6.05 USTEKINUMAB
Injection 130mg in 26mL vial, injection 45mg in 0.5mL vial, Stelara®, Janssen Cilag Australia Pty Ltd

1 Purpose of Application

1.1 Section 100 Authority Required listing for the intravenous (IV) loading dose and Section 85 Authority Required listing for follow on subcutaneous (SC) injections were requested for ustekinumab (UST) for the indications of: 1) severe Crohn's disease (CD) and 2) complex refractory fistulising CD.

2 Requested listing

2.1 The requested listing is similar to that of: i) adalimumab (ADA) and other biological disease modifying anti-rheumatic drugs (bDMARDs) including infliximab (IFX) and vedolizumab (VDZ) for treatment of severe CD and ii) ADA and IFX for fistulising CD. Abbreviated requested restrictions are presented below.

Severe CD

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
INITIAL TREATMENT					
USTEKINUMAB 130mg/26mL injection, 26mL vial	1	0	$[redacted][a] (public) $[redacted][a] (private)	Stelara®	Janssen Cilag
USTEKINUMAB 45mg/0.5mL injection, 0.5mL vial	2	0	$[redacted][b]		
CONTINUING TREATMENT					
USTEKINUMAB 45mg/0.5mL injection, 0.5mL vial	2	2	$[redacted][b]		

Treatment phase: initial treatment (initial 1 - new patient)	
Severity	Severe
Condition	Crohn disease
Restriction	Section 100 (HSD) for 130mg/26mL vial Section 85 (General Schedule) for 45mg/0.5mL vial
Treatment criteria	Must be treated by gastroenterologist or consultant physician (specialising in gastroenterology)
Clinical criteria	Confirmed Crohn disease by gastroenterologist or consultant physician; AND Failed to achieve adequate response to treatment with a tapered course of steroids OR have documented intolerance necessitating treatment withdrawal; AND Failed to achieve adequate response to treatment with immunosuppressive therapy (azathioprine OR 6-mercaptopurine OR methotrexate) for 3 or more months, OR have documented intolerance necessitating treatment withdrawal; AND CDAI ≥220 if affected by small intestine disease OR ≥300 if not affected by small intestine disease, short gut syndrome or an ostomy patient; AND Have evidence of intestinal inflammation (various criteria)
Population criteria	Patient must be aged 18 years or older.
Treatment phase: continuing treatment	
Severity	Severe
Condition	Crohn disease
Restriction	Section 85 (General Schedule)
Treatment criteria	Must be treated by gastroenterologist or consultant physician (specialising in gastroenterology)
Clinical criteria	History of severe Crohn disease AND Had previous prescriptions for this drug and condition AND Demonstrated an adequate response to treatment defined as CDAI score ≤150 if assessment by CDAI OR improvement of intestinal inflammation (various criteria)
Population criteria	Patient must be aged 18 years or older.

[a] Effective DPMQs: $[redacted] (public), $[redacted] (private);
[b] Effective DPMQ: $[redacted]; Effective ex-man: $[redacted].

Fistulising CD

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
INITIAL TREATMENT					
USTEKINUMAB 130mg/26mL injection, 26mL vial	1	0	$[redacted][a] (public) $[redacted][a] (private)	Stelara®	Janssen Cilag
USTEKINUMAB 45mg/0.5mL injection, 0.5mL vial	2	0	$[redacted][b]		
CONTINUING TREATMENT					
USTEKINUMAB 45mg/0.5mL injection, 0.5mL vial	2	2	$[redacted][b]		

Treatment phase: initial treatment (new patient)	
Severity	Complex refractory fistulising
Condition	Crohn disease
Restriction	Section 100 (HSD) for 130mg/26mL vial Section 85 (General Schedule) for 45mg/0.5mL vial
Treatment criteria	Must be treated by gastroenterologist or consultant physician (specialising in gastroenterology)
Clinical criteria	Confirmed Crohn disease by gastroenterologist or consultant physician; AND Patient must have an externally draining enterocutaneous or rectovaginal fistula.
Population criteria	Patient must be aged 18 years or older.
Treatment phase: continuing treatment	
Severity	Complex refractory fistulising
Condition	Crohn disease
Restriction	Section 85 (General Schedule)
Treatment criteria	Must be treated by gastroenterologist or consultant physician (specialising in gastroenterology)
Clinical criteria	History of complex refractory fistulising Crohn disease AND Demonstrated an adequate response to treatment defined as a decrease from baseline in the number of open draining fistulae of greater than or equal to 50% OR a marked reduction in drainage of all fistula(e) from baseline, together with less pain and induration.
Population criteria	Patient must be aged 18 years or older.

[a] Effective DPMQs: $[redacted] (public), $[redacted] (private);
[b] Effective DPMQ: $[redacted]; Effective ex-man: $[redacted]

2.2 For severe CD, the requested listing was cost-minimisation versus a weighted comparator of ADA ([redacted]%), IFX ([redacted]%) and VDZ ([redacted]%) based on assumed substitution rates. Prospection data in March 2016 (PBS 10% sample; Appendix 9 of the submission) showed that ADA had 50.8% of the market, IFX 46.2% and VDZ 3%. As VDZ is not listed on PBS for fistulising CD, the cost-minimisation analysis reasonably excluded VDZ from the weighted comparators (ADA: 61% and IFX: 39%). Similar effective prices were requested for UST in both severe and fistulising CD (a slightly lower price was estimated for UST for fistulising CD based on the cost- minimisation analysis). The nominated clinical comparison for both severe and fistulising CD however was versus ADA only (see "Comparators").

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

3 Background

3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, both the Clinical Evaluation Report and the TGA delegate's overview were available. The TGA have approved ustekinumab for moderate to severe CD on 27 February 2017.

3.2 The PBAC noted the TGA had not approved ustekinumab for fistulising Crohn's disease.

3.3 UST has not been considered by PBAC previously for severe CD or fistulising CD.

4 Clinical place for the proposed therapy

4.1 UST is a human monoclonal antibody that binds to and interferes with the pro-inflammatory cytokines, interleukin (IL)-12 and IL-23. It has a different mechanism of action to other PBS listed bDMARDs which (except for VDZ) are all tumour necrosis factor –α inhibitors.

4.2 UST is expected to be used as an alternative to other PBS-listed bDMARDs for severe CD (ADA, IFX, and VDZ), and fistulising CD (ADA and IFX). These agents are indicated on the PBS for CD only after failure of conventional therapies (such as azathioprine, 6-mercaptopurine or methotrexate).

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

5 Comparator

5.1 For severe CD: ADA was nominated as the clinical comparator and a weighted combination of ADA, IFX and VDZ were nominated as cost comparators. For fistulising CD: ADA was nominated as the clinical comparator and ADA and IFX were nominated as cost comparators. For the clinical comparisons, all currently PBS listed bDMARDs could be replaced in practice and are also relevant comparators.

5.2 The ESC noted the nomination of different clinical and economic comparators is inappropriate and if IFX and VDZ will also be replaced in clinical practice they should be considered relevant comparators.

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 (41), health care professionals (19) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the need for new treatment options for patients with Crohn's disease and a range of benefits including improvement of symptoms and convenience of a subcutaneous injection.

Clinical trials

6.3 For severe CD, the submission was based on:

- Three head-to-head trials comparing UST to placebo: UNITI-1 and UNITI-2 (induction trials), and IM-UNITI (maintenance trial)
- An indirect comparison to ADA, based on five head-to-head trials comparing ADA to placebo: CLASSIC I, and GAIN for induction therapy, CLASSIC II and CHARM for maintenance therapy and Watanabe 2012 for both induction and maintenance therapies.

6.4 Relevant trials for IFX and VDZ were also extracted for indirect comparisons versus UST during the evaluation, including:

- Two RCTs comparing IFX to placebo: T16 for induction therapy and ACCENT I for maintenance therapy.
- Two RCTs comparing VDZ to placebo: GEMINI II for induction and maintenance therapies and GEMINI III for induction therapy.

6.5 The results of all comparator trials have previously been considered by the PBAC, most recently in the March 2015 submission for VDZ.

6.6 For fistulising CD, fistula response (defined as ≥50% reduction in draining fistulas) was reported in UNITI 1, 2 and IM-UNITI trials as a secondary outcome. An indirect comparison with ADA was not conducted as outcome definitions differed across the UST and ADA trials.

6.7 Fistula response (defined as ≥50% reduction in draining fistulas at consecutive visits) and fistula remission (defined as complete closing of fistulas) were reported as secondary outcomes in GAIN and CLASSIC I (for induction) and CHARM (for maintenance).

6.8 As IFX is also listed on the PBS for fistulising CD and is the only biologic agent that is specifically indicated for this population, results for fistula response for IFX were also identified and extracted during the evaluation. Two trials reported results for IFX in fistula remission and response (T20 for induction and ACCENT II for maintenance). However outcome definitions similarly differed across the UST and IFX trials and therefore indirect comparison was not conducted.

6.9 Details of the trials presented in the submission (and further trials sourced during the evaluation) for both severe and fistulising CD are provided in Table 1.

Table 1: Trials and associated reports in the submission (plus additional trials sourced during the evaluation)

Trial ID/First Author	Protocol title/Publication Title	Publication Citation
Ustekinumab vs placebo		
UNITI-1	Clinical Study Report CNTO1275CRD3001. A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of ustekinumab induction therapy in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to TNF antagonist therapy.	17 Sept 2015.
UNITI-2	Clinical Study Report CNTO1275CRD3002. A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of ustekinumab induction therapy in subjects with moderately to severely active Crohn's disease.	13 Oct 2015.
IM-UNITI	Clinical Study Report CNTO1275CRD3003. A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the safety and efficacy of ustekinumab maintenance therapy in subjects with moderately to severely active Crohn's disease.	9 Nov 2015.
CERTIFI	Clinical Study Synopsis. A phase 2b, multicentre, randomized, double blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ustekinumab therapy in subjects with moderate to severely active Crohn's disease previously treated with TNF antagonist therapy.	25 Oct 2011
	Sanborn, W. J, Gasink, C., Gao, L., Blank, M., Johanns, J., Guzzo, C., Sands, B. E., Hanauer, S. B., Targan, S., Rutgeerts, P., Ghosh, S., de Villiers, W. J., Panaccione, R., Greenberg, G., Schreiber, S., Lichtiger, S., and Feagan, B. G. Ustekinumab induction and maintenance therapy in refractory Crohn's disease.	The New England Journal of Medicine, 2012; 367 (16): 1519-1528.
Sandborn (2008)	Clinical Study Synopsis. A multicentre, randomized, Phase 2a study of human monoclonal antibody to IL-12p40 (CNTO 1275) in subjects with moderately to severely active Crohn's disease. Sanborn, W. J., Feagn B. G., Fedorak, R. N., Scherl, E., Fleischer, M. R., Katz, S., Johanns, J., Blank, M., and Rutgeerts, P. A randomised trial of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease.	29 May 2007 Gastroenterology 2008; 135: 1130-1141.
Adalimumab vs placebo		
CLASSIC I	Hanauer, S. B., Sandborn, W. J., Rutgeerts, P., Fedorak, R. N., Lukas, M., MacIntosh, D., Panaccione, R., Wolf, D., and Pollack, P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial.	Gastroenterology 2006; 130 (2): 323-333.
CLASSIC II	Sandborn, W. J., Hanauer, S. B., Rutgeerts, P., Fedorak, R. N., Lulcas, M., MacIntosh, D. G., Panaccione, R., Wolf, D., Kent, J. D., Bittle, B., Li, J., and Pollack, P. F. Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial.	Gut 2007; 56 (9): 1232-1239.
GAIN	Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Colombel, J. F., Panaccione, R., D'Haens, G., Li, J., Rosenfeld, M. R., Kent, J. D., and Pollack, P. F. Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial.	Annals of Internal Medicine 2007; 146 (12): 829-838
Watanabe	Watanabe, M., Hibi, T., Lomax, K. G., Paulson, S. K., Chao, J., Alam, M. S., and Camez, A. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease.	Journal of Crohn's and Colitis 2012; 6 (2): 160-173.
CHARM	Colombel, J., Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Panaccione, R., Schreiber, S., Byczkowski, D., Li, J., Kent, J. D., and Pollack, P. F. Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial.	Gastroenterology 2007; 132 (1): 52-65.

Trial ID/First Author	Protocol title/Publication Title	Publication Citation
	Colombel, J., Sandborn, W. J., Rutgeerts, P., Kamm, M. A., Yu, A. P., Wu, E. Q., Pollack, P. F., Lomax, K. G., Chao, J., and Mulani, P. M. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: Results from the CHARM trial.	The American Journal of Gastroenterology 2009; 104: 1170-1179.
	Feagan, B. G., Panaccione, R., Sandborn, W. J., D'Haens, G. R., Schreiber, S., Rutgeerts, P., Loftus, E.V., Lomax, K. G., Yu, A. P., Wu, E. Q., Chao, J., and Mulani, P. M. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: Results from the CHARM study.	Gastroenterology 2008; 135: 1493-1499.
	Colombel, J., Schwartz, D. A., Sandborn, W. J., Kamm, M. A., D'Haens, G. R., Rutgeerts, P., Enns, R., Panaccione, R., Schreiber, S., Li, J., Kent, J. D., Lomax, K. G., and Pollack, P. F. Adalimumab for the treatment of fistulas in patients with Crohn's disease.	Gut 2009; 58: 940-948.
	Loftus, EV. Feagan, B. G., Colombel, J. F., Rubin, D.T., Wu, E.Q., Yu, A. P., Pollack, P. F., Chao, J., Mulani, P. Effects of Adalimumab Maintenance Therapy on Health-Related Quality of Life of Patients With Crohn's Disease: Patient-Reported Outcomes of the CHARM Trial Patient-Reported Outcomes with Adalimumab for Crohn's Disease. December 2008.	The American Journal of gastroenterology 10 3, 3132-3141.
EXTEND	Rutgeerts, P., Van Assche, G., Sandborn W., J., Wolf, D. C., Geboes, K., Colombel, J., Reinisch, W., Kumar, A., Lazar, A., Lomax, K., G., Pollack, P. F., and D'Haens, G. R. Adalimumab induced and maintains mucosal healing in patients with Crohn's disease. Gastroenterology 2012; 142: 1102-1111.	
Infliximab vs placebo		
T16	Targan, S. R., Hanauer, S. B., van Deventer, S. J. H., Mayer, L., Present, D. H., Braakman, T., DeWoody, K. L., Schaible, T. F., and Rutgeerts, P. J. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor (alpha) for Crohn's Disease.	The New England Journal of Medicine 1997; 337 (15): 1029-1035.
ACCENT I	Hanauer, S. B., Feagan, B. G., Lichtenstein, G. R., Mayer, L. F., Schreiber, S., Colombel, J. F., Rachmilewitz, D., Wolf, D. C., Olson, A., Bao, W., and Rutgeerts, P. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial.	Lancet 2002; 359 (9317): 1541-1549.
T20	Present, D. H., Rutgeerts, P., Targan, S., Hanauer, S. B., Mayer, L., Van Hogezand, R. A., Podolsky, D. K., Sands, B. E., Braakman, T., DeWoody, K. L., Schaible, T. F., and Van Deventer, S. J. Infliximab for the treatment of fistulas in patients with Crohn's disease.	The New England Journal of Medicine; 1999; 340: 1398-1405.
ACCENT II	Sands, B. E., Anderson, F. H., Bernstein, C. N., Chey, W. Y., Feagan, B. G., Fedorak, R. N., Kamm, M. A., Korzenik, J. R., Lashner, B. A., Onken, J. E., Rachmilewitz, D., Rutgeerts, P., Wild, G., Wolf, D. C., Marsters, P. A., Travers, S. B., Blank, M. A., and Van Deventer, S. J. Infliximab maintenance therapy for fistulising Crohn's disease.	The New England Journal of Medicine 2004; 350(9): 876-885.
Vedolizumab vs placebo		
GEMINI II	Sandborn, W. J., Feagan, B. G., Rutgeerts, P., Hanauer, S., Colombel, J. F., Sands, B. E., Lukas, M., Fedorak, R. N., Lee, S., Bressler, B., Fox, I., Rosario, M., Sankoh, S., Xu, J., Stephens, K., Milch, C., and Parikh, A. Vedolizumab as induction and maintenance therapy for Crohn's disease.	New England Journal of Medicine. 2013; 369 (8): 711-721.
GEMINI III	Sands, B. E., Feagan, B. G., Rutgeerts, P., Colombel, J. F., Sandborn, W. J., Sy, R., D'Haens, G., Ben-Horin, S., Xu, J., Rosario, M., Fox, I., Parikh, A., Milch, C., and Hanauer, S. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed.	Gastroenterology, 2014; 147: 618-627.
Meta-analyses of indirectly comparable trials		
Singh 2014	Singh, S., Garg, S. K., Pardi, D. S., Wang, Z., Murad, M. H., and Loftus, E. V. Comparative efficacy of biologic therapy in biologic-naïve patients with Crohn disease: A systematic review and network meta-analysis.	Mayo Clinic Proceedings 2014; 89(12): 1621-1635.

Trial ID/First Author	Protocol title/Publication Title	Publication Citation
Cote-Daigneault 2015	Cote-Daigneault, J., Bouin, M., Lahaie, R., Colombel, H., Poitras, P., Biologics in inflammatory bowel disease.	United European Gastroenterology Journal 2015; 3(5): 419-428.
Khanna 2015	Khanna, R., Preiss, J., MacDonald, J. K., and Timmer, A., Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease (review).	Cochrane Database of Systematic Reviews 2015; 5: CD007572.

NOTE: citations for conference abstracts are not included in the summary.
Source: Table B.2-3, p16 of Section B of the submission.

6.10 The key features of the UST, ADA, IFX and VDZ trials are summarised in Tables 2 and 3 for severe and fistulising CD respectively.

Severe CD

6.11 **Table 2: Key features of the included evidence- Severe CD**

Trial	N	Design	Durations (assessment of outcomes)	Risk of bias	Patient population	Relevant Outcomes
Ustekinumab versus placebo						
UNITI-1	IP: 741	R, DB, MC	IP: 8 weeks	Low	TNFα refractory	CR-100^ (Wk6)*, CR-70, Remission (CDAI < 150)
UNITI-2	IP: 628	R, DB, MC	IP: 8 weeks	Low	TNF naïve and TNF experienced (but non-refractory)	
IM-UNITI	**MP: 397**	R, DB, MC	MP: 52 weeks#	Low	Patients with response (CR-100) to UST induction at W8 of UNITI-1 or UNITI-2	Remission (CDAI < 150)*, Patients maintaining CR-100 at Week 52 # in CR-100 responders to UST initiation.
Adalimumab versus. Placebo						
CLASSIC I	IP: 299	R, DB, MC	IP: 4 weeks	Low	TNFα antagonist naive	Remission (CDAI <150*), CR-100, CR-70
GAIN	IP: 325	R, DB, MC	IP: 4 weeks	Low	TNFα antagonist refractory	Remission (CDAI <150*), CR-100, CR-70
Watanabe 2012	IP: 90 **MP: 43**	R, DB Japan trial	IP: 4 weeks, MP:56 weeks#	Low	TNFα antagonist experienced (≈57 had prior use, % refractory not reported) Must have attained CR-70 to enter MP	Remission (CDAI <150*), CR-100, CR-70
CLASSIC II	**MP: 55[a]**	R, MC OL[a] (IP) + DB (MP)	MP: 56 weeks#	Low	TNFα antagonist naïve Attained clinical remission (CDAI<150) by Week 4 of induction therapy in CLASSIC I.	Remission (CDAI <150*), CR-100, CR-70
CHARM	**MP: 499[b]**	R, MC, OL (IP) +DB (MP)	MP: 56 weeks#	Low	TNFα antagonist naïve and experienced (non-refractory)	Remission (CDAI <150)*, CR-100, CR-70
Infliximab versus placebo						
T16	IP: 108	R, DB, MC	IP: 4 weeks	Low	TNFα antagonist naïve	Remission (CDAI <150), CR-70*
ACCENT I	**MP: 335**	R, MC, OL (IP) + DB (MP)	MP: 54 weeks#	Low	TNFα antagonist naïve	Remission (CDAI <150)*, CR-70
Vedolizumab versus placebo						
GEMINI II	IP: 368 **MP: 461**	R, MC, OL (IP) + DB (MP)	IP: 6 weeks, MP: 52 weeks#	Low	TNFα antagonist naïve or experienced (including≈50% refractory patients)	Remission (CDAI <150*), CR-100* (wk6), CR-70
GEMINI III	IP: 416	R, DB, MC	IP: 6 weeks	Low	TNFα antagonist naïve or experienced (including≈76% refractory patients)	

Abbreviations: DB=double blind; MC=multicentre, IP= induction phase; MP = maintenance phase; OL=open-label; R=randomised, CR-70=clinical response as defined by attaining CDAI ≥ 70 point reduction from baseline; CR-100= clinical response as defined by attaining CDAI ≥ 100 point reduction from baseline.

* denote primary trial outcome

counted from start of induction therapy.

^ Subjects with a baseline CDAI score of ≥220 to ≥248 points were considered to be in clinical response if a CDAI score of <150 was attained. Subjects who met any of the treatment failure rules (Section 3.11.2.6.1), or who were missing more than 4 components of the CDAI score at Week 6, were considered not to have achieved clinical response at Week 6.

[a] CLASSIC II had 55 patients in the randomised cohort; only this cohort is presented here. The 204 patients in this trial who were ineligible for randomisation and received open-label adalimumab have not been included here.

[b] CHARM was considered a maintenance trial, as induction therapy used a lower adalimumab dose than TGA-approved, and there was no placebo comparison in induction. Induction therapy response was conducted at Week 4.

Source: compiled during the evaluation

Fistulising CD

6.12 **Table 3: Key features of the included evidence- Fistulising CD**

Trial	N (with fistulas)	Design	Durations	Risk of bias	Patient population	Relevant Outcomes
Ustekinumab versus placebo						
UNITI-1	IP: 143[c]	R, DB, MC	IP: 8 weeks	Low	TNFα refractory	Fistula response ≥50% reduction in number of opening/draining fistulas+
UNITI-2	IP: 98[c]	R, DB, MC	IP: 8 weeks	Low	TNF naïve and TNF experienced (non-refractory)	
IM-UNITI	MP: 59	R, DB, MC	MP: 52 weeks#	Low	Patients with response (CR-100) to UST induction at W8 of UNITI-1 or UNITI-2	Fistula response ≥50% reduction from baseline of the induction trial in the number of opening/draining fistulas+
Adalimumab versus. Placebo						
CLASSIC I	IP: 32	R, DB, MC	IP: 4 weeks	Low	TNFα antagonist naive	Fistula response ≥50% reduction in number of draining fistulas at 2 consecutive visits (wk 2 and 4). Fistula remission Closing of all draining fistulas at 2 consecutive visits (wk 2 and 4)
GAIN	IP: 45	R, DB, MC	IP: 4 weeks	Low	TNFα antagonist experienced (intolerance or lost response)	Fistula response ≥50% reduction in number of draining fistulas at 2 consecutive visits (wk 2 and 4). Fistula remission Closing of all draining fistulas at 2 consecutive visits (wk 2 and 4)
CHARM[b]	MP: 64	R, MC, OL (IP) +DB (MP)	(IP: 4 weeks) MP: 56 weeks#	Low	TNFα antagonist naive	Fistula remission Complete closure of all draining fistulas (wk 26 and 56#)
Infliximab versus placebo						
T20	IP: 94	R, DB, MC	IP: 18 weeks	Low	Single or multiple draining fistulas fistulas ≥ 3 months; TNFα antagonist naive	Fistula response ≥50% reduction in number of draining fistulas at ≥2 consecutive visits. Fistula remission Absence of any draining fistulas at 2 consecutive visits
ACCENT II[d]	MP: 306	R, MC, OL (IP) + DB (MP)	(IP: 14 weeks) MP: 54 weeks#	Low	Single or multiple draining fistulas ≥ 3 months; Infliximab naive	Fistula response Time to loss of response* ≥50% reduction in number of draining fistulas at consecutive visits ≥4 weeks apart (at wk 54#). Fistula remission Absence of draining fistulas (wk 54#)

Abbreviations: DB=double blind; MC=multicentre, IP= induction phase; MP = maintenance phase; OL=open-label; R=randomised, CR-70=clinical response as defined by attaining CDAI ≥ 70 point reduction from baseline; CR-100= clinical response as defined by attaining CDAI ≥ 100 point reduction from baseline; wk=week

* denotes the primary trial outcome

\# counted from start of induction therapy.

+ Enterocutaneous fistulas (e.g., perianal and abdominal) were to be considered no longer draining (i.e., closed) when there was an absence of drainage despite gentle compression. Rectovaginal fistulas were to be considered closed based on either physical examination or absence of relevant symptoms (eg, passage of rectal material or flatus from the vagina). No treatment failure rules or missing data rules were applied to this endpoint; if the number of draining fistulas at baseline or at the visit of interest was missing, fistula response could not be derived.

[b] CHARM was considered as a maintenance trial. Induction therapy in this trial was with a lower adalimumab dose than TGA-approved, and there was no placebo comparison in induction.

[C] These figures were derived from the total number of patients in the trial with current fistula at baseline (TSIDEM03, p127 of UNITI-1 CSR; TSIDEM03, p132 of UNITI-2 CSR). They are larger than the number of patients with a fistula at baseline on p75 of UNITI-1 CSR (93 patients with fistula), and p80 of UNITI-2 CSR (68 patients with fistula), respectively.

[d] ACCENT II was considered a maintenance trial as all patients had received induction infliximab prior to randomisation.

Source: compiled during the evaluation

Comparative effectiveness

Severe CD

6.13 The submission nominated clinical remission defined as Crohn's disease activity index (CDAI) < 150 as the primary outcome for induction therapy. This is reasonable as this outcome definition is consistent with the continuation criteria for PBS treatment. Trials have also reported outcomes of clinical response defined by either a ≥100 point or 70 point reduction in CDAI from baseline (CR-100 or CR-70).

6.14 For the maintenance phase indirect comparisons, the submission nominated clinical remission in remitters (i.e. those who attained CDAI<150) as the primary outcome, as this most closely reflects the PBS criteria for continuing biologic treatment. This resulted in the exclusion of two (out of three) ADA maintenance trials (CHARM and Watanabe) from the indirect comparisons as the results reported were for clinical remission in responders (CR-70), rather than remitters. For the UST trial (IM-UNITI) the primary outcome was remission in CR-100 responders, so remission in remitters was a post-hoc analysis. Although the logic of this nomination was not wrong, it is considered too restrictive given the timing of initial efficacy assessments varied in the trials, and had all preceded PBS assessments. For example, in the ADA trials, initial response was assessed at Week 4 which is 8 weeks prior to when efficacy would be assessed on the PBS, thus patients who only attained clinical response (CR-70 or CR-100) at Week 4 could very well attain remission by Week 12. Therefore the results of CHARM and Watanabe were included in additional indirect comparisons conducted during the evaluation.

6.15 Results of indirect comparisons of UST versus comparators in severe CD for the outcome of clinical remission are presented in Tables 4 and 5 for induction and maintenance respectively. Results of indirect comparisons for the outcomes of CR-100 and CR-70 are presented in Section B of the commentary.

Table 4: Results from induction phase of trials (ITT) – clinical remission (CDAI <150)

Trial	Drug	Placebo	RR (95% CI)	RD (95% CI)	NNT
UST [wk0: tiered dose/kg] -Wk 8 results					
UNITI-1	52/249 (20.9)	18/247 (7.3)	**2.87 (1.73, 4.75)**	**0.14 (0.08, 0.20)**	7
UNITI-2	84/209 (40.2)	41/209 (19.6)	**2.05 (1.49, 2.82)**	**0.21 (0.12, 0.29)**	5
Meta-analysis			**2.28 (1.68, 3.12)**	**0.16 (0.09, 0.23)**	6
ADA [wk0: 160mg, wk2: 80mg] - Wk 4 results					
CLASSIC-I	27/76 (35.5)	9/74 (12.2)	**2.92 (1.48, 5.78)**	**0.23 (0.10, 0.36)**	4
GAIN	34/159 (21.4)	12/166 (7.2)	**2.96 (1.59, 5.51)**	**0.14 (0.07, 0.22)**	7
Watanabe	11/33 (33.3)	3/23 (13.0)	2.56 (0.80, 8.15)	0.20 (-0.01, 0.41)	N/A
Meta-analysis			**2.89 (1.88, 4.42)**	**0.17 (0.11, 0.23)**	6
IFX [wk0: 5mg/kg] - Wk 4 results					
T16	13/27 (48.1)	1/24 (4.2)	**11.56 (1.63, 81.89)**	**0.44 (0.24, 0.64)**	2
VDZ [wk0: 300mg, wk2:300mg] – Wk 6 results					
GEMINI II	32/220 (14.5)	10/148 (6.8)	**2.15 (1.09, 4.24)**	**0.08 (0.02, 0.14)**	13
GEMINI III	40/209 (19.1)	25/207 (12.1)	**1.58 (1.00, 2.51)**	**0.07 (0.00, 0.14)**	14
Meta-analysis			**1.75 (1.19, 2.56)**	**0.07 (0.03, 0.12)**	14
All bDMARDs (ADA, IFX, VDZ)			**2.35 (1.68, 3.29)**	**0.16 (0.08, 0.23)**	6
Indirect comparisons					
UST v ADA			0.79 (0.47, 1.34)	-0.01 (-0.10, 0.08)	N/A
UST v IFX			0.20 (0.03, 1.43)	**-0.28 (-0.49, -0.07)**	N/A
UST v VDZ			1.30 (0.80, 2.13)	**0.09 (0.01, 0.17)**	N/A
UST v ADA/IFX/VDZ			0.97 (0.61, 1.53)	0.00 (-0.10, 0.10)	N/A

Abbreviations: UST=ustekinumab, ADA=adalimumab, IFX=infliximab, VDZ=vedolizumab, wk=week; IP=induction phase, doses used in trial are depicted in brackets next to drug name as well as the timing of assessment of results. [ ] indicate dosage administered. Statistically significant results are in **bold**.

Source: constructed during the evaluation from sources presented in the submission and published trials of infliximab and vedolizumab in CD.

Table 5: Maintenance trials (ITT) – clinical remission (CDAI <150) in patients with either clinical remission or clinical response after a period of induction

Trial	Drug	Placebo	RR (95% CI)	RD (95% CI)	NNT
UST (90mg q8w) - Wk 52 results (incl. IP)					
IM-UNITI (CR-100 wk8 i[a])	68/128 (53.1)	47/131 (35.9)	**1.48 (1.12, 1.96)**	**0.17 (0.05, 0.29)**	6
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) - Wk 52 or 56 (excl. IP)					
CLASSIC-II (CDAI<150 wk4&8 i[b])	15/19 (78.9)	8/18 (44.4)	**1.78 (1.01, 3.13)**	**0.35 (0.05, 0.64)**	3
CHARM (CR-70 wk4 i[c])	62/172 (36.0)	20/170 (11.8)	**3.06 (1.94, 4.84)**	**0.24 (0.16, 0.33)**	4
Watanabe (CR-70 wk4 i[d])	8/21 (38.1)	2/22 (9.1)	**4.19 (1.00, 17.50)**	**0.29 (0.05, 0.53)**	3
Meta-analysis			**2.54 (1.61, 4.01)**	**0.26 (0.18, 0.33)**	4
IFX (5mg/kg wk2, wk6, q8w) - Wk 56 results (incl. IP)					
ACCENT I (CR-70 wk2 i[e])	32/113 (28.0)	15/110 (13.7)	**2.08 (1.19, 3.61)**	**0.15 (0.04, 0.25)**	7
VDZ (300mg q8w) – Wk 52 results (incl IP)					
GEMINI II (CR-70 wk6 i[f])	60/154 (39.0)	33/153 (21.6)	**1.81 (1.26, 2.59)**	**0.17 (0.07, 0.27)**	6
All bDMARDs (ADA, IFX, VDZ)			**2.16 (1.68, 2.78)**	**0.20 (0.15, 0.26)**	5
Indirect comparisons					
UST_{ITT} v ADA			0.58 (0.34, 1.00)	-0.09(-0.23,0.05)	N/A
UST_{ITT} v IFX			0.71 (0.38, 1.32)	0.02 (-0.12,0.16)	N/A
UST_{ITT} v VDZ			0.82 (0.51, 1.30)	0.00 (-0.16,0.16)	N/A
UST_{ITT} v ADA/IFX/VDZ			0.69 (0.47, 1.00)	-0.03(-0.16,0.10)	N/A
$UST_{POST\text{-}HOC}$ v $ADA_{CLASSIC\text{-}II\ only}$			[redacted]	[redacted]	[redacted]

Abbreviations: UST=ustekinumab, ADA=adalimumab, IFX=infliximab, VDZ=vedolizumab, wk=week; IP=induction phase, doses used in trial are depicted in brackets next to drug name as well as the timing of assessment of results; i=induction phase. Statistically significant results are in **bold**.

[a] CR-100 responders at wk8 following induction with either 130mg, weight-based dose or placebo at wk0 (UNITI-1 or UNITI-2)

[b] CDAI<150 'remission' at wk 4 and wk8 following induction with either 160/80mg, 80/40mg, 40/20mg or placebo at wk0 and wk2 (in CLASSIC-I) then 40mg at wk4 and wk6 (OL phase in CLASSIC-II)

[c] CR-70 responders at wk4 following induction with 80/40mg at wk0 and wk2

[d] CR-70 responders at wk4 following induction with either 160/80mg, 80/40mg or placebo at wk0 and wk2.

[e] CR-70 responders at wk2 following induction with 5mg/kg at wk0

[f] CR-70 responders at wk6 following induction with 300mg at wk0 and wk2

Source: constructed during the evaluation from sources presented in the submission and published trials of infliximab and vedolizumab in CD.

6.16 A discussion of these results is presented under "Clinical claim".

Fistulising CD

6.17 The results of fistula outcomes in the UST, ADA and IFX trials are summarised in Tables 6 and 7 below for induction and maintenance respectively. Treatment effect estimates between active treatment and placebo were conducted during the evaluation, however due to differences in outcome definition no indirect comparisons were able to be conducted.

Table 6: Results of fistula response for ustekinumab, adalimumab and infliximab- induction trials

Trial ID	Drug n/N (%)	Placebo n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
Ustekinumab (fistula response: ≥50% reduction in fistulas) Wk 8					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (fistula response: ≥50% reduction in fistulas at wk2 and 4) Wk 4					
CLASSIC I	1/12 (8)	2/6 (33)	-0.25 (-0.65, 0.13)	0.25 (0.04, 1.67)	0.18 (0.001, 4.88)
GAIN	3/20 (15)	5/25 (20)	-0.05 (-0.28, 0.20)	0.75 (0.21, 2.51)	0.71 (0.10, 4.30)
Adalimumab (fistula remission: complete closure of fistulas) Wk 4					
CLASSIC I	0/12 (0)	1/6 (17)	-0.17 (-0.57, 0.12)	0.25 (0.00, 1.80)	0.21 (0.005, 42.37)
GAIN	1/20 (5)	2/25 (8)	-0.03 (-0.21, 0.17)	0.63 (0.08, 4.46)	0.61 (0.01, 12.61)
Infliximab (fistula response: ≥50% reduction in fistulas at 2 or more visits)					
T20 (wk18)	21/31 (68)	8/31 (26)	**0.42 (0.17, 0.62)**	**2.63 (1.45, 5.13)**	**6.04 (1.78, 21.15)**
ACCENT II^ (Wk14)	195/282 (69)	-	**-**	**-**	**-**
Infliximab (fistula remission : complete closure of fistulas) Wk18					
T20	17/31 (55)	4/31 (13)	**0.42 (0.19, 0.61)**	**4.25 (1.75, 11.15)**	**8.20 (2.06, 38.61)**

Results extracted and estimated during the evaluation. RD, RR and OR was estimated using Stats Direct version 3. Statistically significant results are in **bold**.
^open label induction therapy, no placebo arm comparison, randomisation occurred after assessment of initial response.
Source: Table B.6-3, B.6-4, p88-89 of Section B of the submission and the trial reports.

Table 7: Results of fistula response for ustekinumab, adalimumab and infliximab – Maintenance trials

Trial ID	Drug n/N (%)	Placebo n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
Ustekinumab (fistula response: ≥50% reduction in fistulas) Wk 52#					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (fistula remission: complete closure of all fistulas) Wk 26#					
CHARM^	10/30 (33)	6/47 (13)	**0.21 (0.02, 0.40)**	**2.61 (1.09, 6.31)**	**3.42 (0.95, 12.98)**
Adalimumab (fistula remission: complete closure of all fistulas) Wk 56#					
CHARM^	11/30 (37)	6/47 (13)	**0.24 (0.05, 0.44)**	**2.87 (1.23, 6.83)**	**3.96 (1.12, 14.84)**
Infliximab (fistula response: ≥50% reduction in fistulas at consecutive visits) W 54#					
ACCENT II	42/91 (46)	23/98 (23)	**0.23 (0.09, 0.36)**	**1.97 (1.30, 3.01)**	**2.80 (1.44, 5.49)**
Infliximab fistula remission (complete closure of all fistulas) Wk 54#					
ACCENT II	33/91 (36)	19/98 (19)	**0.17 (0.04, 0.29)**	**1.87 (1.16, 3.05)**	**2.37 (1.17, 4.85)**

Results extracted and estimated during the evaluation. All RD, RR and OR were estimated during the evaluation using Stats Direct version 3.
counted from start of induction therapy. [redacted]. ^ a lower loading dose was used in CHARM of 80mg at Wk0 then 40mg at Wk2. Statistically significant results are in **bold**.
Source: Table B.6-13 and B-14, p111-112 of Section B of the submission, p58 of Colombel 2007 and the trial publications.

6.18 Although not directly comparable across trials, the results for induction therapy show that both UST and ADA were not significantly different to placebo treatment in attaining either fistula response or remission. IFX treatment however was associated with significant improvements for both outcomes (fistula response (RD (95%CI): 0.42 (0.17, 0.62)) and remission (RD (95%CI): 0.42 (0.19, 0.61)).

6.19 During maintenance, significantly greater proportions of ADA and IFX treated patients attained fistula response and remission versus placebo. For UST, the comparison was not statistically significant to placebo. However, the numbers of patients giving results was very small (≤[redacted] patients in each arm), thus the comparison would have lacked statistical power. Importantly as the UST trials do not report on number of patients who attain fistula remission (which was the outcome relied on by the PBAC in previous considerations of fistulising CD), the data supporting the listing of UST in fistulising disease is considered poor and not comparable to those for listed treatments.

Comparative harms

6.20 There were no significant differences in the relative risks of any adverse events, serious adverse events or discontinuations due to adverse events with UST compared to ADA.

Clinical claim

Severe CD

6.21 The submission described UST as non-inferior in terms of comparative effectiveness over ADA for severe CD. The evaluation considered this may not be reasonable particularly in the maintenance phase. For maintenance, the submission's indirect comparison of clinical remission in initial remitters had relied on the results of CLASSIC II for ADA which was a follow-on trial from CLASSIC I, with very small patient numbers (37 patients in total) and no additional statistical power to determine differences. The results used for UST from IM-UNITI were also post-hoc. Additional indirect comparison conducted during the evaluation using results from all ADA maintenance trials (CLASSIC II, CHARM and Wantanabe) also showed that results had consistently favoured ADA (although none reached statistical significance), which is also true for results of indirect comparisons for the initiation phase. No non-inferiority margins were nominated by the submission, however based on the lower confidence intervals of indirect comparisons, UST may be up to [redacted]% (RD) worse than ADA (See Table 5).

6.22 The PBAC noted a number of exchangeability issues in the indirect comparison may have biased results against ustekinumab.

6.23 Based on PBS Therapeutic Relativity Sheets (dated 1 October 2016), the submission also claimed that UST is non-inferior to IFX and VDZ. This conclusion may not be appropriate for IFX. Results of additional indirect comparisons conducted during the evaluation indicated:

- UST may be inferior in terms of comparative effectiveness over IFX.
- During induction, for clinical remission (CDAI<150) UST treated patients had significantly lower response rates versus IFX when tested using the RD statistic (however the differences did not reach statistical significance using the RR and OR statistics). For clinical response (CR-70), UST treatment was associated with significantly lower response compared to IFX (RD (95%CI: 0.32 (0.13, 0.81)).
- For maintenance, the results had favoured IFX, but did not reach statistical significance.
- Although there were no significant differences in comparative effectiveness results between UST and VDZ, in maintenance, they had favoured VDZ. No non-inferiority margin was nominated by the submission to assist with interpretation of the evidence.

6.24 The results of the indirect comparisons need to be interpreted with caution given differences across trials that may affect exchangeability, such as prior treatment and response to TNFα antagonists, timing of treatment assessments, date of the trials and response criteria for enrolment into the maintenance phase. The trial data for IFX during induction (T16) also had extremely wide confidence intervals with very small patient numbers.

6.25 The PBAC considered, on balance, that the claim of non-inferior comparative effectiveness of ustekinumab for the treatment of severe Crohn's disease was reasonable.

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

Fistulising CD

6.26 The submission described UST in fistulising CD as non-inferior in terms of comparative effectiveness over ADA and also versus IFX (based on the PBS Therapeutic Relativity Sheets (dated 1 October 2016)). This claim was poorly supported:

- No comparative results between UST and comparators were presented, and the claim for UST relied on a descriptive comparison versus ADA.
- The UST trials had small numbers of patients with fistulas and the results showed no difference versus placebo in terms of fistula response (≥50% reduction in fistulas from baseline) in either induction or maintenance phases.
- This differs to results from ADA and IFX trials, which particularly for maintenance showed that significantly more patients treated with ADA and IFX had achieved fistula remission (complete closure of fistulas) and/or response (≥50% reduction in fistulas) versus placebo.

6.27 The PBAC considered the claim of non-inferior comparative effectiveness of ustekinumab for the treatment of fistulising Crohn's disease was not supported.

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

Safety

6.28 The submission described UST as non-inferior in terms of comparative safety over ADA. Notwithstanding potential issues of exchangeability and differences in trial durations, this claim appears to be reasonable.

6.29 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

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

Economic analysis

6.30 The submission presented a cost-minimisation analysis. Special pricing arrangements are in place for ADA, and VDZ in Crohn's disease. There is an indication specific price for IFX for the treatment of CD.

6.31 The equi-effective doses are estimated as:

- UST, administered as IV tiered weight-based loading dose at Week 0 and then subcutaneously 90 mg every 8 weeks;

- ADA administered as 160 mg SC injection at Week 0, 80 mg at Week 2, and 40 mg every 2 weeks thereafter;
- IFX 5 mg/kg administered as an IV infusion at Week 0, Week 2, Week 6 and then every 8 weeks; and
- VDZ 300 mg administered as an IV infusion at Week 0, Week 2, Week 6 and then every 8 weeks.
- The trials and previously accepted therapeutic relativities provided the source of the equi-effective doses.

6.32 There is no estimated net cost impact at the prices quoted in Table 8, which included additional offsets for administration costs of IV infusions. IFX now has a lower cost than both ADA and VDZ (using the commercial-in-confidence effective prices) due to a 16% price reduction on 1 December 2015.

6.33 The requested prices for UST in complex refractory fistulising CD are the same as for severe CD, even though the cost-minimised prices were slightly lower for fistulising CD (due to the removal of VDZ as comparator).

Table 8: Ustekinumab effective prices derived from cost-minimisation analyses

Ustekinumab form and strength	Schedule	Derived based on DPMQs		Derived based on AEMPs
		DPMQ (effective)	AEMP (effective)	AEMP (effective)
Severe CD				
1 x 130 mg vial	HSD - public	$[redacted]	$[redacted]	$[redacted]
1 x 130 mg vial	HSD – private	$[redacted]	$[redacted]	$[redacted]
2 x 45 mg vials	Section 85	$[redacted]	$[redacted]	$[redacted]
Fistulising CD				
1 x 130 mg vial	HSD - public	$[redacted]	$[redacted]	$[redacted]
1 x 130 mg vial	HSD – private	$[redacted]	$[redacted]	$[redacted]
2 x 45 mg vials	Section 85	$[redacted]	$[redacted]	$[redacted]

Source: Table D.2.5, p15 of Section D of the submission. The effective AEMP which were derived based on AEMPs were compiled during the evaluation.

6.34 The PBAC noted if treatment with UST was substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing if it is satisfied that the UST provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The lowest cost alternative therapy was noted to be infliximab.

6.35 The pre-PBAC response proposed a new price for ustekinumab consistent with the cost-minimised price to infliximab. The proposed prices offered are $[redacted] for 1 x 30 mg vial and $[redacted] for 2 x 45 mg vials. These new proposed prices correspond to a [redacted]% price reduction for the 130 mg vial and [redacted]% price reduction for the 2 x 45 mg vials.

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

Drug cost/patient/over 2 years

6.36 $[redacted] during the 16 week induction period and $[redacted] for continued maintenance period (based on the effective DPMQs derived from cost-minimisation analysis versus a weighted mixed comparator of ADA [redacted]%, IFX [redacted]% and VDZ [redacted]%). Current utilisation on PBS is: 50.8% ADA, 46.2% IFX and 3% VDZ.

Estimated PBS usage & financial implications

6.37 This submission was not considered by DUSC. The submission primarily used a market share approach based on PBS 10% data to estimate the total use of UST for both indications (severe CD and fistulising CD).

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number on initial IV loading dose (also equal to number of scripts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number continuing from Week 16 to Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number continuing from previous year	[redacted] [a]	[redacted]	[redacted]	[redacted]	[redacted]
Number of 45 mg x 2 scripts [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS (using cost-minimised prices for ustekinumab)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]
Severe CD	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Fistulising CD	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] [redacted]% additional growth due to grandfathered patients

[b] 4.5 packs per patient for patients continuing beyond initiation to end of first year; 6.5 packs per patient per year for patients continuing from previous year.

Source: Tables E.2.4-E.2.6; E.4.1, pp.23-31 of Section E of the submission; E5 worksheet of Section E EXCEL spreadsheet.

The redacted table shows that at year 5, the estimated number of patients was 10,000 – 50,000 per year and the net cost to the PBS would be less than $10 million.

6.38 The submission estimated a net cost to the government budget driven by: i) the assumption of additional market growth (above background growth) for UST as a result of patients who are refractory or intolerant to currently listed biologics returning for treatment, and ii) the grandfathering of a small number of patients on the PBS.

6.39 The evaluation considered the net cost of listing UST may be underestimated because the submission assumed Year 1 to be April 2016-March 2017. The financial implications were most sensitive to the price of UST.

Quality Use of Medicines

6.40 The submission stated that the quality use of UST would be ensured through the provision of educational resources and support for patients, prescribers, dispenser and IBD (Inflammatory Bowel Disease) nurses, and the development of a Patient Support Program.

Financial Management – Risk Sharing Arrangements

6.41 The submission proposed a Special Pricing Arrangement whereby the ex-manufacturer prices of UST for the single 130mg/26mL and 2 x 45mg/0.5mL UST vials $[redacted] and $[redacted] respectively. Identical prices were proposed for the fistulising CD indication.

7 PBAC Outcome

7.1 The PBAC recommended the listing of ustekinumab (UST) for the treatment of severe Crohn's disease in adult patients on the basis of cost-minimisation to infliximab. The PBAC accepted that UST leads to clinical remission and maintenance of clinical remission when compared to placebo and was considered non-inferior when compared with the alternative bDMARDs for severe Crohn's disease (infliximab (IFX), adalimumab (ADA) and vedolizumab (VED)).The PBAC did not recommend the listing of UST for the treatment of complex refractory fistulising Crohn's disease on the basis that it was uncertain whether UST led to fistula remission or response when compared to placebo, and there was insufficient clinical evidence to support non-inferiority with the alternative bDMARDs for fistulising Crohn's disease (ADA and IFX).

7.2 The PBAC noted that UST would provide patients with an alternative treatment option for severe Crohn's disease with a different mechanism of action compared to current PBS-listed treatments of IFX, ADA and VED.

7.3 The PBAC recommended listing in the General Schedule and in the S100 Highly Specialised Drugs Program as an Authority Required (in writing) benefit with the same conditions as IFX, ADA and VED for the treatment of severe Crohn's disease.

7.4 The PBAC noted that IFX and ADA are also currently PBS-listed for the treatment of severe Crohn's disease in patients aged 6 to 17 years. The PBAC considered it appropriate to exclude these patients from the eligible population for UST noting there is insufficient safety and efficacy data for this patient population.

7.5 The PBAC considered that in addition to the nominated comparator ADA, both IFX and VED are also appropriate comparators for the treatment of severe Crohn's disease in adult patients as these alternative treatments may also be replaced in clinical practice.

7.6 The PBAC noted the results of the indirect comparisons between UST (UNITI-1, UNITI-2 and IM-UNITI) and ADA (CLASSIC I, GAIN, CLASSIC II, CHARM and Watanabe); UST and IFX (T16 and ACCENT I) and UST and VED (GEMINI II and GEMINI III) for severe Crohn's disease. The PBAC considered that the indirect comparison results for induction and maintenance phase trials of UST vs ADA, IFX and VED did not strongly support non-inferiority in terms of efficacy of UST over ADA, IFX or VED. However, the PBAC considered that given a more biologic experienced and treatment refractory patient population were recruited to the IM-UNITI trial, the longer biological half-life of UST (compared to ADA) and greater durability of UST IV loading dose (compared to ADA), the indirect comparisons may be biased against UST. Further, the PBAC noted that there were also exchangeability issues between

the UST, VED and IFX trials. The PBAC considered, on balance, that overall, UST may be a reasonable alternative to ADA, IFX and VED for severe Crohn's disease.

7.7 The PBAC considered that the claim of non-inferior comparative safety over ADA was reasonable despite exchangeability issues between the trials and differences in trial duration.

7.8 The PBAC did not consider the proposed weighted price for UST was justified given, if treatment with UST was substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing if it is satisfied that the UST provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. No significant improvement in efficacy or safety for some patients was demonstrated and therefore, the PBAC noted the cost-minimisation should be with the lowest cost alternative therapy, which was infliximab.

7.9 The PBAC considered the equi-effective doses for treatment of severe Crohn's disease in adult patients are:

- IFX – 5 mg/kg administered at week 0, week 2, week 6 and then every 8 weeks thereafter; and
- UST – administered as an IV tiered weight-based loading dose at week 0 and then subcutaneously 90 mg every 8 weeks.

7.10 The PBAC noted that UST was not significantly more effective in inducing fistula response (≥50% reduction in fistulas) compared with placebo in either induction (UNITI-1 and UNITI-2) or maintenance trials (IM-UNITI) whereas the ADA (CHARM) and IFX (ACCENT II) trials showed a significant improvement over placebo for fistula remission during maintenance. The PBAC noted that the trial data for UST for the treatment of fistulising Crohn's disease was poor with only eight patients in the treatment arm of the maintenance trial IM-UNITI. The PBAC therefore concluded that non-inferiority of UST compared with ADA/IFX was not supported in the submission. Further, the PBAC noted that UST was not currently TGA registered for the fistulising Crohn's disease indication.

7.11 The PBAC advised that ustekinumab is not suitable for prescribing by nurse practitioners.

7.12 The PBAC recommended that the Early Supply Rule should not apply to ustekinumab.

7.13 In accordance with subsection 101(3BA) of the Act the PBAC advised that it is of the opinion that, on the basis if the material available to it at its March 2017 meeting, ustekinumab should not be treated as interchangeable on an individual patient basis with any other drugs.

7.14 The PBAC noted that this will be a complex restriction.

7.15 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 The PBAC noted that flow-on restriction changes to IFX, ADA and VED for severe Crohn's disease in adults will be required when UST is listed. The restrictions for IFX, ADA and VED will need to be updated to include UST as one of the biological disease modifying drugs (bDMDs) options for the treatment of severe Crohn's disease (the 4th drug in this setting).

8.2 Add new item (to be finalised):

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
USTEKINUMAB 130mg/26mL injection, 26mL vial	1	0		
USTEKINUMAB 45mg/0.5mL injection, 0.5mL vial	2	0	Stelara®	Janssen Cilag

Category / Program	GENERAL – General Schedule (Code GE) Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	**Severe Crohn disease**
PBS Indication:	**Severe Crohn disease**
Treatment phase:	**Initial treatment (new patient – initial 1)**
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Clinical criteria:	Patient must have confirmed severe Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician, AND Patient must have failed to achieve an adequate response to prior systemic therapy with a tapered course of steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period; OR Patient must have a documented intolerance of a severity necessitating permanent treatment withdrawal or a contraindication to steroids,

	AND Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with azathioprine at a dose of at least 2 mg per kg daily for 3 or more months or have a documented intolerance of a severity necessitating permanent treatment withdrawal or a contraindication to this drug; OR Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more months or have a documented intolerance of a severity necessitating permanent treatment withdrawal or a contraindication to this drug; OR Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with methotrexate at a dose of at least 15 mg weekly for 3 or more months or have a documented intolerance of a severity necessitating permanent treatment withdrawal or a contraindication to this drug, AND Patient must have severity of disease activity which results in a Crohn Disease Activity Index (CDAI) Score greater than or equal to 220 if affected by extensive small intestine disease; OR Patient must have severity of disease activity which results in a Crohn Disease Activity Index (CDAI) Score greater than or equal to 300 if not affected by extensive small intestine disease, short gut syndrome or is an ostomy patient, AND Patient must have evidence of intestinal inflammation and have diagnostic imaging or surgical evidence of short gut syndrome if affected by the syndrome or has an ileostomy or colostomy; OR Patient must have radiological evidence of intestinal inflammation if the patient has extensive small intestinal disease affecting more than 50 cm of the small intestine; OR Patient must (a) have evidence of intestinal inflammation, including: (i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or (ii) faeces: higher than normal lactoferrin or calprotectin level; or (iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery; or (b) be assessed clinically as being in a high faecal output state; or (c) be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient.
Population criteria:	Patient must be aged 18 years or older
Prescriber Instructions	Applications for authorisation must be made in writing and must include: (a) two completed authority prescription forms; and (b) a completed Crohn Disease PBS Authority Application - Supporting Information Form which includes the following:

	(i) the completed current Crohn Disease Activity Index (CDAI) calculation sheet including the date of assessment of the patient's condition if relevant; and (ii) details of prior systemic drug therapy [dosage, date of commencement and duration of therapy]; and (iii) the reports and dates of the pathology or diagnostic imaging test(s) nominated as the response criterion, if relevant; and (iv) the date of the most recent clinical assessment; and (v) the signed patient acknowledgement indicating they understand and acknowledge that the PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment. At the time of authority application, medical practitioners should request the appropriate number of 130 mg vials to provide sufficient drug, based on the weight of the patient, for a single infusion. Up to a maximum of 4 vials will be authorised. Two completed authority prescriptions must be submitted with the initial application. One prescription must be for the IV loading dose for a sufficient number of 130 mg vials for one dose based on the patient's weight with no repeats. The second prescription must be written for the 45 mg vials for SC injection, with a maximum quantity of 2 and no repeats. Where no authority prescription for subcutaneous injection are requested at the time of the initial application, authority approvals for sufficient 45 mg vials to complete a maximum of 16 weeks of treatment with ustekinumab (two 45 mg vials and no repeats) may be requested by telephone by contacting the Department of Human Services and applying through the Balance of Supply restriction. Under no circumstances will telephone approvals be granted for initial authority applications, or for treatment that would otherwise extend the initial treatment period. All assessments, pathology tests and diagnostic imaging studies must be made within 1 month of the date of application. If treatment with any of the specified prior conventional drugs is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application. If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application. Details of the accepted toxicities including severity can be found on the Department of Human Services website. Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS-subsidised therapy. A maximum quantity and number of repeats to provide for an initial 16 week course of this drug will be authorised.

	The assessment of the patient's response to this initial course of treatment must be made following a minimum of 12 weeks of therapy so that there is adequate time for a response to be demonstrated. This assessment, which will be used to determine eligibility for further continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. It is recommended that an application for continuing treatment is posted to the Department of Human Services at the time of the 12 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.

Category / Program	GENERAL – General Schedule (Code GE) Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	**Severe Crohn disease**
PBS Indication:	**Severe Crohn disease**
Treatment phase:	**Change or re-commencement of treatment (Initial 2)**
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Clinical criteria:	Patient must have received prior PBS-subsidised treatment with a biological disease modifying drug for this condition in this treatment cycle, AND Patient must not have failed PBS-subsidised therapy with this drug for this condition more than once in the current treatment cycle
Population criteria:	Patient must be aged 18 years or older
Prescriber Instructions	Applications for authorisation must be made in writing and must include: (a) two completed authority prescription forms; and (b) a completed Crohn Disease PBS Authority Application - Supporting

	Information Form which includes the following: (i) the completed current Crohn Disease Activity Index (CDAI) calculation sheet including the date of assessment of the patient's condition if relevant; and (ii) details of prior systemic drug therapy [dosage, date of commencement and duration of therapy]; and (iii) the reports and dates of the pathology or diagnostic imaging test(s) nominated as the response criterion, if relevant; and (iv) the date of the most recent clinical assessment; At the time of authority application, medical practitioners should request the appropriate number of 130 mg vials to provide sufficient drug, based on the weight of the patient, for a single infusion. Up to a maximum of 4 vials will be authorised. Two completed authority prescriptions must be submitted with the initial application. One prescription must be for the IV loading dose for a sufficient number of 130 mg vials for one dose based on the patient's weight with no repeats. The second prescription must be written for the 45 mg vials for SC injection, with a maximum quantity of 2 and no repeats. To demonstrate a response to treatment the application must be accompanied by the results of the most recent course of biological disease modifying drug (bDMD) therapy within the timeframes specified in the relevant restriction. Where the most recent course of PBS-subsidised bDMD treatment was approved under an initial treatment restriction, the patient must have been assessed for response to that course following a minimum of 12 weeks of therapy for adalimumab or ustekinumab and up to 12 weeks after the first dose (6 weeks following the third dose) for infliximab and vedolizumab and this assessment must be submitted to the Department of Human Services no later than 4 weeks from the date that course was ceased. If the response assessment to the previous course of bDMD treatment is not submitted as detailed above, the patient will be deemed to have failed therapy with that particular course of bDMD. A maximum quantity and number of repeats to provide for an initial 16 week course of this drug will be authorised. The assessment of the patient's response to this initial course of treatment must be made following a minimum of 12 weeks of therapy so that there is adequate time for a response to be demonstrated. This assessment, which will be used to determine eligibility for further continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. It is recommended that an application for continuing treatment is posted to the Department of Human Services at the time of the 12 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	**Severe Crohn disease**
PBS Indication:	**Severe Crohn disease**
Treatment phase:	**Continuing treatment**
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must have demonstrated or sustained an adequate response to treatment with this drug, AND Patient must have an adequate response to this drug defined as a reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; OR Patient must have an adequate response to this drug defined as (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C-reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient.
Population criteria:	Patient must be aged 18 years or older
Prescriber Instructions	Applications for authorisation must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Crohn Disease PBS Authority Application - Supporting Information Form which includes the following: (i) the completed Crohn Disease Activity Index (CDAI) Score calculation sheet including the date of the assessment of the patient's condition, if relevant; or (ii) the reports and dates of the pathology test or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; and (iii) the date of clinical assessment.

	All assessments, pathology tests, and diagnostic imaging studies must be made within 1 month of the date of application. If the application is the first application for continuing treatment with this drug, an assessment of the patient's response to the initial course of treatment must be following a minimum of 12 weeks after the first dose so that there is adequate time for a response to be demonstrated. The assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and posted to the Department of Human Services no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criterion. Where an assessment is not submitted to the Department of Human Services within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with this drug. Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response. At the time of the authority application, medical practitioners should request the appropriate quantity and number of repeats to provide sufficient dose. Up to a maximum of 2 repeats will be authorised. If fewer than the maximum stated repeats in the relevant treatment phase are requested at the time of the application, authority approvals for sufficient repeats to complete the balance of the stated repeats in the relevant treatment phase may be requested by telephone by contacting the Department of Human Services and applying through the Balance of Supply restriction. Under no circumstances will telephone approvals be granted for treatment that would otherwise extend the relevant treatment phase.
Administrative Advice	No applications for increased maximum quantities will be authorised. No increase in the maximum number of repeats may be authorised.

Category / Program	GENERAL – General Schedule (Code GE) Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	**Severe Crohn disease**
PBS Indication:	**Severe Crohn disease**
Treatment phase:	**Initial PBS-subsidised treatment (Grandfather)**
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR

	Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Clinical criteria:	Patient must have previously received non-PBS-subsidised therapy with this drug for this condition prior to <<PBS listing date>>, AND Patient must have had a Crohn Disease Activity Index (CDAI) Score of greater than or equal to 300 prior to commencing treatment with this drug; OR Patient must have a documented history of intestinal inflammation and have diagnostic imaging or surgical evidence of short gut syndrome if affected by the syndrome or has an ileostomy or colostomy; OR Patient must have a documented history and radiological evidence of intestinal inflammation if the patient has extensive small intestinal disease affecting more than 50 cm of the small intestine, AND Patient must have an adequate response to this drug defined as a reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; OR Patient must have an adequate response to this drug defined as (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C-reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient.
Population criteria:	Patient must be aged 18 years or older
Prescriber Instructions	Applications for authorisation must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Crohn Disease PBS Authority Application - Supporting Information Form which includes the following: (i) the completed current Crohn Disease Activity Index (CDAI) calculation sheet including the date of assessment of the patient's condition if relevant; and (ii) details of prior systemic drug therapy [dosage, date of commencement and duration of therapy]; and (iii) the reports and dates of the pathology or diagnostic imaging test(s) nominated as the response criterion, if relevant; and (iv) the date of the most recent clinical assessment; and (v) the signed patient acknowledgement indicating they understand and acknowledge that the PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment. The assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and posted to the Department of Human Services no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criterion. Where an assessment is not submitted to the Department of Human Services within these timeframes, patients will be deemed to have failed to respond, or to

	have failed to sustain a response, to treatment with this drug. Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain the response. At the time of the authority application, medical practitioners should request the appropriate quantity and number of repeats to provide sufficient dose. Up to a maximum of 2 repeats will be authorised. If fewer than the maximum stated repeats in the relevant treatment phase are requested at the time of the application, authority approvals for sufficient repeats to complete the balance of the stated repeats in the relevant treatment phase may be requested by telephone by contacting the Department of Human Services and applying through the Balance of Supply restriction. Under no circumstances will telephone approvals be granted for treatment that would otherwise extend the relevant treatment phase. A patient may qualify for PBS-subsidised treatment under this restriction once only.
Administrative Advice	No applications for increased maximum quantities will be authorised. No increase in the maximum number of repeats may be authorised.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	**Severe Crohn disease**
PBS Indication:	**Severe Crohn disease**
Treatment phase:	**Balance of supply**
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☒ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Clinical criteria:	Patient must have received insufficient therapy with this drug under the Initial 1 (new patient) or Initial 2 (change or re-commencing patient) restriction to complete the initial dose (i.e. the subcutaneous injection at 8 weeks); OR Patient must have received insufficient therapy with this drug under the Continuing treatment restriction to complete 24 weeks of treatment, OR Patient must have received insufficient therapy with this drug to complete 24 weeks of treatment under the Initial PBS-subsidised treatment restriction for patients who had previously received non-PBS subsidised treatment (Grandfathered patient), AND

	The treatment must provide no more than the balance of up to 1 dose (Initial 1 or Initial 2) or 2 repeats (Continuing or grandfathered patients).
Population criteria:	Patient must be aged 18 years or older
Prescriber Instructions	Authority approval for sufficient therapy to complete a maximum of 1 initial dose or 2 repeats may be requested by telephone by contacting the Department of Human Services.
Administrative Advice	No applications for increased maximum quantities will be authorised. No increase in the maximum number of repeats may be authorised.

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

The sponsor had no comment.