6.06 USTEKINUMAB, Solution concentrate for I.V. infusion 130 mg in 26 mL, Solution for injection 90 mg in 1 mL pre-filled syringe, Stelara®, Janssen-Cilag Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested General Schedule and Section 100 (Highly Specialised Drugs Program), Authority Required listings for ustekinumab pre-filled syringes for subcutaneous (SC) administration and vials for intravenous (IV infusion), for the treatment of complex refractory fistulising Crohn disease (CD). This indication has previously been considered by the PBAC when it considered a submission to list UST for both severe CD and fistulising CD in March 2017.

1.2 If listed, UST would become the third biologic disease modifying anti-rheumatic drug (bDMARD) on the PBS for fistulising CD and the first treatment that targets pro-inflammatory cytokines interleukin (IL) 12 and 23. There are currently two bDMARDs listed on the PBS for fistulising CD that target tumour necrosis factor-α (TNF-α), adalimumab (ADA) and infliximab (IFX). Listing was requested on the basis of a cost-minimisation approach versus IFX (assumed to be the least costly alternative treatment).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with complex refractory fistulising Crohn disease (fistulising CD)
Intervention	UST: tiered weight-based (≤55 kg: 260 mg, 55-85 kg: 390 mg, >85 kg: 520 mg) IV infusion at Week 0, 90 mg SC injection at Week 8, then 90mg SC injection every 8 or 12 weeks thereafter.
Comparator	Main comparator: • ADA: 160 mg at Week 0, 80 mg at Week 2, then 40 mg every two weeks thereafter. The product information states patients who experience a decrease in their response may benefit from an increase in dosage to 40 mg every week or 80 mg fortnightly[a]. Secondary comparator: • IFX IV^: 5 mg/kg IV infusion at Week 0, Week 2 and Week 6 then 5 mg/kg IV infusion every 8 weeks thereafter. The product information states consideration may be given to treatment with 10 mg/kg for patients who respond and then lose their response[a].
Outcomes	Direct trial evidence, anchored and unanchored indirect comparisons of UST and the nominated comparators, for the following outcomes, following induction and maintenance therapy: • Fistula response (≥50% reduction in the number of open/draining fistulas), • Fistula remission (complete closure of all open/draining fistulas)
Clinical claim	Effectiveness: ○ UST is as effective as ADA and IFX in induction and maintenance treatment. Safety: ○ UST is non-inferior in terms of safety compared to ADA and IFX in induction and maintenance treatment.

Blue shading indicates data previously seen by the PBAC.
Source: Table 1.1, pp2-3 of the submission.
ADA = adalimumab; IFX = infliximab; IV = intravenous; SC = subcutaneous; UST = ustekinumab.
^ Note: IFX SC formulation is available on the PBS for fistulising CD after patients have completed the first two IFX IV infusions at Week 0 and Week 2. The recommended dose is 120 mg SC injection every two weeks for maintenance therapy (from Week 6).
[a] ADA 40 mg every week and IFX IV 10 mg/kg are not the main equi-effective doses but are mentioned in the product information for specific patients.

2 Background

Registration status

2.1 UST was TGA registered in March 2017 for: 'treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies'.

2.2 The submission acknowledged that the approved TGA indication for CD makes no reference to fistulising disease, but argued fistulising disease is considered a manifestation of moderate to severe disease and the clinical data used to support the TGA indication included some patients with fistulising CD. The submission noted that the TGA indication of ADA for CD also makes no reference to fistulising disease, but the PBAC had 'considered fistulising disease to be a manifestation of moderate to severe CD, and that it was reasonable to interpret that the TGA approved indication [for ADA] includes patients with fistulising disease' (Section 12, ADA Public Summary Document (PSD), November 2010 PBAC meeting).

Previous PBAC consideration

2.3 At the March 2017 PBAC meeting, the PBAC considered a joint submission for listing of UST for the treatment of severe CD and complex refractory fistulising CD. The PBAC recommended listing of UST for the treatment of severe CD but did not recommend listing for the treatment of complex refractory fistulising CD. The PBAC considered it was uncertain whether UST led to fistula remission or fistula response in patients with fistulising CD when compared to placebo and there was insufficient clinical evidence to support non-inferiority with ADA or IFX (paragraph 7.1, UST PSD, March 2017 PBAC Meeting).

2.4 For patients with fistulising CD, the March 2017 submission presented limited clinical data from three trials comparing UST vs placebo (UNITI-1, UNITI-2 and IM-UNITI), three trials comparing ADA vs placebo (CLASSIC I, GAIN, CHARM) and two trials comparing IFX vs placebo (T20, ACCENT II). The UST and ADA trials enrolled patients with moderate to severe CD, with only a small proportion of patients having fistulising disease at baseline. The submission did not formally compare UST versus ADA or IFX in patients with fistulising CD owing to differences across the trials and outcomes reported. The PBAC noted that the trial data for UST for the treatment of fistulising CD was poor (paragraph 7.10, UST PSD, March 2017 PBAC Meeting).

2.5 The current submission presented the following additional clinical evidence:

- Clinical data from two recent trials that enrolled patients with moderate to severe CD and included a subgroup of patients with fistulising disease: SEAVUE, comparing UST versus ADA; and STARDUST, comparing UST 'routine care' to UST 'treat-to-target'.
- A post-hoc analysis of the UST trials presented in the March 2017 submission (UNITI-1 and UNITI-2 pooled; IM-UNITI), reporting results for the fistula remission outcome in patients with perianal fistulas at baseline.
- Anchored indirect comparisons between UST versus ADA and IFX using placebo as the common reference for fistula response and fistula remission following induction treatment (Week 4 to 18) and maintenance treatment (Week 48 to 56).
- Unanchored indirect comparisons between UST versus ADA and IFX, including data from SEAVUE and STARDUST, for fistula response and fistula remission following maintenance treatment (Week 48 to 56).

2.6 ADA and IFX are currently listed for the treatment of fistulising CD. A submission requesting listing of risankizumab for both severe CD and fistulising CD was made to the PBAC for the July 2022 meeting; however, the request for the fistulising CD indication was withdrawn prior to PBAC consideration (the severe CD indication was recommended in November 2022).

3 Requested listing

3.1 For brevity reasons, an abridged version of the restriction is presented below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№. of repeats	Available brands
USTEKINUMAB					
[Induction treatment] 130 mg/26mL injection, 26 mL vial	$15,236.22 (public) published price; $15,284.14 (private) published price; $ (public) effective price $ (private) effective price	4	4	0	Stelara
[Induction treatment] 90 mg/1mL injection, 1 mL vial	$3,970.36 published price $ effective price	1	1	0[a]	Stelara
[Continuing treatment] 90 mg/1mL injection, 1 mL vial	$3,970.36 published price $ effective price	1	1	2[b] / 1[c]	Stelara

Category / Program: Section 100: tiered weight-based IV loading dose General Schedule: SC injection
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing)
Condition: Complex refractory Fistulising Crohn disease
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)].
Treatment Phase: Initial treatment 1 (new patient or recommencement of treatment after more than 5 years break)
Clinical criteria: Patient must have confirmed 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 an externally draining enterocutaneous or rectovaginal fistula.
Prescribing Instructions: A maximum of 16 weeks of treatment with this drug will be approved under this criterion. An assessment of a patient's response to this initial course of treatment must be conducted following a minimum of 12 weeks of therapy and no later than 4 weeks prior the completion of this course of treatment.

Category / Program: Section 100: tiered weight-based IV loading dose General Schedule: SC injection
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing)
Condition: Complex refractory Fistulising Crohn disease
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)].
Treatment Phase: Continuing treatment
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND

Patient must have demonstrated an adequate response to treatment with this drug, defined as: (a) a decrease from baseline in the number of open draining fistulae of greater than or equal to 50%; and/or (b) a marked reduction in drainage of all fistula(e) from baseline, together with less pain and induration as reported by the patient.
Prescribing Instructions: A maximum of 24 weeks treatment will be authorised under this restriction.

Source: Tables 1.8, 1.9, 1.12, pp.35, 36, 40 of the submission.

[a] Week 8 dose for induction treatment.

[b] Continuing treatment; 8-weekly dosing.

[c] Continuing treatment; 12-weekly dosing.

3.2 The sponsor requested PBS listing of the UST 130 mg solution concentrate for IV infusion for initial treatment, and the UST 90 mg in 1mL injection (in a pre-filled syringe) for SC injection for initial and continuing treatment. The sponsor requested equivalent PBS restriction criteria for UST in initial and continuing treatment of adult patients with fistulising CD as other PBS-listed treatments (ADA and IFX).

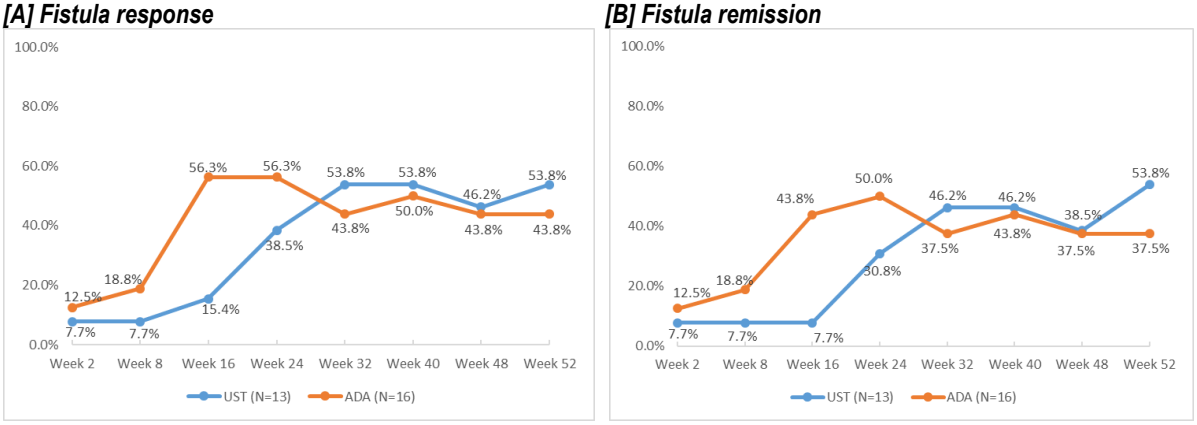
3.3 For initial treatment, the maximum quantity of 4 x 130 mg vials (no repeats) and 1 x 90 mg pre-filled syringe (no repeats) would allow for a 16-week induction period, where clinicians can prescribe the appropriate tiered weight-based IV loading dose at Week 0 (up to a maximum of 520 mg) and the first 90 mg SC injection at Week 8. For continuing treatment, the requested maximum quantity of 1 x 90 mg pre-filled syringe (2 repeats) would provide for 24 weeks of treatment at the recommended 8-weekly dosing regimen, whereas 1 x 90 mg pre-filled syringe (1 repeat) would provide for 24 weeks of treatment at the 12-weekly dosing regimen.

3.4 The submission requested a Special Pricing Arrangement (SPA) to be implemented. The proposed published AEMP of $3,809.08 per 130 mg vial and 90 mg pre-filled syringe was consistent with the published price of UST formulations listed on PBS for other indications (i.e., 130 mg vial and 45 mg pre-filled syringe). The sponsor requested an effective AEMP ($ per 130 mg vial and $ per 90 mg pre-filled syringe) on the basis of a cost-minimisation approach to the least costly alternative (assumed to be IFX IV based on current list prices). By comparison, the effective AEMP of the UST 130 mg vial in severe CD (as of 1 May 2023) is $.

3.5 The current submission presented very limited evidence to support the requested 16-week initial treatment period for patients with fistulising CD. Subgroup data from UNITI-1 and UNITI-2 showed no difference between UST and placebo at Week 8 in terms of fistula response (N=105) or fistula remission (N=81), and subgroup data from SEAVUE (N=29) showed a low proportion of patients with perianal/perirectal fistula at baseline had achieved fistula remission or fistula response with UST by Week 16, illustrated in Figure 1 below. There is a high degree of uncertainty with the available evidence due to the small patient numbers, however the submission stated that time to treatment response would likely take longer to manifest with UST compared to ADA or IFX because it acts at an earlier point in the inflammatory cascade.

Figure 1: Fistula response and remission over time in SEAVUE, patients with open/draining fistulas at baseline

[A] Fistula response ***[B] Fistula remission***



Source: constructed from Tables 2.56 and 2.57, pp153-154 of the submission.

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

4 Population and disease

4.1 Crohn's disease (CD) is a chronic but progressive inflammatory bowel disease that often affects the lower small intestine (ileum) and the large intestine (colon) but may involve the entire gastrointestinal tract. Fistulising CD is a frequent manifestation (with a reported lifetime risk of 20% to 40%), where abnormal connections (i.e., fistulas) form between the inflamed intestine and other parts of the intestine, bladder, skin or vagina. Fistulas can result in chronic, disabling symptoms including local pain, discomfort on sitting, discharge, and faecal incontinence. Perianal fistulas are the most common type of fistulae and indicate worse disease severity if present at diagnosis. Fistulas rarely heal spontaneously and are difficult to treat.

4.2 The Crohn's Disease Activity Index (CDAI) is a composite instrument commonly used to define disease activity in both clinical trials and practice. The instrument consists of several items (stool pattern; abdominal pain; general wellbeing; complications including fistulas; abdominal mass; anaemia; weight change) with a total score ranging from 0 to 1100. Standardised categories of disease severity based on the CDAI score include remission (<150), mild to moderate (150-220), moderate to severe (220-450) and severe (>450). The presence of fistulae only adds 20 points to the overall CDAI score.

4.3 Patients with fistulising disease and a CDAI score ≥ 300 are currently able to access UST (and several other treatments) on the PBS under the listing for severe CD. The PBAC had considered that access to effective treatment for patients with worse fistulae but with a CDAI score < 300 represented an equity issue (Section 12 ADA PSD, November 2010 PBAC Meeting). The population targeted in the submission was adult patients with complex refractory fistulising CD irrespective of CDAI score, who are currently eligible for treatment with ADA and IFX on the PBS under the listing for fistulising CD.

4.4 Patients with fistulising CD and CDAI score < 300 are currently eligible to use two biologic treatments from the same class under the fistulising CD indication (ADA and IFX, both TNF inhibitors) whereas patients with fistulising CD and a CDAI score ≥ 300 are currently eligible to use four biologic treatments from different classes under the severe CD indication (UST, an IL-23/12 inhibitor; ADA and IFX, TNF inhibitors; VDZ, an integrin inhibitor). In November 2022, the PBAC recommended a fifth biologic treatment for severe CD (risankizumab, an IL-23 inhibitor) and considered there was not high or unmet clinical need for the treatment of severe CD (paragraph 11.4, risankizumab PSD, November 2022 PBAC Meeting). The Pre-Sub-Committee Response (PSCR) argued that there remained a clinical need for effective therapies for the treatment of fCD as the current options were both of the same therapeutic class and are associated with safety risks such as serious infections and malignancy. The Pre-PBAC Response further argued the Sponsor hearing further reinforced the need for additional therapies for fCD (see 'Sponsor hearing').

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

5 Comparator

5.1 The submission nominated ADA as the main comparator on the basis that UST would most likely substitute ADA as second-line treatment given IFX is more established as a first-line treatment, and both UST and ADA are administered by SC injection. The submission also nominated IFX as a secondary comparator given UST may also replace IFX in practice.

5.2 The nominated comparators were appropriate. At the March 2017 PBAC meeting, the PBAC considered both ADA and IFX (i.e., all PBS-listed treatments for fistulising CD) were relevant comparators given UST may reasonably replace either of these alternative treatments in practice (paragraph 7.5, UST PSD, March 2017 PBAC Meeting).

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. As the submission did not present any evidence that UST provided a significant improvement in efficacy and/or reduction in toxicity compared to ADA or IFX for fistulising CD, there was no basis for UST to have a price advantage over ADA or IFX.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician described the clinical manifestation of fistulising CD and the severe impacts of the condition, including abscesses and frequent infections, often requiring patients to have repeated painful surgeries to manage. The clinician also described that up to approximately 26% of patients progress to requiring proctectomy and the need for a permanent stoma to be installed, which further has major impacts on patients' lives. The hearing also discussed the high rates of primary non-response to anti-TNF therapies, with up to 1/3rd of patients and ongoing discontinuation rates of approximately 13% per year, due to secondary loss of response, intolerance, risk of infections or immunogenicity. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease and highlighted the need for additional therapeutic options, especially those with new mechanisms of action that are effective over the longer term.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (14) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from health professionals described the high clinical need for additional effective therapies and the severe impacts of fistulising CD on patients' quality of life, and the devastating impacts of repeat surgery, often leading to proctectomy and the need for a permanent stoma to patients. The comments also described that the current TNF inhibitors do not work for all patients, others are ineligible for treatment, and that the response wanes over time, highlighting the need for additional agents with different mechanisms of action.

6.3 The PBAC noted the advice received from Crohn's and Colitis Australia discussed the effectiveness of ustekinumab in CD and highlighted its favourable dosing regimen and immunogenicity profile compared to the current TNF inhibitor options, in addition to reflecting the comments made by health professionals outlining the severe burden of disease and impact on quality of life experienced due to fistulising CD. The PBAC also noted the advice received by the National Paediatric Medicines Forum, describing a cohort of paediatric patients with fistulising CD who are currently receiving treatment with ustekinumab via paediatric hospitals and are responding to treatment. On that basis, the Forum requested no age restriction be applied to the listing of ustekinumab for fistulising CD.

Clinical trials

6.4 There was one head-to-head trial comparing UST versus ADA over 52 weeks in patients with moderate to severe CD including some patients with fistulising disease (SEAVUE). However, the relatively small number of patients enrolled in the trial with a fistula at

baseline limited the conclusions that could be drawn from the trial. To compare UST versus ADA and IFX in patients with fistulising CD, the submission presented an anchored indirect treatment comparison using placebo as the common reference, based on:

- Five RCTs providing evidence for induction therapy:
  - UST vs. placebo (two RCTs): UNITI-1 and UNITI-2;
  - ADA vs. placebo (two RCTs): CLASSIC I and GAIN;
  - IFX vs. placebo (one RCT): T20.
- Three RCTs providing evidence for maintenance therapy:
  - UST vs placebo (one RCT): IM-UNITI;
  - ADA vs. placebo (one RCT): CHARM;
  - IFX vs. placebo (one RCT): ACCENT II.

6.5 The submission also presented an unanchored indirect comparison between UST versus ADA and IFX for maintenance treatment, incorporating additional evidence from SEAVUE and STARDUST. The STARDUST trial compared two UST dosing regimens (UST 'routine care' versus UST 'treat-to-target') for maintenance treatment, which was not directly relevant to the submission. Patients randomised to 'routine care' in STARDUST received the TGA approved dose of UST (90 mg Q8W or Q12W based on clinical judgement), whereas patients in the 'treat-to-target' arm received a dose of UST (90 mg Q12W, Q8W or Q4W) based on individualised targets. During the trial, the majority of patients in the 'treat-to-target' received UST 90 mg Q12W or Q8W.

6.6 In the March 2017 submission, the PBAC considered evidence from all of the placebo-controlled trials for UST (UNITI-1, UNITI-2, IM-UNITI), ADA (CLASSIC I, GAIN, CHARM) and IFX (T20, ACCENT II). The PBAC has not considered evidence from SEAVUE or STARDUST.

6.7 Details of the trials presented in the submission are provided in Table 2. An independent search identified one ongoing trial of UST versus placebo evaluating the efficacy and safety of UST in fistulising perianal CD: USTAP (NCT04496063), estimated completion date in September 2023.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
UST vs ADA		
SEAVUE NCT0346136	Clinical Study Report CNTO1275CRD3007. A phase 3, randomized, blinded, active-controlled study to compare the efficacy and safety of ustekinumab to that of adalimumab in the treatment of biologic naïve subjects with moderately-to-severe active Crohn's disease: Safety and efficacy of adalimumab versus ustekinumab for one year (SEAVUE) Sands BE, Irving PM, Hoops T et al. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naïve patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial.	March 2022 Lancet 2022; 399: 2200-2211.
UST 'routine care' v UST 'treat-to-target'		
STARDUST NCT03107793	Clinical Study Report CNTO1275CRD3005. Study of treat to target versus routine care maintenance strategies in Crohn's disease patients treated with ustekinumab. Danese S, Vermeire S, D'Haens G. Treat to target versus standard of care for patients with Crohn's disease treated with ustekinumab (STARDUST): an open-label, multicentre, randomised phase 3b trial.	June 2022. Lancet Gastroenterol Hepatol 2022; 7: 294-306.
UST vs PBO		
UNITI-1* NCT01369329	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.	Sept 2015
UNITI-2* NCT01369342	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.	Oct 2015
IM-UNITI* NCT01369355	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.	Nov 2015
	Sandborn WJ, Rebuck R, Wang Y et al. Five-Year Efficacy and Safety of Ustekinumab Treatment in Crohn's Disease: The IM-UNITI Trial	Clin Gastroenterol Hepatol 2022; 20: 578-590.
ADA vs PBO		
CLASSIC I	Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial.	Gastroenterology 2006; 130 (2): 323-333.
GAIN	Sandborn, WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial.	Annals of Internal Medicine 2007; 146 (12): 829-838
	Panaccione R, Sandborn WJ, D'Haens G, et al. Clinical benefit of long-term adalimumab treatment in patients with Crohn's disease following loss of response or intolerance to infliximab: 96-week efficacy data from GAIN/ADHERE trials.	J Crohns Colitis 2018; 12 (8): 930-938.
CHARM	Colombel J., Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. Colombel J, Schwartz, DA., Sandborn, WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease.	Gastroenterology 2007; 132 (1): 52-65. Gut 2009; 58: 940-948.
IFX vs PBO		
T20	Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease.	The New England Journal of Medicine 1999; 340: 1398-1405.

Trial ID	Protocol title/ Publication title	Publication citation
ACCENT II	Sands BE., Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulising Crohn's disease.	The New England Journal of Medicine 2004; 350(9): 876-885.

Blue shading indicates data previously seen by the PBAC.
Source: Table 2-6, pp60-63 of the submission.
*The submission listed additional publications, but these were excluded from this table as these publications did not focus on fistulising CD and did not report on fistulising efficacy outcomes.

6.8 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Relevant outcomes
UST v ADA					
SEAVUE [induction and maintenance] (2018-2021)	CD: 386 fCD baseline [1]: 37 fCD outcome [2]: 29	MC, R, DB, IP&MP (52wk), TTD	CD: Low fCD: High	CD; TNF naïve	Fistula response 50% reduction from baseline of open/draining perianal/perirectal fistulas[8] Fistula remission (resolution) Absence/closure of all perianal/perirectal fistulas[8]
UST 'routine care' v UST 'treat-to-target'					
STARDUST [maintenance] (2017-2021)	CD (MP) [3]: 440 fCD (MP): 19	MC, OL IP (16wk) / R OL MP (+32wk), RWD (IP responders)	CD: Low fCD: High	CD patients with response (CR-70) to UST induction at W16; TNF naïve and experienced	Fistula response ≥50% reduction in the number of perianal/perirectal fistulas[8]
UST v placebo					
UNITI-1 [induction]	CD [4]: 496 fCD baseline [1]: 100 fCD W8 outcome [4]: 63	MC, R, DB, IP (8wk)	CD: Low fCD: High	TNF experienced (refractory)	Fistula response ≥50% reduction in number of opening/draining fistulas
UNITI-2 [induction]	CD [4]: 419 fCD baseline [1]: 64 fCD W8 outcome [4]: 42	MC, R, DB, IP (8wk)	CD: Low fCD: High	TNF naïve and experienced (non-refractory)	
IM-UNITI [maintenance]	CD: 397 fCD baseline [1]: 59 fCD outcome: 26	MC, R, DB, MP (+44wk), RWD (IP responders in UNITI-1/2)	CD: Low fCD: High	Patients with response (CR-100) to UST induction at W8 of UNITI-1 or UNITI-2; TNF naïve and experienced	Fistula response ≥50% reduction in the number of opening/draining fistulas
ADA v placebo					
CLASSIC I [induction]	CD [4]: 150 fCD: 18	MC, R, DB, IP (4wk)	CD: Low fCD: High	TNF naive	Fistula response ≥50% reduction in number of draining fistulas at ≥ 2 consecutive visits. Fistula remission Closing of all draining fistulas at ≥ 2 consecutive visits.

Trial	N	Design/ duration	Risk of bias	Patient population	Relevant outcomes
GAIN [induction]	CD: 325 fCD: 45	MC, R, DB, IP (4wk)	CD: Low fCD: High	TNF experienced	Fistula response ≥50% reduction in number of draining fistulas at wks 2 & 4. Fistula remission Closing of all draining fistulas at wks 2 & 4.
CHARM [maintenance]	CD [4]: 521 fCD [4,5]: 77	MC, OP IP (4wk) / R DB MP (+52wk), RWD (IP responders & non-responders)	CD: Low fCD: High	TNF naïve and experienced	Fistula remission Complete closure of all draining fistulas
IFX v placebo					
T20 [induction]	fCD [4]: 62	MC, R, DB (18wk)	Low	Pts with draining fistulas ≥ 3 mths; TNF 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 [maintenance]	fCD (MP) [6]: 282 fCD outcome [7]: 276	MC, OL IP (14wk) / R DB MP (+40wk), RWD (IP responders & non-responders)	Low	Pts with draining fistulas ≥ 3 mths; fistula response at W10 & W14; TNF naive	Fistula response Time to loss of response* ≥50% reduction in number of draining fistulas at consecutive visits ≥4 weeks apart Fistula remission Absence of draining fistulas

Blue shading indicates data previously seen by the PBAC.

Source: compiled during the evaluation based on study reports and publications.

DB = double blind; MC = multi-centre; OL = open label; R = randomised; IP = induction phase; MP = maintenance phase; TTD = treat through design; RWD = randomised withdrawal design; ADA = adalimumab; IFX = infliximab; UST = ustekinumab; CD = Crohn's disease; fCD = fistulising Crohn's disease; 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.

* Denotes the primary trial outcome

[1] Patients with fistula at baseline.

[2] Evaluable patients with an open and draining fistula at baseline (SEAVUE CSR).

[3] STARDUST patients achieving CDAI response at Week 16 and randomized. 498 patients were enrolled in the STARDUST trial to enter the OL induction phase.

[4] Excluding irrelevant treatment arms.

[5] CHARM: 130 patients had fistula at baseline (enterocutaneous or perianal fistula).

[6] ACCENT II: 306 patients received IFX in an OL induction phase; 282 patients (non-responders and responders) were randomised to IFX and PBO at Week 14.

[7] ACCENT II: This comprised 189 responders and 87 non-responders assigned IFX or PBO at Week 14. 189 responders were evaluated for maintenance response although 195 patients with a response at Week 14 were assigned IFX or PBO during the maintenance phase. 87 patients assessed for response had no response and were assigned IFX or PBO at Week 14, then all 87 patients were evaluated for maintenance response.

[8] In patients with perianal/perirectal fistulas at baseline.

6.9 SEAVUE, STARDUST and all of the placebo-controlled trial for UST (UNITI-1, UNITI-2, IM-UNITI) and ADA (CLASSIC I, GAIN, CHARM) enrolled patients with moderate to severe CD (defined as a CDAI score of 220-450 points with or without other criteria) including some patients with fistulising disease. In these trials, the patient-relevant outcomes of fistula response and fistula remission were pre-specified

exploratory/secondary or post-hoc outcomes reported for the subgroup of patients with fistulising disease at baseline. In contrast, the IFX trials (T20, ACCENT II) only enrolled patients with fistulising CD (abdominal and perianal fistulas) irrespective of CDAI score / disease severity. The selection criteria also differed with respect to prior use of biologic treatments (and the type of failure with prior use). Four trials excluded patients with any prior use (SEAVUE, CLASSIC I, T20, ACCENT II), two trials excluded patients without any prior use (UNITI-1, GAIN) and four trials included patients with and without prior use (STARDUST, UNITI-2, IM-UNITI and CHARM).

6.10 The placebo-controlled induction trials (UNITI-1, UNITI-2, CLASSIC I, GAIN, T20) randomised eligible patients to active treatment or control at Week 0 and assessed response to treatment at Week 4 to 16 depending on the trial. The placebo-controlled maintenance trials (IM-UNITI, CHARM, ACCENT II) all used a randomised withdrawal design (i.e., patients were randomised to active or control following induction treatment), but the exact design differed across the trials. IM-UNITI randomised patients with CR-100 response (i.e. ≥ 100 point decrease in CDAI score from baseline) to UST induction at Week 8 in the UNITI-1/2 and assessed response at Week 52. CHARM randomised all patients treated with ADA induction at Week 4 stratified by CR-70 response and assessed response at Week 56. ACCENT II randomised all patients treated with IFX induction at Week 14 stratified by fistula response and assessed response at Week 54. Although CHARM randomised patients to maintenance treatment stratified by ADA induction response, the fistula response and fistula remission outcomes presented in the submission were aggregated across induction non-responders and induction responders (i.e., unconditional on induction response, similar to results from a 'treat-through' trial design).

6.11 The SEAVUE trial randomised patients to UST or ADA and assessed response through to Week 52 using a treat-through design, with results reported for induction and maintenance time points. In contrast, STARDUST used a randomised responder design, and randomised patients with CR-70 response to UST induction treatment at Week 16 to either UST 'routine care' or UST 'treat-to-target' for maintenance treatment and assessed response at Week 48.

6.12 Most included trials were considered to have a low overall risk of bias for the ITT analysis, but there was a high risk of bias in the UST and ADA trials for the subgroup of patients with fistulising CD at baseline. In a number of trials (SEAVUE, UNITI-1, UNITI-2, IM-UNITI), there was a difference between the number of patients with fistulising CD at baseline and the number of patients with 'evaluable' disease included in the results. These trials stated that fistula outcomes were evaluated in patients with one or more open/draining fistulas (restricted to perianal or perirectal in SEAVUE) at baseline but presumably excluded patients with missing data (i.e., no missing data rules were applied). Missing data rules for the fistula response and fistula remission outcomes were generally not reported across the trials.

6.13 Baseline data was not reported for patients with fistulising CD enrolled in the UST and ADA trials, with the exception of the CHARM trial. Therefore, the submission assessed

the exchangeability of the trials based mainly on the ITT populations. Despite limited available/comparable baseline data, there were some notable differences in baseline characteristics across the placebo-controlled trials included in the indirect treatment comparisons:

- A very small proportion of patients enrolled in the UST and ADA trials had a fistula at baseline (8-22%), whereas all patients enrolled in the IFX trials had fistulising CD based on the selection criteria. For the indirect treatment comparisons, the submission restricted the analysis to patients with fistulising CD at baseline.
- The average CDAI score was much higher in the UST and ADA trials (approximately 300) compared to the IFX trials (approximately 190 in T20, 41%/67% <150/220 in ACCENT II). The UST and ADA trials required patients to have moderate to severe CD whereas the IFX trials enrolled patients with fistulising CD irrespective of CDAI score. Hence, the subgroup of patients with fistulising CD in the UST and ADA trials also had moderate to severe CD, whereas patients in the IFX also included patients with mild CD defined by CDAI score.
- The average duration of disease was not reported in the ADA trials but appeared slightly longer in the IFX maintenance trial (average 10.5 to 12.3 years in ACCENT II) compared to the UST maintenance trial (average 9.5 to 10.6 years in IM-UNITI). The average duration of disease was much shorter in the head-to-head trial comparing UST to ADA (SEAVUE) with an average duration of disease approximately 5.5 years.
- Based on data for patients with fistulising CD, a higher proportion of patients had more than one fistula in the IFX maintenance trial (59% in ACCENT II) compared to the ADA trial (38% in CHARM subgroup). As noted, none of the other ADA or UST trials reported baseline data for the subgroup of patients with fistulising CD to inform any other comparisons.
- Across the induction trials, a higher proportion of patients in the ITT population had used prior biologic therapy in the ADA trials (68% pooled across CLASSIC I, GAIN) compared to UST trials (54% pooled across UNITI-1, UNITI-2) and the IFX trial (0% in T20). Across the maintenance trials, a similar proportion of patients had used prior biologic therapy in the ITT population of the UST trial (60% in IM-UNITI) and the fistulising CD subgroup in the ADA trial (63% in CHARM subgroup), which were both higher than prior use in the IFX trial (0% in ACCENT II). The submission argued that the patients in UST trials were more refractory (harder to treat) compared to the other trials which biased the indirect comparisons against UST, particularly versus IFX.

6.14 The fistula response and fistula remission outcomes reported in the UST trials are not directly comparable to those reported in the ADA and IFX trials. Across the placebo-controlled induction trials: the fistula response and fistula remission outcomes were more stringent for the ADA and IFX trials; the fistula response and fistula remission

were reported at different time points across the trials (Week 8 in the UST trials, Week 4 in the ADA trials and Week 18 in the IFX trial); and the (post-hoc) fistula remission outcome in the UST trials (UNITI-1, UNITI-2) was only reported for patients with perianal fistula at baseline, whereas the (pre-specified) fistula remission outcomes in the ADA and IFX trials included patients with any open/draining fistula. Across the maintenance trials, fistula response and fistula remission reported at the end of the maintenance trials were conditional on clinical response to induction treatment in the UST trial (IM-UNITI) and IFX trial (ACCENT II), but unconditional on induction response in the ADA trial (CHARM); and the (post-hoc) fistula remission outcome in the UST trial (IM-UNITI) was only reported for patients with perianal fistula at baseline, whereas the (pre-specified) fistula remission outcomes in the ADA and IFX trials included patients with any open/draining fistula.

Comparative effectiveness

6.15 Aside from overall remission and response criteria based on CDAI score, the clinically relevant outcomes for patients with fistulising CD include fistula remission (i.e., closure of all open/draining fistulae) and fistula response (i.e., ≥50% reduction in number of open/draining fistulae). The current/proposed PBS criteria defines an adequate response to treatment for patients with fistulising CD (irrespective of CDAI score) as: (a) a decrease from baseline in the number of open/draining fistulae of greater than or equal to 50%; and/or (b) a marked reduction in drainage of all fistula(e) from baseline, together with less pain and induration as reported by the patient. The PBS criteria is similar to the fistula response outcome reported in the clinical trials, the submission noted that the PBAC had also relied on the fistula remission outcome in previous considerations (paragraph 6.19, UST PSD, March 2017 PBAC meeting).

6.16 Table 4 summarises fistula response and fistula remission outcomes for patients with fistulising CD enrolled in the induction trials, and the anchored indirect treatment comparisons between UST versus ADA and IFX for induction treatment.

Table 4: Induction trial results and anchored indirect comparisons for fistula response and fistula remission

Trial ID	Drug n/N (%)	Control n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
OUTCOME: FISTULA RESPONSE					
UST v ADA					
[1] SEAVUE (Wk8)	1/13 (7.7)	3/16 (18.8)	-0.11 (-0.35,0.13)	0.41 (0.05,3.49)	0.36 (0.03,3.96)
[2] SEAVUE (Wk16)	2/13 (15.4)	9/16 (56.3)	**-0.41 (-0.72, -0.10)**	0.27 (0.07,1.05)	**0.14 (0.02,0.86)**
[3] SEAVUE (Wk24)	5/13 (38.5)	9/16 (56.3)	-0.18 (-0.54, 0.18)	0.68 (0.30, 1.54)	0.49 (0.11, 2.16)
UST v PBO					
[4] UNITI-1 (Wk8)	4/29 (13.8)	4/34 (11.8)	0.02 (-0.15,0.19)	1.17 (0.32,4.28)	1.20 (0.27,5.29)
[5] UNITI-2 (Wk8)	6/19 (31.6)	4/23 (17.4)	0.14 (-0.12,0.40)	1.82 (0.60,5.51)	2.19 (0.51,9.33)
[6] Meta-analysis	10/48 (20.8)	8/57 (14.0)	0.06 (-0.08,0.20)	1.51 (0.65,3.50)	1.63 (0.58,4.61)
ADA v PBO					
[7] CLASSIC I (Wk4)	1/12 (8)	2/6 (33)	-0.25 (-0.66,0.16)	0.25 (0.03,2.24)	0.18 (0.01,2.60)
[8] GAIN (Wk4)	3/20 (15)	5/25 (20)	-0.05 (-0.27,0.17)	0.75 (0.20,2.77)	0.71 (0.15,3.40)
[9] Meta-analysis	4/32 (12.5)	7/31 (22.6)	-0.10 (-0.29,0.10)	0.56 (0.18,1.73)	0.50 (0.13,1.92)
IFX v PBO					
[10] T20 (Wk18)	21/31 (68)	8/31 (26)	**0.42 (0.19,0.64)**	**2.63 (1.38,5.00)**	**6.04 (2.01,18.17)**
OUTCOME: FISTULA REMISSION					
UST v ADA					
[11] SEAVUE (Wk8)	1/13 (7.7)	3/16 (18.8)	-0.11 (-0.35,0.13)	0.41 (0.05,3.49)	0.36 (0.03,3.96)
[12] SEAVUE (Wk16)	1/13 (7.7)	7/16 (43.8)	**-0.36 (-0.64, -0.08)**	0.18 (0.02,1.25)	0.11 (0.01,1.03)
[13] SEAVUE (Wk24)	4/13 (30.8)	8/16 (50.0)	-0.19 (-0.54, 0.16)	0.62 (0.24, 1.59)	0.44 (0.10, 2.06)
UST v PBO					
[14] UNITI-1/2 pooled (Wk8)	9/38 (23.7)	4/43 (9.3)	0.14 (-0.02, 0.30)	2.55 (0.85, 7.60)	3.03 (0.85, 10.80)
ADA v PBO					
[15] CLASSIC I (Wk4)	0/12 (0.0)	1/6 (16.7)	-0.17 (-0.49, 0.15)	0.18 (0.01, 3.85)	0.15 (0.01, 4.20)
[16] GAIN (Wk4)	1/20 (5.0)	2/25 (8.0)	-0.03 (-0.17, 0.11)	0.63 (0.06, 6.41)	0.61 (0.05, 7.20)
[17] Meta-analysis	1/32 (3.1)	3/31 (9.7)	-0.05 (-0.18, 0.08)	0.40 (0.06, 2.53)	0.37 (0.05, 2.69)
IFX v PBO					
[18] T20 (Wk18)	17/31 (55)	4/31 (13)	**0.42 (0.21, 0.63)**	**4.25 (1.61, 11.20)**	**8.20 (2.31, 29.07)**
ANCHORED INDIRECT COMPARISONS					
		FISTULA RESPONSE			
		UST Wk8 [6] v ADA Wk4 [9]	0.16 (-0.08, 0.40)	2.70 (0.66, 11.05)	3.26 (0.60, 17.83)
		UST Wk8 [6] v IFX Wk16 [10]	**-0.36 (-0.63, -0.10)**	0.57 (0.20, 1.66)	0.27 (0.06, 1.22)
		FISTULA REMISSION			
		UST [14] v ADA [17]	0.19 (-0.02, 0.40)	6.38 (0.73, 55.72)	8.19 (0.77, 87.04)
		UST [14] v IFX [18]	**-0.28 (-0.54, -0.02)**	0.60 (0.14, 2.59)	0.37 (0.06, 2.22)

Blue shading indicates data previously seen by the PBAC.
Source: Table 2.32 p106, Table 2.33 p108, Table 2.56 p153; Table 2.34 p110, Table 2.35 p111, Table 2.57 p154 of the submission.
ADA = adalimumab; IFX = infliximab; PBO = placebo; UST = ustekinumab.

6.17 The results of the placebo-controlled induction trials showed no significant difference in the proportion of patients achieving fistula response or fistula remission with UST versus placebo or with ADA versus placebo. The submission argued these results were likely due to type II error given the corresponding trials were not powered for these outcomes. In contrast, the T20 trial demonstrated that patients treated with IFX induction treatment were more likely to achieve fistula response and fistula remission compared to placebo. In the SEAVUE trial, the results of the fistulising CD subgroup showed fewer patients achieved fistula response or fistula remission with UST compared to ADA between Week 2 to Week 24 (not statistically significantly different, with the exception of results at Week 16 favouring ADA). The submission

acknowledged the small number of patients with fistulising CD in SEAVUE limited the conclusions that can be drawn. The results of the anchored indirect treatment comparisons for induction treatment found no statistically significant differences between UST versus ADA or IFX, with the exception of the risk difference statistic favouring IFX for both fistula response and fistula remission. The submission argued that the UST and ADA trials were likely exchangeable but differences between the UST and IFX trials meant the corresponding anchored indirect comparisons were likely biased against UST. The submission noted that the UST trials enrolled more (harder to treat) TNF experienced patients evidenced by the lower fistula response and fistula remission rates in the placebo control arms of the UST trials and the outcomes were assessed 10 weeks earlier in the UST trials (after one dose of UST compared to three doses of IFX).

6.18 Based on the evidence presented in the March 2017 submission, the PBAC noted that UST was not significantly more effective in inducing fistula response compared with placebo in the induction trials (UNITI-1 and UNITI-2). The PBAC noted that the clinical evidence of UST for the treatment of fistulising CD was poor, with very small patient numbers with fistulising disease and comparisons that lacked statistical power. Overall, there was insufficient clinical evidence to support non-inferiority with ADA or IFX (paragraphs 6.19, 6.26, and 7.1, UST PSD, March 2017 PBAC meeting).

6.19 Compared to the March 2017 submission, new data presented in the current submission does not change the overall interpretation of the evidence for induction treatment. The new post hoc analysis of the UNITI-1 and UNITI-2 trials showed UST was not significantly more effective in inducing fistula remission at Week 8 compared to placebo in the small subgroup of patients with perianal fistula at baseline (N=81). The direct head-to-head comparison in SEAVUE showed fewer patients achieved fistula response and fistula remission with UST compared to ADA at Week 8 to 24 (statistically significant at Week 16 favouring ADA), but the subgroup analysis was based on very small patient numbers (N=29). The results of the anchored indirect treatment comparisons generally found no statistically significant differences between UST and ADA or IFX, but the results were highly uncertain and may not be meaningful given the many differences across the trials and lack of statistical power in the UST and ADA trials (neither showed a difference to placebo). The arguments presented in the submission that the anchored indirect comparisons for induction treatment bias against UST were generally reasonable on face value (i.e., 'easier to treat' TNF naïve patients, longer time for patients to respond), but the results were still difficult to interpret due to the low level of evidence available.

6.20 The PSCR argued that as UST acts at an earlier point in the inflammatory cascade compared to the tumour necrosis factor alfa inhibitors (both ADA and IFX), it is expected that UST would generally take a longer time to onset of action than other bDMARDs/tsDMARDs. The ESC noted the arguments in the PSCR and considered that while it is plausible that UST may have a slower onset of effect than ADA or IFX because of where it exerts its effects in the inflammatory response cascade, also considered

the substantial differences in SEAVUE in terms of proportions in fistula response and fistula remission up to week 24 (Table 4) and converging by week 32 (fistula response UST 53.8%/ADA 43.8%; fistula remission UST 46.2%/ADA 37.5%, see Figure 1) was relevant, as patients will likely continue to experience worse fistulae related symptoms over this initial period of treatment with UST. The ESC acknowledged, however, that similar to all analyses in the submission, small patient numbers in the fCD subgroups made drawing definitive conclusions difficult.

6.21 Table 5 summarises fistula response and fistula remission outcomes for patients with fistulising CD patients enrolled in the maintenance trials, and the anchored indirect treatment comparisons between UST versus ADA and IFX for maintenance treatment.

Table 5: Maintenance trial results and anchored indirect comparisons for fistula response and fistula remission

Trial ID	Drug n/N (%)	Control n/N (%)	RD (95% CI)	RR (95% CI)	OR (95% CI)
OUTCOME: FISTULA RESPONSE					
UST v ADA					
[1] SEAVUE (Wk52)	7/13 (53.8)	7/16 (43.8)	0.10 (-0.26,0.46)	1.23 (0.58,2.60)	1.50 (0.34,6.53)
UST v UST 'treat-to-target'					
[2] STARDUST (Wk48 | CR-70 Wk16)	4/7 (57.1)	6/12 (50.0)	0.07 (-0.39, 0.53)	1.14 (0.49, 2.69)	1.33 (0.20, 8.71)
UST v PBO					
[3] IM-UNITI (Wk52 | CR-100 Wk8), Q8W	7/8 (87.5)	5/11 (45.5)	**0.42 (0.05,0.79)**	1.93 (0.96,3.87)	8.40 (0.76,93.34)
[4] IM-UNITI (Wk52 | CR-100 Wk8), Q8/12W	12/15 (80.0)	5/11 (45.5)	0.35 (-0.01,0.70)	1.76 (0.88,3.53)	4.80 (0.85,27.20)
IFX v PBO					
[5] ACCENT II (Wk54)	51/134 (38.1)	30/142 (21.1)	**0.17 (0.06,0.28)**	**1.80 (1.23,2.65)**	**2.29 (1.35,3.91)**
[6] ACCENT II (Wk54 | FR Wk10/14)	42/91 (46.2)	23/98 (23.5)	**0.23 (0.09,0.36)**	**1.97 (1.29,3.00)**	**2.80 (1.50,5.21)**
[7] ACCENT II (Wk54 | no-FR Wk10/14)	9/43 (20.9)	7/44 (15.9)	0.05 (-0.11,0.21)	1.32 (0.54,3.22)	1.40 (0.47,4.17)
OUTCOME: FISTULA REMISSION					
UST v ADA					
[8] SEAVUE (Wk52)	7/13 (53.8)	6/16 (37.5)	0.16 (-0.20,0.52)	1.44 (0.64,3.22)	1.94 (0.44,8.61)
UST v UST 'treat-to-target'					
[9] STARDUST (Wk48 | CR-70 Wk16) [A]	UST pooled: 8/17 (47.1)		-	-	-
[10] STARDUST (Wk48 | CR-70 Wk16) [B]	UST pooled: 8/19 (42.1)		-	-	-
UST v PBO					
[11] IM-UNITI (Wk52 | CR-100 Wk8), Q8/12W	11/14 (78.6)	4/9 (44.4)	0.34 (-0.05,0.73)	1.77 (0.81,3.86)	4.58 (0.73,28.65)
ADA v PBO					
[12] CHARM (Wk56)	11/30 (36.7)	6/47 (12.8)	**0.24 (0.04, 0.44)**	**2.87 (1.19, 6.95)**	**3.96 (1.27, 12.29)**
IFX v PBO					
[13] ACCENT II (Wk54 | FR Wk10/14)	33/91 (36.3)	19/98 (19.4)	**0.17 (0.04, 0.29)**	**1.87 (1.15, 3.04)**	**2.37 (1.22, 4.57)**
ANCHORED INDIRECT COMPARISONS					
FISTULA RESPONSE					
Base case: UST (4) v IFX (6)			0.12 (-0.26,0.50)	0.89 (0.40,2.01)	1.71 (0.27,10.81)
Sensitivity: UST (4) v IFX (5)			0.18 (-0.19,0.55)	0.98 (0.44,2.16)	2.10 (0.34,12.84)
Sensitivity: UST (4) v IFX (7)			0.30 (-0.09,0.69)	1.33 (0.43,4.13)	3.43 (0.44,26.58)
FISTULA REMISSION					
UST (11) v ADA (12)			0.10 (-0.34,0.54)	0.62 (0.19,2.00)	1.16 (0.13,10.00)
UST (11) v IFX (13)			0.17 (-0.24,0.58*)	0.95 (0.38,2.37)	1.93 (0.28,13.59)

Blue shading indicates data previously seen by the PBAC.

Source: Table 2.73, p173, Table 2.58 p154, Table 2.74 p174, Table 2.75 p174, Table 2.71 p 168 of the submission

ADA = adalimumab; IFX = infliximab; PBO = placebo; UST = ustekinumab; 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, FR = fistula response; QxW = once every x weeks.

* This result differs substantially from that calculated in the submission (Table 2.75; p174 of the submission; 0.17: -0.05, 0.39)

[A] STARDUST: Exclusion of patients who received UST Q4W.

[B] STARDUST: Non-responder imputation where patients who received UST Q4W were considered non-responders.

6.22 The results of the placebo-controlled maintenance trials generally showed comparisons favoured active treatment over placebo. In the IM-UNITI trial, in patients with a perianal fistula at baseline and a clinical response to UST induction treatment at Week 8, a higher proportion of patients achieved fistula response and fistula

remission at Week 52 with UST compared to placebo. The submission acknowledged the result did not reach statistical significance but noted the small numbers of patients and argued that the long carry-over effect with UST biased the comparison against UST. In the ACCENT II trial, in patients with fistulising CD and fistula response to IFX induction treatment, a higher proportion of patients maintained fistula response and achieved fistula remission at Week 54 with IFX compared to placebo. In the CHARM trial, in patients with fistulising CD at baseline who received ADA induction treatment to Week 4 (responders and non-responders), a higher proportion of patients achieved fistula remission at Week 56 with ADA compared to placebo. The results of the SEAVUE trial found no difference between UST and ADA at Week 52 in the fistulising CD subgroup in terms of fistula response or fistula remission.

6.23 The results of the anchored indirect treatment comparisons for maintenance treatment found no statistically significant differences between UST versus ADA or IFX. For the comparisons versus IFX, the common reference arms reflected withdrawal of treatment following induction response, but the submission argued the indirect analysis may still bias against UST given longer carry over effect compared to IFX. The submission cited the higher fistula response and remission rates in the placebo arm of IM-UNITI (45.5% and 44.4% respectively) compared to ACCENT II (23.5% and 19.4% respectively) as evidence of this bias. For the comparison versus ADA, the submission argued that the indirect analysis was biased against UST because the ADA induction dose in CHARM was lower than the TGA approved dose, the placebo arm of CHARM included induction responders and non-responders whereas IM-UNITI included induction responders only, and UST has a longer carry over effect compared to ADA. The submission cited the higher fistula remission rates in the placebo arm of IM-UNITI (44.4%) compared to CHARM (12.8%) as evidence of this bias.

6.24 The submission also conducted an unanchored indirect comparison between UST versus IFX and ADA for maintenance treatment incorporating evidence from SEAVUE and STARDUST. The unanchored indirect comparisons favoured UST versus IFX for maintenance treatment in terms of clinical response (65.7% versus 46.2%) and clinical remission (59.1% versus 36.3%), and favoured UST versus ADA for maintenance treatment in terms of clinical remission (59.1% versus 37.0%). The submission argued that the unanchored indirect comparisons may offer a more relevant comparison due to the transitivity issues across the UST and IFX clinical trials identified with the indirect treatment comparisons. The evaluation considered this argument was not reasonable, given unanchored indirect comparisons are more prone to bias from and make no adjustment for differences across trials.

6.25 Based on the evidence presented in the March 2017 submission, the PBAC noted that UST was not significantly more effective in term of fistula response compared with placebo for maintenance (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 was poor with only eight patients in the (UST Q8W) treatment arm of IM-UNITI.

6.26 Compared to the March 2017 submission, new data presented in the current submission adds limited additional evidence to support the use of UST for maintenance treatment of fistulising CD. A new pooled analysis across the two UST arms in IM-UNITI (with 15 patients in the pooled UST arms) still showed UST was no different at maintaining fistula response at Week 52 compared to placebo in patients with fistula response at Week 8, and a new post-hoc analysis of IM-UNITI showed UST was no different at inducing fistula remission at Week 52 compared to placebo (in patients with fistula remission at Week 8). The evidence supporting superiority of ADA and IFX over placebo for maintenance treatment was unchanged. The direct head-to-head comparison in SEAVUE showed the proportion of patients with fistula response and fistula remission at Week 52 was similar for UST and ADA (i.e. no statistically significant difference), but the subgroup analysis was based on very small patient numbers (N=29). The anchored indirect treatment comparisons also showed no difference between UST versus ADA and IFX for maintenance treatment, but the results were highly uncertain given differences across the trials and the lack of statistical power in the UST and ADA trials. The arguments presented in the submission that the indirect comparisons for maintenance treatment bias against UST were generally reasonable on face value (the longer 'carry over' effect with UST compared to TNF drugs, and the 'treat through' results for ADA compared to the 'randomised withdrawal' results for UST), but the results were still difficult to interpret due to the low level of evidence available. Although the unanchored indirect comparisons did increase the sample size of the analysis, the results were still considered highly uncertain due to the many differences across the trials. The ESC agreed with the evaluation and considered the unanchored indirect comparisons were largely uninformative for assessing the clinical claim due to the sample sizes remaining small and the differences between the relevant trials. The Pre-PBAC Response disagreed with the ESC and argued that although there were differences in the trials, the unanchored indirect comparisons provide useful information.

6.27 The PSCR argued that despite the small sample sizes, the available evidence was sufficient to demonstrate the non-inferior comparative effectiveness of UST to the comparator treatments. Furthermore, the PSCR and Pre-PBAC Response also re-iterated submission arguments that the ITCs were biased against UST (paragraphs 6.19 and 6.26) refer.

Comparative harms

6.28 Consistent with the March 2017 submission, the current submission conducted anchored indirect treatment comparisons based on the ITT / safety populations of the included placebo-controlled trials. The submission stated that there is no biological reason why the safety profile of UST would differ in patients with moderate to severe CD compared to fistulising CD. The submission concluded that the safety profile of UST in the induction and maintenance phase was similar compared to ADA and IFX. The results of the anchored indirect treatment comparisons for comparative harms were

difficult to interpret given the trials were not powered for safety outcomes and the induction trials reported outcomes at different time points (e.g., Week 4 to Week 18).

6.29 The submission also presented safety data for the ITT/safety populations of SEAVUE and STARDUST, summarised in Table 6. In SEAVUE, the incidence of adverse events (AEs) was similar between UST and ADA, but more patients treated with ADA experienced injection site reactions and more patients treated with ADA discontinued treatment due to AEs. In STARDUST, the incidence of AEs was similar for UST routine care and UST treat-to-target. Overall, the most frequently reported AEs with UST in SEAVUE and STARDUST included abdominal pain, Crohn's disease event, headache and nasopharyngitis, which are consistent with the known safety profile of UST.

Table 6: Summary of adverse events in SEAVUE and STARDUST (whole trial population of moderate to severe CD)

SEAVUE	UST n/N (%)	ADA n/N (%)	RR (95% CI)	RD (95% CI)
Week 52				
Any adverse event	153/191 (80.1)	152/195 (77.9)	1.03 (0.93, 1.14)	0.02 (-0.06, 0.10)
Serious adverse event	25/191 (13.1)	32/195 (16.4)	0.80 (0.49, 1.29)	-0.03 (-0.10, 0.04)
Discontinuation due to AE	12/191 (6.3)	22/195 (11.3)	0.56 (0.28, 1.09)	-0.05 (-0.11, 0.01)
Infections	65/191 (34.0)	79/195 (40.5)	0.84 (0.65, 1.09)	-0.06 (-0.16, 0.03)
Serious Infections	4/191 (2.1)	5/195 (2.6)	0.82 (0.22, 3.00)	-0.00 (-0.03, 0.03)
Injection site reactions	6/191 (3.1)	20/195 (10.3)	**0.31 (0.13, 0.75)**	**-0.07 (-0.12, -0.02)**
Deaths	0/191	0/195	-	-
Week 76^				
Any adverse event	156/191 (80.1)	156/195 (77.9)	1.02 (0.93, 1.13)	0.02 (-0.06, 0.10)
Serious adverse event	29/191 (13.1)	38/195 (16.4)	0.78 (0.50, 1.21)	-0.04 (-0.12, 0.03)
Discontinuation due to AE	12/191 (6.3)	24/195 (11.3)	**0.51 (0.26, 0.99)**	**-0.06 (-0.12, -0.00)**
Infections	71/191 (34.0)	84/195 (40.5)	0.86 (0.68, 1.10)	-0.06 (-0.16, 0.04)
Serious Infections	7/191 (2.1)	6/195 (2.6)	1.19 (0.41, 3.48)	0.01 (-0.03, -0.04)
Injection site reactions	6/191 (3.1)	20/195 (10.3)	**0.31 (0.13, 0.75)**	**-0.07 (-0.12, -0.02)**
Deaths	0/191	1[a]/195	-	-
STARDUST	**UST RC n/N (%)**	**UST T2T n/N (%)**	**RR (95% CI)**	**RD (95% CI)**
Week 48				
Any adverse event	179/221 (81.0)	188/219 (85.8)	0.94 (0.87, 1.03)	-0.05 (-0.12, 0.02)
Serious adverse event	29/221 (13.1)	26/219 (11.9)	1.11 (0.67, 1.81)	0.01 (-0.05, 0.07)
Discontinuation due to AE	20/221 (9.0)	11/219 (5.0)	1.80 (0.88, 3.67)	0.04 (-0.01, 0.09)
Infections	65/191 (34.0)	79/195 (40.5)	0.84 (0.65, 1.09)	-0.06 (-0.16, 0.03)
Deaths	0/221 (0)	2[a]/219 (0.9)	0.20 (0.01, 4.10)	-0.01 (-0.02, 0.01)

Source: Tables 2-63, p158 of the submission; Table 23, p102 of SEAVUE CSR.

CI=confidence interval; n=number of participants with event; N=total participants in group, NE=not estimable, RD=risk difference, RR=risk ratio, ADA = adalimumab; UST=ustekinumab; RC = randomised controlled; T2T = treat to target.

^ Patients were treated through Week 56 and followed up for safety through Week 76.

[a] One patient died of "sudden death" (assessed by the investigator as not related to study treatment) approximately 5 weeks after the las dose at Week 50.

Benefits/harms

6.30 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

Clinical claim

6.31 The submission described UST as non-inferior in terms of effectiveness and safety for induction and maintenance treatment compared to ADA and IFX for the treatment of patients with fistulising CD. At the March 2017 PBAC Meeting, the PBAC accepted the claim of non-inferior comparative safety but considered there was insufficient evidence to support the claim of non-inferior effectiveness for patients with fistulising CD (paragraphs 6.29 and 7.1, UST PSD, March 2017 PBAC Meeting).

6.32 On balance, the evaluation considered the evidence presented in the current submission may still not adequately support the claim of non-inferior effectiveness between UST versus IFX and ADA. The new evidence from the placebo-controlled trials did not show any difference between UST and placebo for induction or maintenance treatment. Although the anchored indirect treatment comparisons generally found no statistically significant differences between UST versus ADA and IFX for induction or maintenance treatment, the analyses were considered highly uncertain and difficult to interpret owing to poor level of evidence available and differences across the trials. The direct head-to-head evidence presented in SEAVUE showed fewer patients achieved fistula response and fistula remission with UST compared to ADA between Week 2 to Week 24 (statistically significant at Week 16 favouring ADA) and a similar proportion of patients achieving the outcomes between Week 32 to Week 52 (i.e. no statistically significant difference), but the subgroup analysis was based on a very small sample size (N=29). Similarly, the unanchored indirect comparisons for maintenance treatment favouring UST over ADA and IFX for maintenance treatment were also considered highly uncertain for determining comparative effectiveness between UST versus IFX and ADA. The Pre-PBAC Response argued the level of evidence presented for UST was similar to that for ADA for fCD.

6.33 The ESC considered there were substantial uncertainties with the presented analyses that made drawing meaningful conclusions on the comparative effectiveness of UST and the nominated comparators challenging. Overall, the ESC considered evidence presented did not strongly support a claim that UST is of non-inferior comparative effectiveness to ADA due to its substantial limitations. However, it was of the view the head-to-head data for UST versus ADA in SEAVUE (new to this submission) may, on balance, suggest UST may be similarly effective to ADA in terms of maintenance treatment (beyond 24-32 weeks). However, the ESC considered the evidence indicated patients treated with UST took substantially longer to realise a clinical benefit.

6.34 The PBAC noted that while the evidence for UST was limited and based on small subgroup analyses, there was some head-to-head data vs. ADA available which indicated comparable outcomes over longer-term treatment and considered, on balance, the claim of non-inferior comparative effectiveness versus ADA was likely supported by the data. While the data versus IFX was very limited, the PBAC recalled its previous recommendation for ADA in November 2010 was based on similarly

uncertain clinical data and considered that, on balance, a claim of non-inferiority versus IFX was likely to be reasonable.

6.35 The PBAC noted that while the claim of non-inferior comparative safety to both ADA and IFX was based on a broader CD dataset, considered there was no reason to assume the safety of UST would meaningfully differ between severe CD and fistulising CD and therefore considered the claim was likely to be reasonable.

Economic analysis

6.36 The submission presented a cost-minimisation approach comparing the total cost of treatment with UST versus IFX (IV only) over the first two years (104 weeks), accounting for IV infusion administration costs. The submission stated IFX was the least costly alternative based on the current list prices of IFX and ADA. Over the first two years, the average cost of treatment with ADA is $17,329.20 (calculated during the evaluation assuming an AEMP of $618.90 for 2x ADA 40 mg pre-filled syringe), compared to the average cost of treatment with IFX of $16,378.00 (calculated in the submission, see details below).

6.37 The proposed equi-effective doses were based on the recommended doses:

- UST IV weight-based dose at Week 0, UST SC 90 mg at Week 8, then UST SC 90 mg Q8W thereafter;
- UST IV weight-based dose at Week 0, UST SC 90 mg at Week 8, then UST SC 90 mg Q12W thereafter;
- IFX IV 5 mg/kg at Weeks 0, 2, 6, then Q8W thereafter.

The submission did not consider the IFX SC formulation in the cost-minimisation approach, which the PBAC recommended for fistulising CD in November 2020 on the basis of cost-minimisation versus IFX IV.

6.38 Table 7 shows the results of the cost-minimisation approach presented in the submission, based on the following assumptions:

- The cost minimisation approach assumed equivalent total cost of treatment with IFX IV and UST over the first two years (104 weeks). Given UST includes both IV and SC formulations for initial treatment, and the SC formulation for continuing treatment, the cost-minimisation approach was conducted separately for initial and continuing treatment periods. The submission first calculated the AEMP for the UST SC formulation to ensure cost equivalence for continuing treatment then calculated the AEMP for the UST IV formulation to ensure cost equivalence for initial treatment.
- The cost minimisation approach also included separate calculations for patients treated with the UST Q8W regimen and UST Q12W, given they require a different number of scripts for maintenance therapy. The submission then derived the average weighted AEMPs for the UST 130 mg vial and UST 90 mg pre-filled syringe

assuming 88% of patients will use the UST Q8W regimen and 12% of patients will use the UST Q12W regimen. The proportional use of the Q8W and Q12W regimens was based on a clinician survey (N=27), presented in the UST July 2022 submission for ulcerative colitis.

- For IFX IV, the submission assumed an average of 4.17 x IFX 100 mg vials per infusion based on the distribution body weight of adults treated with a bDMARD for CD in Australia (using EPISOFT data presented in March 2017 submission). For the UST IV loading dose, the submission assumed 3 x UST 130 mg vials would be required. The submission did not provide any detail of the method used to estimate the 3 vials of UST. Presumably, an average of 4.17 vials of IFX corresponds to an average weight of 83 kg and 3.0 vials of UST is required for patients weighing >55 kg and ≤85 kg.
- The calculations used the published AEMP for IFX IV, which the submission stated was the same as the effective AEMP because IFX is listed on the F2 formulary and is no longer subject to confidential pricing arrangements. The derived weighted AEMPs for UST 130 mg vial and UST 90 mg pre-filled syringe reflect the requested effective AEMP under the proposed special pricing arrangement for UST.
- The calculations included administration costs for IV infusions (UST IV loading dose at Week 0 and every dose of IFX IV), assuming a unit cost per infusion of $88.05 (corresponding to the 85% schedule fee of MBS item 14245). The submission incorrectly attributed the unit cost to MBS item 116, but the PBAC had considered MBS item 14245 closely aligned to the administration duration of UST in practice (paragraph 6.57, UST PSD, July 2022 PBAC Meeting).

Table 7: Results of the cost-minimisation approach presented in the submission (based on published AEMP)

Component	IFX IV		UST (Q8W)			UST (Q12W)		
	Initial	Continuing	Initial		Continuing	Initial		Continuing
PBS item (max qty)	100 mg vial (1)	100 mg vial (1)	130 mg vial (1)	90 mg PFS (1)	90 mg PFS (1)	130 mg vial (1)	90 mg PFS (1)	90 mg PFS (1)
AEMP	$	$	$	$	$ [a]	$	$	$ [a]
Units /104wk	3 x 4.17 vials	11.25 x 4.17[c] vials	3	1	11	3	1	7
Drug cost /104wk	$	$	$ [b]	$	$	$ [b]	$	$
IV admin. /104wk	3	12	1	0	0	1	0	0
IV admin. costs	$	$	$	$0	$0	$	$0	$0
Total	$	$	$		$	$		$
Total / 104 weeks	$		$			$		
Weighted average AEMP								
Dosing regimen	**Proportional use**		**130 mg vial (1)**			**90 mg PFS (1)**		
UST Q8W	88%		$			$		
UST Q12W	12%		$			$		
	Requested AEMP		**$**			**$**		

Source: Tables 3-3; 3-4; 3-5, pp.198-199 of the submission.

IV=intravenous; PFS = pre-filled syringe; QxW = once every 8 weeks; SC= subcutaneous; IFX = infliximab; UST=ustekinumab.

[a] Firstly, this is derived as total PBS costs for continuing period / number of vials in continuing period.

[b] Secondly, this cost plus the IV infusion cost plus PBS costs for Wk 8 dose has to equal the total costs for initial period.

[c] Table 3.2 (submission) and Attachment 3.2 of the submission stated the number of IFX IV vials per script was 3.91 for continuing treatment. 3.91 vials per script was implicitly calculated as the total number of vials for the infusions from Week 14 to Week 104 (2 years), assuming a quarter of the 4.17 vials per infusion for the Week 102 infusion, divided by 12 infusions (the 12th infusion occurring at Week 102).

6.39 This assumed average 3.0 x UST 130 mg vials required for the loading dose differs to the 3.12 x UST 130 mg vials calculated in the UST March 2017 submission, based on the same weight distribution used to calculate the corresponding 4.17 x IFX 100 mg vials in the current submission. The estimate also differs to the 3.27 x UST 130 mg vials (i.e. 425 mg) calculated in the risankizumab submission July 2022, which was also consistent with the average doses administered in the UNITI-1 and UNITI-2 trials (i.e. 417 mg and 431 mg, respectively) (paragraph 6.64, risankizumab PSD, July 2022). The estimated AEMP for UST 130 mg vial decreased from $ to $ assuming an average of 3.27 vials of UST for the loading dose.

6.40 The ESC reiterated it considered the evidence did not strongly support a claim of non-inferior comparative effectiveness of UST and the alternative therapies, and that UST was likely inferior to ADA in the first 24-32 weeks of treatment (paragraph 6.19 refers).

Drug cost/patient: $ (first two years)

6.41 Based on the proposed effective AEMPs, the average drug cost for UST per patient over the first two years of treatment is $ (excluding IV administration costs) based on the assumptions in Table 7. For patients treated with UST Q8W regimen, drug cost over the first two years is $ ($*3+$*12). For patients treated with UST Q12W, the drug cost over the first two years is $ ($*3+$*8), owing to less frequent dosing for maintenance treatment.

Estimated PBS usage & financial implications

6.42 This submission was not considered by DUSC. The submission used a market share approach to the financial estimates based on the effective prices. Table 8 summarises the inputs used for the financial estimates.

Table 8: Key inputs for financial estimates

<table>
<tr><th>Parameter</th><th>Value applied and source</th></tr>
<tr><td>Patient-weeks per comparator script.</td><td>To convert script numbers to patient weeks on treatment, the submission estimated the average number of weeks of treatment per script based on the TGA approved and PBS listed dosing schedules for each agent, for the initial and continuing treatment.
Table: Average weeks of treatment per dispensed script
<table>
<tr><th>Comparator & script type</th><th>Item numbers</th><th>Max Qty</th><th>Max Rpts</th><th>Wks/ script</th></tr>
<tr><td>ADA, 80 mg/0.8mL</td><td>12360M, 12393G</td><td>3</td><td>0</td><td>4.0</td></tr>
<tr><td>ADA 40 mg/0.4-0.8ml</td><td>12380N, 12381P, 12331B, 12386X</td><td>6</td><td>0</td><td>4.0</td></tr>
<tr><td>ADA 40 mg/0.4-0.8mL</td><td>12340L, 12397L, 12405X, 12446C, 8963R, 8965W, 12353E, 12367X, 8964T, 8966X</td><td>2</td><td>2/5</td><td>4.0</td></tr>
<tr><td>IFX IV 100 mg</td><td>11423F</td><td>5</td><td>2</td><td>8.0</td></tr>
<tr><td>IFX IV 100 mg</td><td>11432Q</td><td>5</td><td>2</td><td>8.0</td></tr>
<tr><td>IFX IV 100 mg</td><td>9654D, 11424G</td><td>1</td><td>0</td><td>6.9^</td></tr>
<tr><td>IFX IV 100 mg</td><td>9674E, 11412P</td><td>1</td><td>0</td><td>6.9^</td></tr>
<tr><td>IFX SC 120 mg</td><td>13055D, 13061K, 13074D, 13060J, 13073C, 13072B</td><td>2</td><td>0/5</td><td>4.0</td></tr>
</table>
Source: Table 4.2, p203 of the submission
^ Average assumed because scripts cover induction and maintenance at different dosing frequencies.</td></tr>
<tr><td>Current market and market shares</td><td>The submission used script data for IFX and ADA extracted from the PBS/RPBS Services Australia database 2015 to 2022, along with the average weeks of treatment to estimate patient weeks of treatment and corresponding market shares.</td></tr>
<tr><td>Market growth</td><td>For extrapolation of the market in terms of patient-weeks on treatment, the submission applied a linear function for the total market on the basis it provided the best fit to the historical data points, and a logarithmic function to derive the market shares of IFX and ADA. The submission acknowledged the volatility in market shares in 2020-2022, with the COVID-19 pandemic likely explaining the sharp decrease in use of IFX (requiring IV infusion) as patients minimised time in hospital. Given this volatility, the submission assumed that the market share of IFX would re-stabilise following the COVID-19 pandemic according to the applied function. The submission assumed the proposed listing of UST would not influence the current background rate of growth in the market.</td></tr>
<tr><td>Substitution rate</td><td>The submission assumed that the majority of UST scripts will be sourced from substituting ADA (30% in Year 1, increasing to 50% in Year 6) compared to IFX (10% in Year 1, increasing to 15% in Year 6). The submission argued UST would be more likely to replace ADA compared to IFX, as a second-line treatment after IFX. Overall, the market share for UST would increase from 21.2% in Year 1 to 35.3% in Year 6.</td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Value applied and source</th></tr>
<tr><td>Script equivalence</td><td>To estimate the number of UST scripts, the submission first estimated the reduction in comparator scripts using the assumed substitution rates then estimated the corresponding number of UST scripts based on script equivalence between UST and the comparators. In calculating the script equivalence ratios, the submission incorrectly assumed that each dose of ADA and IFX SC requires one script (i.e., 52 doses of ADA Q2W are required over 104 weeks). Given each script of ADA and IFX SC provides on average 4 weeks of treatment (see patient-weeks per comparator script above), patients only require 26 scripts of ADA or IFX SC over 104 weeks, corresponding to a script equivalence of 1:0.48.
Table: Estimate script equivalence between UST and comparators
<table>
<tr><th></th><th>Scripts / 104 weeks</th><th>Script equivalence to UST</th></tr>
<tr><td>ADA</td><td>52 scripts</td><td>1 : 0.24</td></tr>
<tr><td>IFX IV</td><td>15 scripts</td><td>1 : 0.83</td></tr>
<tr><td>IFX SC</td><td>51 scripts</td><td>1 : 0.23</td></tr>
<tr><td>UST</td><td>12.52 scripts, weighted 88%*13 (Q8W) + 12%*9 (Q12W)</td><td>NA</td></tr>
</table>
Source: Text on p207 of the submission; ‘Attachment 4.1 Stelara fCD UCM March 2023 (BASE).xlsx’</td></tr>
<tr><td>Drug costs for UST and comparators</td><td>The submission applied the ‘effective’ DPMQ prices to the estimated change in UST and comparator scripts. The submission stated both comparators (ADA, IFX) are F2 drugs; therefore, the effective price is the published price.
The submission’s approach to costing variable dose scripts may not be reasonable, given the maximum quantity (corresponding to the DPMQ) may not reflect the average quantity of drug dispensed per script. This approach was also inconsistent with the cost-minimisation approach presented in Section 3 (based on average number of vials per dose for UST IV and IFX IV) as well as other assumptions in Section 4. In addition, the published prices applied for ADA scripts in the submission are higher than the current prices, owing to a statutory price reduction in April 2023 (note, there is now a different price for different brands of ADA).</td></tr>
<tr><td>MBS costs</td><td>The submission indicated that the IV formulations of IFX and UST require MBS-funded administration and costed these services using MBS item 14245 for IV infusion, at 85% benefit ($88.05). At time of PBAC consideration, the MBS schedule fee for item 14245 was $91.25. The financial estimates spreadsheet costed one IV administration per IFX IV script but only half an IV administration per UST IV script. Estimates were updated during evaluation assuming one IV administration per UST IV script.</td></tr>
</table>

Source: pp203-207 of the submission.
ADA = adalimumab; IFX = infliximab; IV = intravenous; SC = subcutaneous; UST = ustekinumab.

6.43 Overall, the estimated net cost savings to the PBS/RPBS in the submission was unreliable for the following reasons:

- The submission’s approach to costing IFX IV scripts based on the maximum quantity rather than average quantity of vials per dose, likely underestimated the cost-offsets associated with IFX. Given the submission assumed each IFX IV script (maximum quantity 1) provided one dose (i.e., one IV infusion and 6.9 weeks of treatment on average), then the costs should reflect the average number of vials per dose (4 vials) rather than the maximum quantity (1 vials). Disaggregated results showed that the proposed substitution of IFX explained the $10 million to < $20 million of the total cost for UST but only $0 to < $10 million of the cost offsets over the first six years. Given the cost-minimisation approach presented, the substitution of IFX for UST would likely be (approximately) cost neutral.

- The submission's approach to costing UST IV scripts based on the maximum quantity of 4 vials rather than average quantity of 3 vials per dose used in the cost-minimisation approach, likely overestimated the cost of UST IV scripts. However, the overall impact of this assumption on the financial estimates was likely to be small given the proportional use of UST IV formulation (i.e., the loading dose only) was low.
- The submission's approach to estimating script equivalence appeared to confuse the number of doses of ADA and IFX SC required over 104 weeks (i.e., 52 doses) with the number of scripts of ADA and IFX SC required over 104 weeks (i.e., 26 scripts). The submission had correctly noted that 1 script provided 4 weeks of treatment with ADA and IFX SC when estimating patient-weeks on treatment, but then inconsistently assumed 1 script provided only 2 weeks of treatment when estimating script equivalence. This error likely considerably overestimated the cost savings as a result of substitution with ADA. A sensitivity analysis assuming each ADA script provided 4 weeks of treatment (i.e., a script equivalence with UST of 1:0.48) reduced the estimated net cost savings to the PBS/RPBS from $20 million to < $30 million to $0 to < $10 million over six years.

6.44 The PSCR acknowledged the issues raised in the evaluation and provided updated utilisation and financial estimates accounting for different script equivalence for ADA and IFX, amended maximum quantities, an updated price for ADA based on the 1 April 2023 price of the Humira/reference brand and changes to MBS services associated with UST administration outlined in paragraph 6.43 above. The revised utilisation and financial estimates are presented in the table below.

Table 9: Estimated use and financial implications (PSCR updated)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
UST IV	[redacted][2]	[redacted][2]	[redacted][1]	[redacted][2]	[redacted][1]	[redacted][2]
UST SC	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total UST scripts	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted]	[redacted][3]
Estimated financial implications of UST for fistulising CD						
Cost to PBS/RPBS less copay	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]
Estimated financial implications for ADA, IFX						
Cost to PBS/RPBS less copay	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
ADA	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
IFX	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net financial implications						
Net cost to PBS/RPBS	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net cost to MBS	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net cost to health budget	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]

Source: Derived from PSCR updated utilisation and financial estimates (Stelara fCD UCM March 2023 (PSCR submitted).xlsx

CD = ADA = adalimumab; IFX = infliximab; IV = intravenous; SC = subcutaneous; UST = ustekinumab.

The redacted values correspond to the following ranges:

[1] *<500*

[2] *500 to < 5,000*

[3] *5,000 to <10,000*

[4] *$0 to < $10 million*

[5] *$10 million to < $20 million*

[6] *net cost saving*

6.45 Based on the revised estimates in the PSCR, the total net cost savings to the PBS/RPBS of listing UST for fistulising CD was estimated to be approximately $0 to < $10 million in Year 6, and a total of approximately $0 to < $10 million in the first 6 years of listing.

6.46 Updates to the estimates provided in the PSCR notwithstanding, assuming UST were to be listed on a cost-minimisation basis to the least costly alternative therapy and current market growth was unchanged, the evaluation and ESC considered the requested listing would be expected to be cost neutral to the PBS/RPBS (and potentially a slight cost saving as it would only replace therapies that are the same cost or more expensive).

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) and General Schedule listings of ustekinumab (UST) for the treatment of fistulising Crohn's disease (CD). The recommendation for the Section 100 listing was for the intravenous (IV) induction dosing at initiation, and the General Schedule listing was for the subcutaneous injection for subsequent dosing. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of UST would be acceptable if it were cost minimised to the least costly alternative therapy of infliximab (IFX) and adalimumab (ADA). The PBAC considered that while the evidence supporting the clinical claims of non-inferior efficacy and safety versus the nominated comparators was limited, on balance when considering the clinical need

for additional therapies for fistulising CD, the claims versus IFX and ADA were likely to be reasonable.

7.2 The PBAC considered the equi-effective doses of UST and the alternative therapies could be derived with reference to the therapeutic relativity sheets and relevant Product Information documents, noting the UST equi-effective dose component includes an IV dose at week 0 (based on a tiered weight-based regimen), followed by 90 mg SC dosing at Week 8 and every 8 or 12 weeks thereafter, with a split of use of 88% receiving a 8 weekly regimen and 12% receiving a 12 weekly regimen (see Table 8).

7.3 The PBAC considered there was a high clinical need for additional effective therapies for the treatment of fistulising CD for patients who do not otherwise meet the criteria for PBS-subsidised treatment for severe CD, where more biologic or targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs) are available. The PBAC noted that fistulising CD has a severe impact on patients' quality of life and that only two bDMARD/tsDMARD options were currently available for the requested population, with both IFX and ADA being tumour necrosis factor alfa (TNF-α) inhibitors.

7.4 The PBAC noted the comments received from health professionals and organisations highlighted the severe impacts of fistulising CD on quality of life and the risks of repeat surgeries, which can often end in proctectomy and the need for a permanent stoma, and the need for additional therapeutic options. The Committee also noted the comments highlighted the current TNF inhibitors lose efficacy over time and considered that the listing of UST, as the first non-TNF inhibitor bDMARD/tsDMARD for fistulising CD, would be beneficial to patients both as a first line option or for patients who did not achieve or had lost response to the currently available PBS-subsidised options.

7.5 The PBAC considered it was reasonable for the listing of UST to be consistent with other bDMARDs/tsDMARDs for the treatment of fistulising CD, with prescribing limited to eligible medical practitioners, an initial treatment period of 16 weeks followed by maintenance therapy with re-assessment at 24-week intervals, with maintenance dose regimens once every 8 or 12 weeks. The PBAC also considered it was reasonable to allow patients who are currently or have been treated with ADA and/or IFX to also use UST prior to requiring a treatment break, given patients currently have few treatment options and UST was the first therapy in over 10 years and first non-TNF inhibitor to be recommended for fistulising CD. The Committee noted the flow-on changes to other fistulising CD listings to included UST in the list of eligible therapies.

7.6 The PBAC considered the nominated comparators of ADA (primary) and IFX (secondary) were reasonable.

7.7 The PBAC noted the submission presented information from the SEAVUE and STARDUST UST trials, in addition to the three UST, three ADA and two IFX trials

presented in the 2017 submission for fistulising CD. The Committee noted the two additional trials were conducted in a broader CD population (similar to the original evidence base considered in 2017) and the fistulising CD evidence remained limited to small subgroups of these broader trials. While the PBAC considered the STARDUST trial to be of limited usefulness to assess the claims (as a comparison of UST 'routine care' or 'treat to target' regimens), the Committee noted the SEAVUE trial was a head-to-head trial vs ADA and considered that although limited by small patient numbers, provided direct evidence to assess the comparative effectiveness of UST and ADA.

7.8 The PBAC noted the available evidence versus placebo, which included small subgroup data from the same trials as previously presented in the 2017 submission (UNITI-1, UNITI-2 and IM-UNITI) did not show any statistically significant difference between UST and placebo on key fistula outcomes for either induction or maintenance treatment, however also noted a numerical trend in favour of UST over placebo. Overall, the PBAC considered the very small size of the fistulising CD subgroups in the placebo-controlled trials, with less than 50 UST patients in induction (pooled UNITI-1/2) and less than 20 in maintenance (IM-UNITI), led to substantial uncertainty and complicated assessment of the clinical claim. The PBAC noted the indirect treatment comparisons based on this data did not show a statistically significant difference between UST and ADA, but did favour IFX over UST; however, considered these comparisons were similarly limited by the available data.

7.9 The PBAC considered the results of the subgroup analysis from SEAVUE, while also limited, indicated UST may be similarly effective to ADA over the longer term (beyond 24 weeks). The PBAC noted UST appeared to be less effective than ADA in early treatment, with a lower proportion achieving response and/or remission out to week 24 but converging by week 32. The Committee considered the pharmacological profile of UST, as an IL-12/23 inhibitor, was generally well understood and its effects on the underlying inflammatory pathway resulted in a longer time to achieve similar effectiveness than the TNF inhibitors, with a longer tail of effect post-cessation of treatment. While it agreed with the ESC that a higher proportion of patients who responded to treatment would continue to experience worse symptoms associated with their disease for a longer period, was of the view that on balance, UST was likely to be similarly effective to ADA for the treatment of fistulising CD over the longer term. With regards to the claims versus IFX, the PBAC recalled it had recommended ADA on a cost minimisation basis with IFX with a similar level of data to what was currently available for UST and considered there remained a high clinical need for additional therapies for the treatment of fistulising CD. On balance, the PBAC considered a claim of non-inferior comparative effectiveness between UST and IFX was also likely to be reasonable.

7.10 The PBAC noted the submission claims for comparative safety versus ADA and IFX were based upon the ITT populations of the UST trials for severe CD, on the basis there was no reason to expect a difference in safety between severe CD and fistulising CD and considered this was reasonable. The Committee also noted the new trials found

no difference in safety between the routine care and treat to target regimens (STARDUST) and found ADA was associated with higher rates of injection site reactions and treatment discontinuations compared with UST in SEAVUE. Overall, the PBAC considered there were no new safety signals in the data and given the safety profile of UST is well established, also considered the claim of non-inferior comparative safety to ADA and IFX was reasonable.

7.11 Given its view on the comparative effectiveness of UST to ADA and IFX, the PBAC considered that listing based on a cost minimisation approach with costs over two years, consistent with the approach previously used for bDMARDs/tsDMARDs, was appropriate to determine the cost minimised price of UST. The PBAC considered the cost of UST should be no greater than the alternative therapies, accounting for the split of maintenance regimens of 88% at 8-weekly and 12% at 12-weekly dosing (paragraph 7.2 refers).

7.12 The PBAC considered that, under the parameters of its recommended listing on a cost minimisation basis with the least costly of ADA and IFX, the listing of UST would most likely be cost neutral to the PBS or result in a modest save as it will only replace therapies that are either of equivalent cost or more expensive.

7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because UST is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the alternative therapies, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.14 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new items:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
IV loading dose (Section 100 HSDP – Public and Private Hospitals)					
USTEKINUMAB					
Ustekinumab 130 mg/26 mL injection, 26 mL vial	NEW	4	4	0	Stelara
SC injection – initial treatment (General Schedule)					
USTEKINUMAB					
ustekinumab 90 mg/1 mL injection, 1 mL pre-filled syringe	NEW	1	1	0	Stelara

Restriction Summary			
		Category / Program: Section 100 – Highly Specialised Drugs Program {Public and Private Hospitals}	
		Prescriber type: ☒Medical Practitioners	
		Restriction Level / Method: ☒Authority Required – (in writing only via post/HPOS upload)	
		Administrative Advice: *Changes to the overarching administrative advice concept 27614 at the end of this section.*	
		Administrative Advice: ~~Increase in the maximum quantity or number of units up to 4 may be authorised for the purpose of weight-based loading dose.~~ *No increase in the maximum quantity or number of units may be authorised*	
		Administrative Advice: No increase in the maximum number of repeats may be authorised.	
		Administrative Advice: Special Pricing Arrangements apply.	
		Administrative advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001	
	Indication: Complex refractory Fistulising Crohn disease		
	Treatment Phase: Initial treatment - Initial 1 (new patient or recommencement of treatment after a break in biological medicine of more than 5 years)		
	Clinical criteria:		
	Patient must have confirmed 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		
	Clinical criteria:		
	Patient must have an externally draining enterocutaneous or rectovaginal fistula		
	AND		
	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)]		
	Prescribing Instructions: Applications for authorisation must be made in writing and must include: (1) two completed authority prescription forms; and, (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes a completed current Fistula Assessment Form including the date of assessment of the patient's condition of no more than 4 weeks old at the time of application.		

	Prescribing Instructions: Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for 1 vial or pre-filled syringe of 90 mg and no repeats.
	~~**Prescribing Instructions:**~~ ~~A maximum of 16 weeks of treatment with this drug will be approved under this criterion.~~ *(Use 21164 below instead)*
	Prescribing Instructions: An assessment of a patient's response to this initial course of treatment must be conducted between 8 and 16 weeks of therapy.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: A maximum quantity of a weight-based loading dose is up to 4 vials with no repeats and the subsequent first dose of 90 mg with no repeats provide for an initial 16-week course of this drug will be authorised.
	Prescribing Instructions: Where fewer than 6 vials in total are requested at the time of the application, authority approvals for a sufficient number of vials based on the patient's weight to complete dosing at weeks 0 and 8 may be requested by telephone through the balance of supply restriction.
	Prescribing Instructions: Under no circumstances will telephone approvals be granted for initial authority applications, or for treatment that would otherwise extend the initial treatment period.
Restriction Summary	
	Indication: Complex refractory Fistulising Crohn disease
	Treatment Phase: Initial treatment - Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle
	AND
	Clinical criteria:
	Patient must not have failed PBS-subsidised therapy with this drug for this condition more than once in the current treatment cycle
	AND
	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)]
	Prescribing Instructions: To demonstrate a response to treatment the application must be accompanied with the assessment of response, conducted between 8 and 16 weeks of therapy and no later than 4 weeks from cessation of the most recent course of biological medicine. It is recommended that an application for the continuing treatment be submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This is to ensure treatment continuity for those who meet the continuing restriction.

	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: Applications for authorisation must be made in writing and must include:, (1) two completed authority prescription forms; and, (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes the following:, (i) a completed current Fistula Assessment Form including the date of assessment of the patient's condition; and, (ii) details of prior biological medicine treatment including details of date and duration of treatment.
	Prescribing Instructions: Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for 1 vial or pre-filled syringe of 90 mg and no repeats.
	Prescribing Instructions: The most recent fistula assessment must be no more than 4 weeks old at the time of application.
	~~**Prescribing Instructions:**~~ ~~A maximum of 16 weeks of treatment with this drug will be approved under this criterion.~~ *(Use 21164 below instead)*
	Prescribing Instructions: A maximum quantity of a weight-based loading dose is up to 4 vials with no repeats and the subsequent first dose of 90 mg with no repeats provide for an initial 16-week course of this drug will be authorised.
	Prescribing Instructions: Where fewer than 6 vials in total are requested at the time of the application, authority approvals for a sufficient number of vials based on the patient's weight to complete dosing at weeks 0 and 8 may be requested by telephone through the balance of supply restriction.
	Prescribing Instructions: Under no circumstances will telephone approvals be granted for initial authority applications, or for treatment that would otherwise extend the initial treatment period.
Restriction Summary	
	Indication: Complex refractory Fistulising Crohn disease
	Treatment Phase: Initial 1 (new patient or recommencement of treatment after a break in biological medicine of more than 5 years), Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) - balance of supply
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more) restriction to complete 16 weeks treatment; OR Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (change or recommencement of treatment after a break of less than 5 years) restriction to complete 16 weeks treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions
	AND
	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)]
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
USTEKINUMAB					
ustekinumab 90 mg/1 mL injection, 1 mL pre-filled syringe	New	1	1	1	STELARA
**A maximum of 2 repeats is required for patients using an 8-weekly course of ustekinumab.*					

Restriction Summary		
		Category / Program: GENERAL – General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction Level / Method: ☒Authority Required – (in writing only via post/HPOS upload)
		Administrative Advice: *Changes to common administrative advice concept 27614 at the end of this section.*
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
		~~**Administrative Advice:**~~ ~~No increase in the maximum number of repeats may be authorised.~~
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)., Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au, Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos, or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	Indication: Complex refractory Fistulising Crohn disease	
	Treatment Phase: Continuing treatment	
	Clinical criteria:	
	Patient must have previously received PBS-subsidised treatment with this drug for this condition	
	AND	
	Clinical criteria:	

	Patient must have demonstrated an adequate response to treatment with this drug
	AND
	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)]
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and, (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: An adequate response is defined as: (a) a decrease from baseline in the number of open draining fistulae of greater than or equal to 50%; and/or, (b) a marked reduction in drainage of all fistula(e) from baseline, together with less pain and induration as reported by the patient.
	Prescribing Instructions: The most recent fistula assessment must be no more than 1 month old at the time of application.
	Prescribing Instructions: At the time of the authority application, medical practitioners should request the appropriate quantity and number of repeats; up to 1 repeat will be authorised for patients whose dosing frequency is every 12 weeks. Up to a maximum of 2 repeats will be authorised *for patients whose dosing frequency is every 8 weeks.*

	TREATMENT OF COMPLEX REFRACTORY FISTULISING CROHN DISEASE The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological medicines for patients with complex refractory fistulising Crohn disease. Where the term 'biological medicine' appears in the following notes and restrictions, it refers to adalimumab, infliximab and ustekinumab only. A patient is eligible for PBS-subsidised treatment with only 1 of the PBS-subsidised biological medicines for this condition at any one time. From 1 April 2011, under the PBS, all patients will be able to commence a treatment cycle where they may trial PBS-subsidised adalimumab, infliximab or ustekinumab without having to experience a disease flare when swapping to the alternate agent. Under these arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with adalimumab, infliximab or ustekinumab while they continue to show a response to therapy. A patient who received PBS-subsidised adalimumab, infliximab or ustekinumab treatment prior to 1 April 2011 is considered to have started their treatment cycle as of 1 April 2011. Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised adalimumab, infliximab or ustekinumab more than twice. Once a patient has either failed or ceased to respond to treatment for this condition 3 times, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 5-year break in PBS-subsidised biological medicine therapy for this condition before they are eligible to commence the next cycle. The 5-year break is measured from the date of the last approval for PBS-subsidised adalimumab, infliximab or ustekinumab treatment in the most recent cycle to the date of the first application for initial treatment with adalimumab, infliximab or ustekinumab under the new treatment cycle.

	A patient who has failed fewer than 3 trials of biological medicine therapy in a treatment cycle and who has a break in therapy of less than 5 years, may commence a further course of treatment within the same treatment cycle. A patient who has failed 3 trials or fewer of biological medicine therapy in a treatment cycle and who has a break in therapy of more than 5 years, may commence a new treatment cycle. There is no limit to the number of treatment cycles a patient may undertake in their lifetime. (1) How to prescribe PBS-subsidised adalimumab, infliximab or ustekinumab therapy after 1 April 2011. (a) Initial treatment. Applications for initial treatment should be made where: (i) a patient has received no prior PBS-subsidised adalimumab, infliximab or ustekinumab therapy in this treatment cycle and wishes to commence such therapy (Initial 1- new patient or recommencement of treatment after a break in biological medicine of more than 5 years); or (ii) a patient has received prior PBS-subsidised (initial or continuing) adalimumab, infliximab or ustekinumab therapy and wishes to trial an alternate agent (Initial 2 - change or recommencement of treatment after a break in biological medicine of less than 5 years) [further details are under 'Swapping therapy' below]; or (iii) a patient wishes to recommence treatment with adalimumab, infliximab or ustekinumab following a break in PBS-subsidised therapy with that agent (Initial 2 - change or recommencement of treatment after a break in biological medicine of less than 5 years). Initial treatment authorisations will be limited to provide for a maximum of 16 weeks of therapy for adalimumab and ustekinumab and 14 weeks of therapy for infliximab. From 1 April 2011, a patient must be assessed for response to any course of initial PBS-subsidised treatment following a minimum of 12 weeks of therapy for adalimumab and ustekinumab and up to 12 weeks after the first dose (6 weeks following the third dose) for infliximab, and this assessment must be conducted no later than 4 weeks from the date that course was ceased. Where a response assessment is not conducted within these timeframes, the patient will be deemed to have failed to respond to treatment with that biological medicine unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment. (b) Continuing treatment. Following the completion of an initial treatment course with a biological medicine, a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response. For the first continuing treatment course of PBS-subsidised biological medicine treatment, it is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment under the Initial 1, or Initial 2 treatment restrictions.

	For the second and subsequent continuing courses of PBS-subsidised biological medicine treatment, it is recommended that an assessment of a patient's response is conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment. Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with that biological medicine, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment. (2) Swapping therapy. Once initial treatment with the first PBS-subsidised biological medicine is approved, a patient may swap if eligible to the alternate biological medicine within the same treatment cycle. A patient may trial the alternate biological medicine at any time, regardless of whether they are receiving therapy (initial or continuing) with adalimumab, infliximab or ustekinumab at the time of the application. However, they cannot swap to a particular biological medicine if they have failed to respond to prior treatment with that drug two times within the same treatment cycle. To ensure a patient receives the maximum treatment opportunities allowed under these arrangements, it is important that they are assessed for response to every course of treatment within the timeframes specified in the relevant restriction. A patient who is not able to complete an initial treatment course for a biological medicine will be deemed to have failed treatment with that biological medicine unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment. (3) Baseline measurements to determine response. A response to treatment is to be determined by comparison of current disease activity measurements relative to the baseline measurements submitted with the first authority application for adalimumab, infliximab or ustekinumab. However, prescribers may provide new baseline measurements any time that an initial treatment authority application is submitted within a treatment cycle and the eligibility for continuing treatment must be assessed according to these revised baseline measurements. (4) Recommencement of treatment after a 5-year break in PBS-subsidised therapy. A patient who wishes to recommence treatment following a break in PBS-subsidised biological medicine therapy of at least 5 years, must requalify for initial treatment with respect to the indices of disease severity.

Flow on changes to adalimumab and infliximab will also be required to include the updated administrative note for Complex refractory Fistulising Crohn disease. These listings include: 12340L, 12381P, 12446C, 13230H, 12380N, 12397L, 12405X, 13220T, 8965W, 8966X, 12353E, 12386X, 8963R, 8964T, 12331B, 12367X, 12360M, 12393G, 12393G, 9674E, 11412P, 11423F, 11424G, 11432Q, 13055D, 13060J, 13061K, 13072B, 13073C, 13074D.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.