indirect comparison between the adalimumab (IMAGINE-1) and infliximab (REACH) trials. The PBAC considered the concerns raised by the ESC and agreed that there is a trend for inferiority with adalimumab in patients who have had previous infliximab exposure (compared to infliximab-naïve patients) and that there is an apparent reduction in efficacy at 52-54 weeks, which may meet the specified inferiority limit. It was also noted, however, that the assumed MCID of 20% was not sufficiently justified.
- 7.8 The PBAC noted that there was no apparent reduction in adalimumab efficacy over time for the adult population, with adalimumab showing consistent non-inferior efficacy to infliximab (PBAC Minutes November 2007). However, the PBAC noted the limitations of the available data for paediatric patients, including the small number of patients in the infliximab-naïve sub-group analysis, and acknowledged that more reliable data would be difficult to obtain.
- 7.9 The PBAC therefore considered that, on the basis of the available evidence, it is reasonable to conclude that adalimumab is non-inferior in terms of efficacy and comparable in terms of safety to infliximab.
- 7.10 The PBAC considered the cost-minimisation analysis of adalimumab against infliximab. The PBAC agreed with ESC that the outcomes of the cost-minimisation analysis are biased in favour of adalimumab by the inclusion of the in-patient resource cost of \$████ per infliximab infusion. As the methodology used to reach this estimate was not provided and that the cost of infliximab infusion may vary significantly across jurisdictions, the PBAC did not accept the submission's proposed offset for the cost of infliximab infusion.
- 7.11 The PBAC agreed with the issues regarding the utilisation and financial estimates outlined in paragraph 6.31.

7.12 Advice to the Minister under subsection 101(3BA) of the Act

In accordance with subsection 101(3BA) of the Act the PBAC advised that it is of the opinion that, on the basis of the material available to it at its November 2014 meeting, adalimumab should not be treated as interchangeable on an individual patient basis with any other drugs.

7.13 The PBAC advised that adalimumab is not suitable for prescribing by nurse practitioners.

7.14 The PBAC recommended that the Safety Net 20 Day Rule should apply for continuing treatment as it is currently applied to adalimumab for continuing treatment of Crohn's disease in adults.

**Outcome:**

Recommended

**8 Recommended listing**

8.1 Amend existing/recommended listing. Restriction to be finalised including flow-on changes to current infliximab restriction.

**9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**10 Sponsor's Comment**

AbbVie is pleased that adalimumab will be available for patients with paediatric Crohn's disease.