6.14 UPADACITINIB, Tablet 15 mg, Tablet 30 mg, Tablet 45 mg, Rinvoq®, AbbVie Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested General Schedule, Authority Required, listing for upadacitinib for the treatment of complex refractory fistulising Crohn's disease (FCD).

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) vs infliximab, adalimumab and ustekinumab. Table 1 summarises the components of the clinical claim addressed by the submission.

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

Component	Description
Population	Patients with complex refractory fistulising Crohn's disease who have externally draining enterocutaneous or rectovaginal fistula
Intervention	Induction regimen: upadacitinib 45 mg oral modified release tablet once daily for 12 weeks Extended induction: optional upadacitinib 30 mg oral tablet once daily for additional 12 weeks Maintenance regimen: upadacitinib 15 mg or 30 mg oral tablet once daily thereafter
Comparator	Main: infliximab Additional: adalimumab, ustekinumab
Outcomes	Fistula remission, fistula response
Clinical claim	Upadacitinib is non-inferior to infliximab at achieving fistula remission and fistula response and non-inferior in terms of safety

Source: Table 1-1, p4 of the submission.

2 Background

Registration status

2.1 Upadacitinib was approved by the Therapeutic Goods Administration (TGA) (28 April 2023) for the following indication: 'the treatment of adult patients with moderately to severely active Crohn's disease (CD), who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biological medicine'.

2.2 A separate TGA approval request for upadacitinib in FCD was not proposed. The requested PBS restrictions for FCD were within the scope of the upadacitinib CD TGA indication. This approach was reasonable and aligns with the PBAC precedent that interpreted the TGA indication for moderate to severe CD as also covering fistulising disease (paragraph 3, adalimumab, Public Summary Document [PSD], November 2010 PBAC Meeting; paragraph 2.2, ustekinumab, PSD, July 2023 PBAC Meeting).

2.3 A class-wide boxed warning for Janus Kinase (JAK) covering mortality, major cardiovascular events, thrombosis, mortality, infections and use in the elderly has been added to the Australian Product Information for baricitinib, tofacitinib and upadacitinib (TGA, Important safety information for JAK inhibitors, Medicines Safety Update, 2023).[1]

Previous PBAC considerations

2.4 Upadacitinib was recommended by the PBAC for Crohn's disease at its July 2023 meeting and was listed on the PBS on 1 December 2023. Upadacitinib is also listed on the PBS for ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis and non-radiographic axial spondyloarthritis.

3 Requested listing

3.1 For brevity, 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 Rpts	Available brands
UPADACITINIB					
[Initial treatment] Upadacitinib 45 mg tablet, 28	$2,717.78 published price $[redacted] effective price	1	28	2	Rinvoq
[Initial treatment-extended induction] Upadacitinib 30 mg tablet, 28	$2,078.09 published price $[redacted] effective price	1	28	2	Rinvoq
[Continuing treatment] Upadacitinib 30 mg tablet, 28	$2,078.09 published price $[redacted] effective price	1	28	5	Rinvoq
[Continuing treatment] Upadacitinib 15 mg tablet, 28	$1,273.11 published price $[redacted] effective price	1	28	5	Rinvoq

Category/Program	Section 85 – General Schedule
Prescriber type	Medical Practitioners
Severity	Complex refractory
Condition	Fistulising Crohn disease
PBS indication	Complex refractory fistulising Crohn disease
Restriction level	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Population criteria	Patient must be aged 18 years or older.

[1] Therapeutic Goods Administration (TGA). Important safety information for Janus kinase (JAK) inhibitors Medicines Safety Update (2023). Accessed: 21 November 2025. https://www.tga.gov.au/news/safety-updates/important-safety-information-janus-kinase-jak-inhibitors

The above criteria apply to all treatment phases outlined below:	
Treatment phase	**Initial treatment 1 (new patient, or change or re-commencement of treatment after break > 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 Patient must have an externally draining enterocutaneous or rectovaginal fistula.
Prescriber 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. A maximum quantity and number of repeats to provide for an initial 12 week course of this drug will be authorised under this item code.
Treatment phase	**Initial treatment 2 (change or re-commencement of treatment after break < 5 years)**
Clinical criteria	Patient must have received prior PBS-subsidised treatment with a biologic for this condition in this treatment cycle; AND Patient must not have failed PBS-subsidised therapy with this drug for this condition more than once in the current treatment cycle; AND The treatment must not exceed 12 weeks under this restriction.
Prescriber instructions	As per initial treatment 1
Treatment phase	**Initial treatment – balance of supply for initial (induction) treatment phases**
Clinical criteria	The treatment must have been prescribed in a quantity in the most recent prescription which did not seek the full quantity available in regards to any of: (i) the quantity per dispensing, (ii) repeat prescriptions The treatment must provide no more than the balance available under the treatment phase from which the immediately preceding supply was obtained under.
Prescriber instructions	Initial (induction) treatment phases and 'Extended induction' treatment phases for this benefit aim to provide 12 weeks treatment duration.

Category/Program	Section 85 – General Schedule
Prescriber type	Medical Practitioners
Severity	Complex refractory
Condition	Fistulising Crohn disease
PBS indication	Complex refractory fistulising Crohn disease
Restriction level	☐ Restricted benefit ☐ Authority Required - In Writing ☒ Authority Required - Telephone ☐ Authority Required – Emergency ☒ Authority Required - Electronic ☐ Streamlined
Treatment criteria	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Population criteria	Patient must be aged 18 years or older.
Treatment phase	**Extended induction period (optional) from weeks 12 to 24**
Clinical criteria	Patient must have experienced an inadequate therapeutic benefit following at least one of:

	i) dosing with 45 mg daily in the initial 12-week induction period ii) dosing with 15 mg daily
Prescriber instructions	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). No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Category/Program	Section 85 – General Schedule
Prescriber type	Medical Practitioners
Severity	Complex refractory
Condition	Fistulising Crohn disease
PBS indication	Complex refractory fistulising Crohn disease
Restriction level	☐ Restricted benefit ☒ Authority Required - Telephone ☐ Authority Required – In Writing ☐ Authority Required – Emergency ☒ Authority Required - Electronic ☐ Streamlined
Treatment criteria	Must be treated by a gastroenterologist (code 87); OR Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; OR Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)].
Population criteria	Patient must be aged 18 years or older.
Treatment phase	**Continuing (maintenance) treatment**
Clinical criteria	Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition; AND Patient must have demonstrated an adequate response to treatment with this drug; OR The condition must have not met the improvements specified below due to the prescribed dose being too low - this authority application seeks higher dosing.
Prescriber 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. The most recent fistula assessment must be no more than 1 month old at the time of application.
Treatment phase	**Balance of supply for the continuing (maintenance) treatment phase**
Clinical criteria	The treatment must have been prescribed in a quantity in the most recent prescription which did not seek the full quantity available in regards to any of: (i) the quantity per dispensing, (ii) repeat prescriptions; AND The treatment must provide no more than the balance available under the treatment phase from which the immediately preceding supply was obtained under.

3.2 A Special Pricing Arrangement (SPA) was requested for upadacitinib.

3.3 The submission requested the Authority level for continuing prescriptions be reduced to real time Online and Telephone Authority, aligned with the restriction level already in place for the PBS listing for upadacitinib in moderate to severe ulcerative colitis. The evaluation noted this would be inconsistent with the authority requirements applied to the existing complex fistulising CD therapies for originator brands (where a biosimilar is listed), which require authority applications to be made in writing. The Pre-Sub-Committee Response (PSCR) and Pre-PBAC Response reiterated this request

and noted the disparity in authority levels for continuing treatment between CD/FCD and ulcerative colitis (UC) and argued consistency across inflammatory bowel disease (IBD) indications would enhance quality use of medicines by reducing unnecessary delays and ensuring patient equity.

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

4 Population and disease

4.1 CD is an incurable, progressive, inflammatory gastrointestinal disorder, characterised by relapsing and remitting episodes of inflammation. FCD is a complication of CD, where an abnormal passageway forms between an organ and another part of the body. Anal or perianal fistulas are the most common type of fistulising Crohn's disease and typically develop as a complication of a perianal abscess. Abscesses occur when inflammation penetrates the bowel wall layers, leading to a collection of pus. As the abscess enlarges it can create a tract or tunnel that evolves into a fistula allowing the passage of pus, blood, mucous and faecal matter either externally or into adjacent organs.

4.2 Fistulas are associated with significant morbidity and have a marked impact on patients' quality of life. Fistula-related pain and discharge are prominent symptoms faced by patients daily and are considerable sources of impaired wellbeing. Simple activities such as standing and sitting have been described as unbearable, and many patients report experiencing social isolation, restricted participation in daily life, diminished body image and adverse effects on sexual health and interpersonal relationships. In comparison to the general CD cohort, fistulising patients experience higher rates of hospitalisation, with longer admission times, and more frequent outpatient appointments.

4.3 The presence of an actively draining fistula contributes only 20 points to the Crohn's disease activity index (CDAI) score, meaning a substantial proportion of patients with this debilitating manifestation of CD are unable to access advanced therapies subsidised under the severe CD PBS criteria (which requires a CDAI of ≥ 300 or ≥ 220 with extensive intestinal inflammation). Fistula treatment is challenging, and recurrence is common. Despite optimal medical and surgical management, up to 70% of patients do not achieve remission, and fistula relapse occurs in 20-30% of cases. The submission stated that access to additional advanced treatments under specific FCD PBS criteria was therefore essential to ensure equity for affected patients, to address the unmet clinical need, and improve outcomes for those facing this particularly severe and distressing presentation of CD. This has been previously acknowledged by the PBAC (adalimumab PSD, November 2010 PBAC meeting).

4.4 The 2025 American College of Gastroenterology, Management of Crohn's Disease in Adults guidelines suggest upadacitinib for induction of remission of perianal fistulising

CD.[2] The 2024 European Crohn's and Colitis Organisation Guidelines on Therapeutics in Crohn's Disease state upadacitinib may represent a therapeutic alternative in patients with prior anti-tumour necrosis factor (TNF) failure, intolerance, or contraindications.[3]

4.5 The submission proposed the target PBS population for upadacitinib was identical to the existing PBS population for other advanced therapies (i.e., PBS listed infliximab, adalimumab, and ustekinumab) in FCD.

4.6 Upadacitinib is an orally administered, small molecule that works by inhibiting members of the JAK family of enzymes.

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

5 Comparator

5.1 The submission nominated infliximab as the main comparator and adalimumab, ustekinumab as additional comparators. The main arguments provided in support of this nomination were:

- Infliximab was chosen as the main comparator based on market utilisation, as it represents the medicine that was prescribed on the PBS for the largest number of patients in the target population.
- Adalimumab and ustekinumab were presented as additional comparators.

5.2 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.

5.3 For the requested population, the following PBS listed medicines may be considered alternative therapies because they could be replaced in practice: infliximab, adalimumab and ustekinumab. Some of these alternative therapies may be less costly than upadacitinib.

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 discussed the severe and

[2] Lichtenstein, G. R., Loftus, E. V., et al. (2025). ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol, 120(6), 1225-1264. https://doi.org/10.14309/ajg.0000000000003465

[3] Gordon, H., Minozzi, S., et al. (2024). ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. Journal of Crohn's and Colitis, 18(10), 1531-1555. https://doi.org/10.1093/ecco-jcc/jjae091

debilitating impacts of FCD for patients, which often includes surgery with poor wound healing, scarring and disfigurement, and highlighted the importance of additional treatment options, as current biologic options do not work for all patients and effectiveness can wane over time. The clinician also highlighted that the clinical trial data for upadacitinib found a substantial number of patients had resolution of drainage and closure of external fistula openings, with many responders sustaining a response out to 52 weeks. In addition, the clinician discussed the adverse event profile of upadacitinib being well established, allowing clinicians to proactively manage expected side effects.

Consumer inputs

6.2 The PBAC noted and welcomed the input from health care professionals (3) and a consumer organisation via the Office of Health Technology Assessment Consultation Hub, all strongly supportive of the submission. The PBAC noted the input from health care professionals highlighted the effectiveness of upadacitinib in FCD, including in patients who had previously not responded to or lost response to tumour necrosis factor inhibitors (such as adalimumab and infliximab), and outlined that many patients do not respond to currently available therapies. The input also noted the safety profile of upadacitinib does mean it may not be the preferred therapy for all patients, but noted the safety profile is considered acceptable in younger patients, where FCD is most prevalent (noting it should not be used in pregnancy).

6.3 The PBAC also welcomed the input from Crohn's and colitis Australia (CCA) supported the listing, and highlighted the patient benefits of having an oral treatment option available and presented a patient testimonial discussing the life-changing impacts of upadacitinib for their ulcerative colitis and the hope it can provide similar benefits for patients with FCD.

Clinical trials

6.4 No head-to-head trials comparing upadacitinib with infliximab, adalimumab or ustekinumab were identified. The submission conducted a series of pairwise, indirect treatment comparisons using meta-analysed outcomes for upadacitinib and infliximab, adalimumab and ustekinumab in patients with the FCD subgroup using placebo as the common reference. The submission was based on:

- Induction therapy evidence (7 randomised controlled trials vs placebo)
    - Upadacitinib:
        - U-EXCEED (N=495);
        - U-EXCEL (N=526);

- U-EXCEED and U-EXCEL pooled FCD subgroup[4] (n=66[5]).
  - Infliximab:
    - T20 (N=94; FCD subgroup analysed n=62[6]).
  - Adalimumab:
    - CLASSIC-I (N=150[7]; FCD subgroup n=18);
    - GAIN (N=325[8]; FCD subgroup n=45).
  - Ustekinumab:
    - UNITI-1 (N=496[9]; FCD subgroup n=63);
    - UNITI-2 (N=419[10]; FCD subgroup n=42).
- Maintenance therapy (4 randomised controlled trials vs placebo)
  - Upadacitinib:
    - U-ENDURE (N=502; FCD subgroup n=36).
  - Infliximab:
    - ACCENT II (N=282[11]; evaluated for maintenance response n=276).
  - Adalimumab:
    - CHARM (N=521[12]; FCD subgroup n=77).
  - Ustekinumab:
    - IM-UNITI (N=397; FCD at baseline n=59[13]).

6.5 The submission also identified 2 published ad-hoc analyses of trials evaluating upadacitinib vs placebo for the FCD subgroup:

[4] Colombel et al. (2025), Efficacy and Safety of Upadacitinib for Perianal Fistulizing Crohn's Disease: A Post Hoc Analysis of 3 Phase 3 Trials, Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association, 23(6), 1019–1029. https://doi.org/10.1016/j.cgh.2024.08.032
[5] Draining FCD
[6] Dose relevant arms: infliximab 5 mg/kg; placebo
[7] Dose relevant arms: adalimumab 160 mg at Week 0 and 80 mg at Week 2; placebo
[8] Randomly assigned
[9] Dose relevant arms: ustekinumab 6 mg/kg; placebo
[10] Dose relevant arms: ustekinumab 6 mg/kg; placebo
[11] 306 patients received infliximab in an open label induction phase; 282 patients (non-responders and responders) were randomised to infliximab and placebo arms at Week 14; 276 patients were consistent with paragraph 6.21, ustekinumab PSD, July 2023 PBAC Meeting (Table 5, p19; n=282) however was unable to be verified in publication (Sands et al., 2004)
[12] Dose relevant arms: adalimumab 40 mg every other week; placebo
[13] n=59 at baseline (paragraph 6.8, ustekinumab PSD, July 2023 PBAC Meeting)

- Colombel et al., 2025 included patients with any fistula at baseline. This publication was a post-hoc pooled analysis of the upadacitinib U-EXCEED/U-EXCEL trials and was relied upon to support the efficacy clinical claim.
- Colombel et al., 2023 included patients with draining fistula at baseline. The conference abstract presented a pooled, post-hoc analysis and was relied upon to support the safety clinical claim.

6.6 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
UPA vs PBO		
U-EXCEED (M14-431) NCT03345836	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy.	21 March 2022
U-EXCEL (M14-433) NCT03345849	A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Conventional and/or Biologic Therapies.	23 May 2022
U-ENDURE (M14-430) NCT03345823	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Crohn's Disease Who Completed the Studies M14-431 or M14-433.	27 June 2022
UPA Post Hoc		
Post Hoc Analysis (U-EXCEED, U-EXCEL, U-ENDURE)	Colombel et al. Efficacy and Safety of Upadacitinib for Perianal Fistulizing Crohn's Disease: A Post Hoc Analysis of 3 Phase 3 Trials; Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association.	*American Gastroenterological Association* 2025; 23(6): 1019–1029
	Colombel et al. 2023; P491 – Efficacy and Safety of Upadacitinib for the Treatment of Fistulas and Fissures in Patients with Crohn's Disease	*Journal of Crohn's and Colitis* 2023; 17(S1): i620–i623
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
ACCENT II NCT00207766	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
ADA vs PBO		
CLASSIC-I NCT00055523	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 NCT00105300	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 NCT00077779	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.	*Gastroenterology* 2007; 132 (1):52-65

Trial ID	Protocol title/ Publication title	Publication citation
	Colombel J, Schwartz, DA., Sandborn, WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease.	*Gut* 2009; 58:940-948
UST vs PBO		
UNITI-I NCT01369329	Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease;	*New England Journal of Medicine*. 2016; 375(20):1946-60
UNITI-II NCT01369342	Sandborn WJ, Rutgeerts P, Gasink C, Jacobstein D, Zou B, Johanns J, Sands BE, Hanauer SB, Targan S, Ghosh S, de Villiers WJS, Colombel JF, Feagan BG. Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy;	*Aliment Pharmacol Ther.* 2018; 48(1):65-77
IM-UNITI NCT01369355	Hanauer SB, Sandborn WJ, Feagan BG, Gasink C, Jacobstein D, Zou B, Johanns J, Adedokun OJ, Sands BE, Rutgeerts P, de Villiers WJS, Colombel JF, Ghosh S. IM-UNITI: Three-year Efficacy, Safety, and Immunogenicity of Ustekinumab Treatment of Crohn's Disease;	*J Crohns Colitis.* 2020; 14(1):23-32
	Sandborn WJ, Rebuck R, Wang Y, Zou B, Adedokun OJ, Gasink C, Sands BE, Hanauer SB, Targan S, Ghosh S, de Villiers WJS, Colombel JF, Feagan BG, Lynch JP. Five-Year Efficacy and Safety of Ustekinumab Treatment in Crohn's Disease: The IM-UNITI Trial;	*Clin Gastroenterol Hepatol.* 2022; 20(3):578-590.e4.

Blue shading indicates data previously seen by the PBAC.
Source: Table 2-3, p22-24 of the submission.
ADA = adalimumab; IFX = infliximab; PBO = placebo; UPA = upadacitinib; UST = ustekinumab.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Bias	Population	Relevant Outcomes
Upadacitinib trials					
U-EXCEED	U-EXCEED: 495; U-EXCEL: 526; Pooled dFCD:66[a]	R, DB, PC, MC 12 Week induction period	CD: Low FCD: High	18-75 years CDAI ≥220 and ≤450 at baseline. dFCD: Single or multiple draining fistula at baseline.	Fistula response (≥50% reduction in number of draining fistulas) Fistula remission (complete closure/ absence of all draining fistulas)
U-EXCEL		R, DB, PC, MC 12 Week induction period	CD: Low FCD: High	18-75 years CDAI ≥220 and ≤450 at baseline. dFCD: Single or multiple draining fistula at baseline.	Fistula response (≥50% reduction in number of draining fistulas) Fistula remission (complete closure/ absence of all draining fistulas)
U-ENDURE	CD: 502 dFCD: 36[b]	R, DB, PC, MC 52 weeks (maintenance)	CD: Low FCD: High	Patients that completed U-EXCEED or U-EXCEL	Fistula response (≥50% reduction in number of draining fistulas) Fistula remission (complete closure/ absence of all draining fistulas)
Infliximab trials					
T20	CD: 94 dFCD: 6[c]	R, DB, PC 18 Week induction	FCD: Low	18-65 years. Single or multiple draining fistula for ≥ 3 months. TNF untreated.	Fistula response (≥50% reduction in number of draining fistulae at ≥2 consecutive visits) Fistula remission (absence of any draining fistulas at 2 consecutive visits)
ACCENT II	CD:282 dFCD: 276[d]	MC, OL (14wk)/R, DB, (+40wk), RWD (induction	FCD: Low	≥18 years. Single or multiple draining fistula for ≥ 3 months.	Fistula response (time to loss of response, ≥50% reduction in number of draining fistulae at consecutive visits ≥ 4 weeks apart)

Trial	N	Design/ duration	Bias	Population	Relevant Outcomes
		phase responders & non-responders) 54 Week maintenance			Fistula remission (absence of draining fistulas)
Adalimumab trials					
CLASSIC-I	CD: 150 dFCD: 18[e]	R, DB, PC, MC, IP 4 Week induction period	CD: Low FCD: High	18-75 years. CDAI ≥220 and ≤450 at baseline. TNF untreated.	Fistula response (≥50% reduction in number of draining fistulae at ≥2 consecutive visits) Fistula remission (closing of all draining fistulas at ≥ 2 consecutive visits)
GAIN	CD: 325 dFCD: 45	R, DB, PC, MC, IP 4 Week induction period	CD: Low FCD: High	18-75 years. CDAI ≥220 and ≤450 at baseline. TNF-experienced (infliximab) – intolerant or lost response.	Fistula response (≥50% reduction in number of draining fistulae at weeks 2 & 4) Fistula remission (closing of all draining fistulas at weeks 2 & 4)
CHARM	CD: 521 dFCD:77[f]	R, DB for MP, PC, MC, MP 52 Week maintenance (from start of maintenance)	CD: Low FCD: High	18-75 years. CDAI ≥220 and ≤450 for ≥ 4 months. dFCD: draining fistulas at baseline	Fistula remission (complete closure of all draining fistulas)
Ustekinumab trials					
UNITI-I	CD: 496 dFCD: 63[g]	R, DB, PB, MC 8 Week induction	CD: Low FCD: High	≥ 18 years CDAI ≥220 and ≤450 for ≥ 3 months. TNF-experienced – intolerant or lost response. dFCD: draining fistulas at baseline	Fistula response (≥50% reduction in number of opening/draining fistulas)
UNITI-II	CD: 419 dFCD:42[h]	R, DB, PB, MC 8 Week induction	CD: Low FCD: High	CDAI ≥220 and ≤450 for ≥ 3 months. TNF untreated and TNF-experienced (non-refractory). dFCD: draining fistulas at baseline	Fistula response (≥50% reduction in number of opening/draining fistulas)
IM-UNITI	CD: 397 dFCD:59[i]	R, DB, PB, MC 44 Week maintenance	CD: Low FCD: High	Patients that completed UNITI-I or UNITI-II	Fistula response (≥50% reduction in the number of opening/draining fistulas)
Indirect comparison using placebo as a common reference					
UPA vs IFX	Induction: U-EXCEED and U-EXCEL pooled FCD subgroup vs T20 Maintenance: U-ENDURE FCD subgroup vs ACCENT II				
UPA vs ADA	Induction: U-EXCEED and U-EXCEL pooled FCD subgroup vs CLASSIC-I and GAIN FCD subgroups Maintenance: U-ENDURE FCD subgroup vs CHARM FCD subgroup				
UPA vs UST	Induction: U-EXCEED and U-EXCEL pooled FCD subgroup vs UNITI-1 and UNITI-2 FCD subgroups Maintenance: U-ENDURE FCD subgroup vs IM-UNITI FCD subgroup				

Blue shading indicates data previously seen by the PBAC.

Source: 2-6, pp35-37; Table 2-11, p55; Table 2-12, pp56-57; Table 2-13, pp57-58; Table 2-18, p79; Table 2-38, p101; Table 239, pp101-102; Table 2-40, p102-103; Table 2-41, p103 of the submission; U-EXCEED CSR_m14431; U-EXCEL CSR_m14-433; U-ENDURE CSR_m14430; T20 Present et al., 1999; ACCENT II Sands et. al 2004; CLASSIC-I Sands et al 2004; CLASSIC-I Hanauer et al., 2006; GAIN Sandborn et al. 2007; CHARM Colombel et al., 2007; UNITI-I and UNITI-II Feagan et al., 2016; Table 3, ustekinumab, PSD, July 2024 PBAC Meeting.

ADA= adalimumab; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; DB = double-blind; dFCD = draining fistulising Crohn's disease (population relevant to this submission); EOW = every other week; FCD = fistulising Crohn's disease; IFX = infliximab; IP = Induction period; MC = multicentre; MP = Maintenance Phase; OL = Open-label; PC = placebo-controlled; R = randomised; RWD = Real-world data; TNF = Tumour Necrosis Factor.

[a] The upadacitinib FCD population (N=143) included patients with any fistula. Patients with draining fistula in the U-EXCEED/U-EXCEL trials n=66. CD populations obtained from trial CSRs.

[b] CD population obtained from trial CSR. N for U-ENDURE corresponds to Cohort 1.

[c] T20 also included 32 patients randomised to receive IFX 10 mg/kg. This dose was excluded as not relevant to the submission.

[d] ACCENT II analysed 276 patients maintenance response (Table 2-41 p103 of the submission) and 189 patients (maintenance remission (Table 2-40, pp102-103 of the submission); ACCENT II, CD N=282 (306 patients received IFX at induction phase; 282 patients (non-responders and responders) were randomised to IFX and PBO at Week 14, Sands et al., 2004

[e] The CD population of CLASSIC-I also included 149 patients randomised to receive doses not relevant to the submission. Of these, 14 patients with FCD received doses not relevant to the submission.

[f] The CD population of CHARM also included 257 patients randomised to receive ADA 40 mg weekly, which was not relevant to the submission.

[g] The CD population of UNITI-I also included 249 patients randomised to receive UST 6 mg/kg, which was not relevant to the submission.

[h] The CD population of UNITI-II also included 209 patients randomised to receive UST 6 mg/kg, which was not relevant to the submission.

[i] n=59 at baseline; n=26 outcome (Paragraph 6.8, ustekinumab PSD, July 2023 PBAC Meeting)

6.8 The infliximab, adalimumab and ustekinumab trials were considered to have a low overall risk of bias for the intention-to-treat (ITT) analysis, but there was a high risk of bias in the adalimumab and ustekinumab trials for the subgroup of patients with FCD at baseline (paragraph 6.12, ustekinumab, PSD, July 2023 PBAC Meeting). This limitation also applied to the upadacitinib U-EXCEED/U-EXCEL (pooled) and U-ENDURE trials (Colombel et al., 2025) post-hoc subgroup analyses.

6.9 The upadacitinib, adalimumab, and ustekinumab FCD subgroups were taken from broader moderate to severe CD trials. In contrast the infliximab T20 trial enrolled only patients with FCD. Patients in the infliximab trials had lower CDAI scores likely due to targeting patients with FCD and not CDAI severity at baseline. The infliximab trials also required all patients to have actively draining fistula at baseline, compared with only small fistula subpopulations in upadacitinib, adalimumab and ustekinumab trials. There was also variation in prior exposure to biologics across the trials, with upadacitinib enrolling more refractory patients. Comparison between the upadacitinib, adalimumab and ustekinumab FCD subgroups at baseline was not possible as the comparator subgroup data was not presented.

6.10 In the upadacitinib U-EXCEED, U-EXCEL, U-ENDURE trials, fistula outcomes were post-hoc and not prespecified primary or secondary endpoints. In contrast, the adalimumab CLASSIC-I, GAIN, CHARM trials and ustekinumab UNITI-1, UNITI-2, IM-UNITI trials included fistula response and fistula remission as assessed pre-specified fistula subgroups within broader CD trials in the subset of patients with draining fistulas at baseline. The infliximab T20 and ACCENT II trials exclusively enrolled patients with FCD and assessed fistula response and fistula remission as primary outcomes.

6.11 The post-hoc approach of the FCD subgroup analysis was aligned with the evidence used to support the comparator treatments on the PBS, where prespecified

exploratory/secondary or post-hoc data were used to support listing for fistula response (≥ 50% reduction in draining fistulae) and fistula remission (complete closure/absence of all draining fistulas) (paragraph 12, infliximab, PSD, March 2010 PBAC meeting; paragraph 7, adalimumab, PSD, November 2010 PBAC Meeting; paragraph 6.16 and paragraph 6.21, ustekinumab, PSD, July 2023 PBAC meeting).

6.12 The upadacitinib trials assessed fistula outcomes at a single, fixed timepoint, defining response as a ≥50 % reduction and remission as complete closure at one visit (Week 12 for induction; Week 52 for maintenance). Comparator trials assessed fistula activity earlier and more frequently, for example, the infliximab T20 trial required response to be confirmed at ≥2 consecutive visits, while the infliximab ACCENT II trial required confirmation at ≥4 consecutive visits with assessments scheduled at weeks 0, 2, 6, 10, 14, 22, 30, 38, 46 and 54 and the ustekinumab UNITI-I, UNITI-II trials incorporated structured assessments at Week 6 and 8, allowing repeated verification of fistula status.

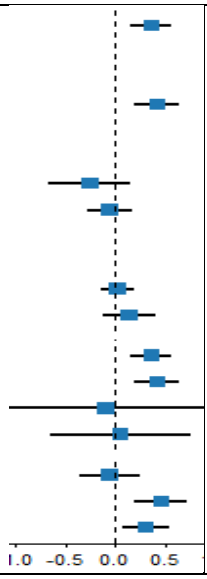
6.13 The submission did not nominate a non-inferiority margin. This was consistent with infliximab, adalimumab, ustekinumab where non-inferiority margins were not provided (paragraph 12, infliximab PSD, March 2010 PBAC Meeting; paragraph 12, adalimumab PSD, November 2010 PBAC meeting; paragraph 7.1, ustekinumab PSD, July 2023 PBAC Meeting).

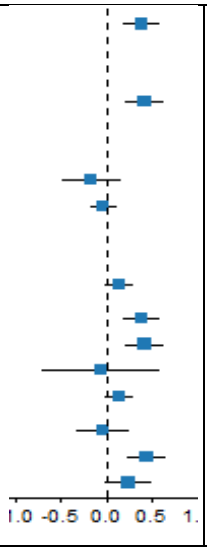
Comparative effectiveness

6.14 Table 4 summarises fistula response and fistula remission outcomes for patients with fistulising CD enrolled in the induction trials.

Table 4: Induction results of FCD across the trials: fistula response and fistula remission

Trial	Active treatment n/N (%)	PBO n/N (%)	OR (95%CI) (result > 1 favours intervention)	RD (95%CI)[a] (result > 0 favours intervention)	NNT (95% CI)
Induction					
Fistula Response (≥50% reduction in number of draining fistula from baseline), n (%)					
UPA (45 mg) – Week 12					
U-EXCEED/ U-EXCEL	22/44 (50.0)	3/22 (13.6)	6.33 (1.64, 24.52)	0.36 (0.16, 0.57)	3 (2, 6)
IFX (wk0: 5mg/kg) Week 18[b]					
T20	21/31 (67.7)	8/31 (25.8)	6.04 (2.01, 18.17)	0.42 (0.19, 0.64)	2 (2, 5)
ADA (wk0: 160 mg, wk 2: 80 mg) – Week 4					
CLASSIC-I	1/12 (8.3)	2/6 (33.3)	0.18 (0.01, 2.60)	-0.25 (-0.66, 0.16)	NS
GAIN	3/20 (15.0)	5/25 (20.0)	0.71 (0.15, 3.40)	-0.05 (-0.27, 0.17)	NS
UST (wk 0: tiered dose/kg) – Week 8					
UNITI-1	4/29 (13.8)	4/34 (11.8)	1.20 (0.27, 5.29)	0.02 (-0.15, 0.19)	NS
UNITI-2	6/19 (31.6)	4/23 (17.4)	2.19 (0.51, 9.33)	0.14 (-0.12, 0.40)	NS
Meta analysis UPA vs PBO			6.33 (1.64,24.52)	0.36 (0.16, 0.57)	3 (2, 6)
Meta analysis IFX VS PBO			6.04 (2.01,18.17)	0.42 (0.19, 0.64)	2 (2, 5)
Meta analysis ADA vs PBO			0.50 (0.13, 1.92)	-0.10 (-1.16, 0.97)	NS
Meta analysis UST vs PBO			1.63 (0.58, 4.61)	0.06 (-0.64, 0.76)	NS
Indirect comparison: UPA vs IFX			1.05 (0.18, 6.01)	-0.06 (-0.36, 0.25)	NS
Indirect comparison: UPA vs ADA			12.74 (1.88,86.34)	0.46 (0.20, 0.72)	2 (1, 5)
Indirect comparison: UPA vs UST			3.88 (0.70, 21.32)	0.31 (0.08, 0.54)	3 (2,13)
Fistula Remission (complete closure/absence of all draining fistula), n (%)					
UPA (45 mg) – Week 12 results					
U-EXCEED/ U-EXCEL	21/44 (47.7)	2/22 (9.1)	9.13 (1.90, 43.86)	0.39 (0.20, 0.58)	3 (2, 5)
IFX (wk0: 5mg/kg) – Week 18[c]					
T20	17/31 (55.8)	4/31 (12.9)	8.20 (2.31, 29.07)	0.42 (0.21, 0.63)	2 (2, 5)
ADA (wk0: 160 mg, wk 2: 80 mg) – Week 4					
CLASSIC-I[c]	**0**	1/6 (16.7)	0.15 (0.01, 4.20)	-0.17 (-0.49,0.15)	NS
GAIN[c]	1/20 (5.0)	2/25 (8.0)	0.61 (0.05, 7.20)	-0.03 (-0.17,0.11)	NS
UST (wk 0: tiered dose/kg) – Week 8					
UNITI-1/2[d]	9/38 (23.7)	4/43 (9.3)	3.03 (0.85, 10.80)	0.14 (-0.02, 0.30)	NS
Meta analysis UPA vs PBO			9.13 (1.90,43.86)	0.39 (0.20, 0.58)	3 (2, 5)
Meta analysis IFX vs PBO			8.20 (2.31,29.07)	0.42 (0.21, 0.63)	2 (2, 5)
Meta analysis ADA vs PBO			0.37 (0.05, 2.69)	-0.05 (-0.70, 0.59)	NS
Meta analysis UST vs PBO			3.03 (0.85,10.80)	0.14 (-0.02, 0.30)	NS
Indirect comparison: UPA vs IFX			1.11 (0.15, 8.37)	-0.03 (-0.32, 0.25)	NS
Indirect comparison: UPA vs ADA			24.87 (1.97, 314.11)	0.44 (0.22, 0.65)	2 (2, 5)
Indirect comparison: UPA vs UST			3.02 (0.40, 22.75)	0.24 (-0.01, 0.49)	NS





Source: 2-18, p79, Table 2-19, p80; Table 2-21, pp81-82; Table 2-35, pp95-96; Table 2-38, p101; Table 2-39, pp101-102 of the submission; Table 1.3, pp5-6, Attachment 2.9 of the submission. U-EXCEED and U-EXCEL: Colombel et al., 2023; T20 Present et al., 1999; Table 4, ustekinumab, PSD, July 2023 PBAC meeting. Italicised text added during the evaluation.

ADA = adalimumab; IFX = infliximab; PBO = placebo; NNT = Number needed to treat; NS = not significant; PBO = placebo; RD = risk difference; UPA = upadacitinib; UST = ustekinumab.

Note: Significance was not bolded due to post-hoc subgroup analysis

[a] RD results were presented as a percentage in the submission and Attachment 2.9 and not as a proportion therefore they differed from the ustekinumab submission considered at the July 2023 PBAC Meeting. Results were converted to proportions during the evaluation to match the ustekinumab PSD, July 2023 PBAC Meeting for comparison.

[b] IFX – Presented in the submission as Week 4. 18 weeks was consistent with Present et al., 1999, page:1401 'median duration of response was approximately 3 months (Table 2)'

[c] Data in the submission appear to be duplication of 'response' results. Data presented are from Attachment 2.9
[d] Pooled UNITI-1/2 pooled results from Attachment 2.9.

6.15 During induction, upadacitinib achieved significantly higher rates of fistula response and fistula remission compared to placebo (risk difference (RD) = 0.36 (0.16, 0.57) and 0.39 (0.20, 0.58), respectively).

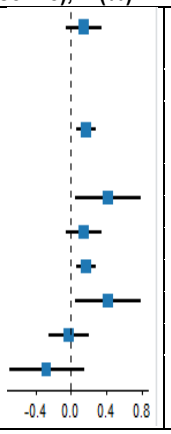
6.16 For the outcome of fistula response (≥50% reduction in number of draining fistulae from baseline) in the induction trials, the indirect comparison favoured upadacitinib over adalimumab and ustekinumab (RD = 0.46 and 0.31, respectively); however, the comparison favoured infliximab over upadacitinib (RD = -0.06).

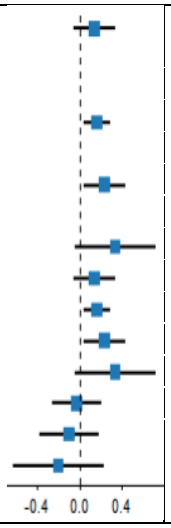
6.17 For the outcome of fistula remission (complete closure/absence of all draining fistulae) in the induction trials, the indirect comparison favoured upadacitinib over adalimumab and ustekinumab (RD = 0.44 and 0.24, respectively); however, the comparison numerically favoured infliximab over upadacitinib (RD = -0.03).

6.18 Table 5 summarises fistula response and fistula remission outcomes for patients with fistulising CD enrolled in the maintenance trials.

Table 5: Maintenance results of FCD across the trials: fistula response and fistula remission

Trial	Active treatment n/N (%)	PBO n/N (%)	OR (95%CI) (result >1 favours intervention)	RD (95%CI)[a]	NNT (95% CI)
Maintenance - Fistula Response (≥50% reduction in number of draining fistula from baseline), n (%)					
U-ENDURE (15/30 mg)	4/28 (14.3)	0/8 (0.0)	3.12 (0.15, 64.25)	0.14 (-0.06, 0.34)	NS
IFX (5mg/kg Q8W) – Week 56					
ACCENT II[b]	51/134 (38.1)	30/142 (21.2)	2.29 (1.35,3.91)	0.17 (0.06, 0.28)	6 (4, 16)
UST (90 mg Q8W) – Week 52					
IM-UNITI[c-d]	7/8 (87.5)	5/11 (45.5)	8.40 (0.76,93.35)	0.42 (0.05, 0.79)	2 (1, 21)
Meta analysis UPA vs PBO			3.12 (0.15, 64.25)	0.14 (-0.06, 0.34)	NS
Meta analysis IFX vs PBO			2.29 (1.35,3.91)	0.17 (0.06, 0.28)	6 (4, 16)
Meta analysis UST vs PBO			8.40 (0.76,93.35)	0.42 (0.05, 0.79)	2 (1, 21)
Indirect comparison: UPA vs IFX			1.36 (0.06, 29.34)	-0.03 (-0.25, 0.20)	NS
Indirect comparison: UPA vs UST			0.37 (0.01, 17.75)	-0.28 (-0.70, 0.15)	NS
Maintenance – Fistula Remission					
UPA (15/30 mg) – Week 52 results					
U-ENDURE (15/30 mg)	4/28 (14.3)	0/8 (0.0)	3.12 (0.15, 64.25)	0.14 (-0.06, 0.34)	NS
IFX (5mg/kg Q8W) – Week 56					
ACCENT II	33/91 (36.3)	19/98 (19.4)	2.37 (1.22, 4.57)	0.17 (0.04, 0.29)	6 (3, 23)
ADA (40 mg Q2W) Week 52					
CHARM	11/30 (36.7)	6/47 (12.8)	3.96 (1.27, 12.29)	0.24 (0.04, 0.44)	4 (2, 24)
UST (90 mg Q8W) – Week 52					
IM-UNITI	11/14 (78.6)	4/9 (44.4)	4.58 (0.72, 28.65)	0.34 (-0.05, 0.73)	NS
Meta analysis UPA vs PBO			3.12 (0.15, 64.25)	0.14 (-0.06, 0.34)	NS
Meta analysis IFX vs PBO			2.37 (1.22, 4.57)	0.17 (0.04, 0.29)	6 (3, 23)
Meta analysis ADA vs PBO			3.96 (1.27, 12.29)	0.24 (0.04, 0.44)	4 (2, 24)
Meta analysis UST vs PBO			4.58 (0.72, 28.65)	0.34 (-0.05, 0.73)	NS
Indirect UPA (45 mg) vs IFX			1.32 (0.06,29.15)	-0.03 (-0.26, 0.21)	NS
Indirect UPA (45 mg) vs ADA			0.79 (0.03,19.95)	-0.10 (-0.38, 0.18)	NS
Indirect UPA (45 mg) vs UST			0.68 (0.02,23.39)	-0.20 (-0.64, 0.24)	NS





Blue shading indicates data previously seen by the PBAC.

Source: Table 2-21, pp81-82; Table 2-40, pp102-103 & Table 2-41, p103 of the submission; Table 3.3, p23 and 3.5, pp24-27, Attachment 2.9 of the submission; Table 5, ustekinumab, PSD, July 2023 PBA Meeting.

ADA = adalimumab; CI = confidence interval; IFX = infliximab; NNT = Number needed to treat; NS = not significant; OR = odds ratio; PBO = placebo; RD = risk difference; UPA = upadacitinib; UST = ustekinumab.

Note: Significance was not bolded due to post-hoc subgroup analysis

[a] RD results were presented as a percentage in the submission and Attachment 2.9 and not as a proportion therefore they differed from the ustekinumab submission considered at the July 2023 PBAC. Results were converted to proportions during the evaluation to match the ustekinumab PSD, July 2023 PBAC Meeting for comparison.

[b] The submission presented results for patients at week 54 who had a fistula response at week 10/14 (n=189). The July 2023 ustekinumab submission also included results for patients at week 54 who had no fistula response at week 10/14 (n=87) and all analysed patients at week 54 (n=276) (Table 5, ustekinumab, PSD, July 2023 PBAC Meeting).

[c] The submission presented results for patients receiving ustekinumab Q8W (n=19). The July 2023 ustekinumab submission also presented results for patients receiving ustekinumab Q8/12W (n=26) (Table 5, Ustekinumab PSD, July 2023 PBAC Meeting).

[d] OR for this comparison in the ustekinumab PSD was 8.40 (0.75, 93.34) with the difference likely due to rounding.

[e] Table 2-40 of the submission reported this as the results of UST Q8W; however, they are consistent with the results presented for UST Q8/12W in Table 5, ustekinumab, PSD, July 203 PBAC Meeting.

[f] *Results differed slightly from Table 5, ustekinumab, PSD, July 2023 PBAC meeting ([UST PSD results were: OR 4.58 (0.73, 28.65)). This difference is likely due to rounding.*

6.19 The submission claimed the indirect comparison results for maintenance demonstrated that upadacitinib showed similar efficacy compared to infliximab, adalimumab and ustekinumab, with odds ratios crossing unity, indicating no statistically significant differences.

6.20 For the outcome of fistula response (≥50% reduction in number of draining fistulae from baseline) in the maintenance trials, the indirect comparison *numerically* favoured infliximab and ustekinumab over upadacitinib (RD -0.03 and -0.28, respectively); however, the comparison between upadacitinib and adalimumab was not estimable because fistula response rates were not presented in the adalimumab CHARM trial.

6.21 For the outcome of fistula remission (complete closure/absence of all draining fistulae) in the maintenance trials, the indirect comparison numerically favoured infliximab, adalimumab and ustekinumab over upadacitinib (RD = -0.03, -0.10 and -0.20, respectively).

Comparative harms

6.22 The submission argued that a FCD specific safety analysis was uninformative due to the small sample size. In its consideration of ustekinumab as treatment for FCD, the PBAC previously considered that there was no reason to expect a difference in safety between severe CD and fistulising CD (paragraph 7.10, ustekinumab, PSD, July 2023 PBAC Meeting).

6.23 Table 6 presents a summary of key adverse events in the trials, based on the whole trial analysis. The submission stated that safety outcomes by dosage arm were not reported in the infliximab induction trial (T20). Results for the safety of infliximab induction were not included in this submission.

Table 6: Summary of key adverse events in the whole trial populations

Trial type or estimate	Trial ID	RR (95% CI)	OR (95% CI)	RD (95% CI)
Induction				
Any AE				
ITC result	UPA v ADA	1.22 (1.05, 1.42)	1.81 (1.15, 2.85)	0.13 (0.03, 0.23)
	UPA v UST	1.03 (0.90, 1.18)	1.10 (0.76, 1.61)	0.02 (-0.07, 0.11)
Serious AEs				
ITC result	UPA v ADA	2.18 (0.76, 6.24)	2.23 (0.75, 6.66)	0.03 (-0.02, 0.08)
	UPA v UST	1.09 (0.55, 2.17)	1.10 (0.53, 2.30)	-0.03 (-0.09, 0.03)
Serious infections				
ITC result	UPA v ADA	1.84 (0.32, 10.48)	1.88 (0.33, 10.88)	0.01 (-0.02, 0.04)
	UPA v UST	0.85 (0.20, 3.53)	1.03 (0.13, 8.44)	0.00 (-0.03, 0.03)
AEs leading to discontinuations				
ITC result	UPA v ADA	2.27 (0.56, 9.26)	2.33 (0.56, 9.60)	0.02 (-0.02, 0.06)
	UPA v UST	NA	NA	NA
Maintenance				
UPA 30/15				
Any AE				
ITC result	UPA v ADA	0.98 (0.88, 1.10)	0.85 (0.47, 1.54)	-0.02 (-0.11, 0.06)
	UPA v IFX	NA	NA	NA
	UPA v UST	1.02 (0.89, 1.18)	1.13 (0.54, 2.37)	0.02 (-0.10, 0.13)
SAE				
ITC result	UPA v ADA	1.43 (0.77, 2.63)	1.49 (0.75, 2.97)	0.04 (-0.03, 0.12)
	UPA v IFX	0.85 (0.43, 1.71)	0.83 (0.38, 1.84)	-0.02 (-0.11, 0.07)
	UPA v UST	1.21 (0.56, 2.64)	1.24 (0.51, 3.02)	0.02 (-0.07, 0.12)
Serious infection				
ITC result	UPA v ADA	1.36 (0.41, 4.46)	1.38 (0.40, 4.70)	0.01 (-0.03, 0.05)
	UPA v IFX	1.02 (0.29, 3.51)	1.02 (0.28, 3.71)	0.00 (-0.05, 0.05)
	UPA v UST	0.98 (0.17, 5.71)	0.98 (0.16, 5.98)	0.00 (-0.05, 0.05)
AE resulting in discontinuation				
ITC result	UPA v ADA	3.82 (1.53, 9.57)	4.31 (1.63, 11.36)	0.11 (0.05, 0.16)
	UPA v IFX	0.32 (0.10, 1.06)	0.29 (0.08, 1.01)	-0.10 (-0.16, -0.03)
	UPA v UST	NA	NA	NA

Source: Table 2-42, pp104-106; Table 2-44, pp109-110 of the submission.
ADA = adalimumab; AE = adverse event; CD = Crohn's disease; CI = confidence interval; IFX = infliximab; ITC = indirect trial comparison; NA = not applicable; OR = odds ratio; RD = risk difference; RR = relative risk; UPA = upadacitinib; UST = ustekinumab
Note: Evidence was from the CD trials for upadacitinib, adalimumab, and ustekinumab (not the FCD subpopulation), and the FCD trial for infliximab.

6.24 The indirect comparisons in Table 6 suggest during induction a higher incidence of any adverse event with upadacitinib vs adalimumab, while no consistent differences were observed vs ustekinumab. For serious adverse events, serious infections and discontinuations, estimates were imprecise with wide confidence intervals.

6.25 In the upadacitinib FCD subgroup any AEs were similar within the induction (~70%) and maintenance (~80%) arms. There were twice as many AE leading to study drug discontinuation in maintenance period upadacitinib 15 mg (10.6%) vs placebo (5%) and no AEs leading to death.

Benefits/harms

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

Clinical claim

6.27 The submission described upadacitinib as non-inferior in terms of efficacy and safety compared with infliximab, adalimumab and ustekinumab.

6.28 The evaluation considered the therapeutic conclusion presented in the submission may not be adequately supported by the evidence presented in the submission because:

- There were multiple differences between the trials and the trials differed in baseline characteristics, outcome definitions and assessment methods:
  - Differences in baseline characteristics: the infliximab trial population had lower CDAI scores (mean of 184-193) compared to the upadacitinib, adalimumab, and ustekinumab trials, likely due to likely due to targeting patients with FCD and not CDAI severity at baseline (actively draining fistula only contributing 20 points to the CDAI); maintenance trial entry was determined by overall clinical response for upadacitinib, adalimumab and ustekinumab whereas the infliximab ACCENT II trial required fistula response. There was some variation on prior exposure to biologics and in proportion of patients with failure to biologics across the whole trial populations, but this was due to eligibility criteria (see Table 3.
  -). Comparison between the upadacitinib, to adalimumab and ustekinumab FCD subgroups at baseline was not possible as the comparator subgroup data was not presented.
  - The upadacitinib trials used post-hoc, single timepoint assessments whereas comparator trials required sustained response or remission across multiple consecutive visits. Comparator trials applied stricter response criteria, such as ≥2 consecutive visits in the infliximab T20 trial and ≥4 in the infliximab ACCENT II trial and conducted earlier and more frequent assessments throughout follow-up (see paragraph 6.12 for discussion).
  - These differences reduced the transitivity between the trials, and thus limit confidence in the indirect comparisons.
- The use of subgroup analyses reduced the sample sizes and decreased the likelihood of finding a statistically significant difference in the treatment effect.
- The indirect comparison results for induction and maintenance demonstrated that upadacitinib showed similar efficacy compared to infliximab, adalimumab and ustekinumab, with odds ratios crossing unity, suggesting no statistically significant differences. However, for maintenance fistula remission (complete closure/absence of all draining fistula) the indirect comparison numerically favoured infliximab, adalimumab and ustekinumab over upadacitinib (RD = -0.03, -0.10 and -0.20, respectively).

6.29 In its assessment of ustekinumab as treatment for FCD, the PBAC previously noted the following, which may also apply in the current assessment:

- Although the anchored indirect treatment comparisons generally found no statistically significant differences between ustekinumab vs adalimumab and infliximab 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 (paragraph 6.32, ustekinumab, PSD, July 2023 PBAC Meeting).
- While the evidence supporting the clinical claims of non-inferior efficacy and safety vs the nominated comparators was limited, on balance when considering the clinical need for additional therapies for fistulising CD, the claims vs infliximab and adalimumab were likely to be reasonable (paragraph 7.1, ustekinumab, PSD, July 2023 PBAC Meeting).

6.30 The PSCR argued that whilst there were limitations with the available evidence the indirect treatment comparison results presented support the claims of non-inferiority to the other listed FCD therapies, noting that the results indicated upadacitinib was numerically favoured for some comparisons (e.g. induction response/remission vs adalimumab and ustekinumab) and the established relativities of these therapies in severe Crohn's disease further support the clinical claims. The PSCR also argued the evidence for other biologics for FCD considered by the PBAC had similar uncertainties. The ESC considered the evidence, while limited for multiple reasons (outlined in the paragraphs above), was of similar quality to that used to support other biologic submissions for FCD.

6.31 The PBAC noted that the claims of non-inferior comparative effectiveness and safety were supported by limited and uncertain data but considered, on balance, were likely to be reasonable.

Economic analysis

6.32 The submission proposed a cost-minimisation approach (CMA) comparing upadacitinib with infliximab, ustekinumab and adalimumab for the treatment of FCD, on the basis of non-inferior comparative effectiveness and safety. A 2-year time horizon was assumed to capture the induction and maintenance phases of treatment. Drug acquisition costs were estimated using ex-manufacturer prices (AEMP), with administration-related MBS costs applied where relevant. The submission used a weighted-average comparator AEMP price to propose a cost-minimised price for upadacitinib.

6.33 The analysis assumed no differential monitoring or AE management costs between treatments. The TGA PI documents reviewed during the evaluation indicated that upadacitinib includes monitoring recommendations (e.g., lipid testing, laboratory thresholds), while biologic comparators include precautions for serious infections and screening requirements. The recent PBAC CMAs for complex refractory FCD (e.g. ustekinumab July 2023; infliximab Nov 2020) did not incorporate laboratory

monitoring or AE management costs. Therefore, the omission of differential monitoring costs in the submission seems consistent with the PBAC precedent for the proposed indication.

6.34 The proposed equi-effective doses were based on the PI-recommended doses and average vial requirements based on utilisation:

- Ustekinumab: weight based intravenous (IV) dose at Week 0 (estimated at 3.3 × 130 mg vials based on 2024-2025 PBS/RPBS utilisation), followed by 90 mg subcutaneous (SC) at Week 8, then 90 mg SC every 8 weeks (88%) or 12 weeks (12%) thereafter.
- Infliximab (IV): 5 mg/kg at Weeks 0, 2 and 6, then every 8 weeks thereafter, with an average of 4.36 × 100 mg vials per infusion based on the 2024-2025 PBS/RPBS utilisation.
- Infliximab (IV + SC): 5 mg/kg IV at Weeks 0 and 2, followed by 120 mg SC every 2 weeks from Week 6.
- Adalimumab: 160 mg at Week 0, 80 mg at Week 2, then 40 mg every 2 weeks.
- Upadacitinib: 45 mg once daily for 12 weeks followed by 30 mg or 15 mg once daily maintenance.

6.35 Table 7 shows the CMA results presented in the submission with amendments from the PSCR, based on the following key assumptions:

- The analysis was conducted at the published AEMP level for all comparators, however it was confirmed at time of evaluation that no special pricing arrangements exist for these agents.
- The submission proposed a flat effective AEMP for upadacitinib across all strengths (45 mg, 30 mg and 15 mg).
- The PSCR amended the costs of the adalimumab, infliximab SC and ustekinumab regimens to reflect GP administration costs (MBS item 23) rather than IV administration costs for the SC treatment components (see paragraph 6.36).
- The submission cost-minimised upadacitinib to a utilisation-weighted average of comparator AEMPs, with weights derived from 2024 initiation script utilisation, which placed greater weight on higher-cost comparator therapies such as adalimumab and infliximab. The PBAC has previously advised that, in a CMA, the proposed medicine should be cost-minimised to the least costly alternative therapy (paragraph 7.1, ustekinumab, PSD, July 2023 PBAC meeting). Also, as initiation scripts capture incident patients (new treatment starts) only rather than the prevalent treated population, the cost-minimisation approach in the submission may not reflect proportional use across ongoing therapy in a chronic condition.

- Because infliximab and ustekinumab dosing is weight-based and PBS dispensing does not record patient weight, the submission estimated the average number of vials from recent PBS utilisation data (Aug 2024-Jul 2025, Services Australia). The submission estimated 3.3 vials for the initial ustekinumab infusion and 4.36 vials for infliximab infusions. These differ slightly from the earlier values considered by the PBAC (3.0 vials for ustekinumab and 4.17 vials for infliximab, (paragraph 6.38, ustekinumab PSD, July 2023 PBAC meeting)).

Table 7: Results of the cost-minimisation approach over 104 weeks (per patient, AEMP level)

Component	Infliximab- IV only		Infliximab- IV + SC		Adalimumab		Ustekinumab (Q8W + Q12W combined)	
	Initial (IV)	Cont. (IV)	Initial (IV)	Initial + Cont. (SC)	Initial (SC)	Cont. (SC)	Initial (IV)	Cont. (SC)
Formulation	100 mg vial	100 mg vial	100 mg vial	120 mg/ mL pen/ syringe	80 mg/ 0.8mL syringe	40 mg/ 0.8 mL syringe	130 mg/ 26 mL injection	90 mg/mL syringe
AEMP (A)	$[redacted]	$[redacted]	$[redacted]	$[redacted][a]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Drug costs								
Units /104 wk (B)	3 x 4.36 vials	12 x 4.36 vials	2 x 4.36 vials	49 x 1 pen/ syringe	3 x 1 pen device	50 x 1 pen device	1 x 3.3 vials	11.52 x 1 syringe
Admin. / 104wk (C)	3	12	2	49	1[b]	51[b]	1	11.52
Drug cost / 104 wk (A x B)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted][c]
IV/SC admin costs (C x IV admin cost)[d]	$342.90	$1,371.60	$228.60	$ 215.11	$11.43	$ 228.28	$114.30	$50.57
Total (drug + admin costs)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total (initial + cont.)	$[redacted]		$[redacted]		$[redacted]		$[redacted]	
Cost-min price of upadacitinib								
Packs/104 wk[e]	26		26		26		26	
Cost-minimised AEMP[f]	$[redacted]		$[redacted]		$[redacted]		$[redacted]	
Upadacitinib weighted average AEMP								
Comparison			**Effective AEMP**		**Weighting**		**Weighted effective AEMP**	
Versus ustekinumab			$[redacted]		22.2%		$[redacted]	
Versus adalimumab			$[redacted]		39.9%			
Versus infliximab			$[redacted][g]		37.9%			

Source: Tables 3-6 to 3-10, pp123-125 of the submission; Economic Evaluation worksheet, Attachment 3 of the submission. Updated from evaluation based on PSCR attachment UPA FCD Section 3 CMA spreadsheet

Admin. = administration; AEMP = approved ex-manufacturer price; Cont. = continuing; IV = intravenous; mg = milligram; mL = millilitre; Q8W = every 8 weeks; Q12W = every 12 weeks; SC = subcutaneous, wk = week.

Note: Minor numerical differences between the values in this table and the submission's Excel workbook reflect rounding conventions. All final comparisons and conclusions in the evaluation used the exact values from the submission's economic evaluation workbook to ensure consistency.

[a] The infliximab SC AEMP of $[redacted] reflects a weighted average of the 2 infliximab 120 mg SC presentations (pen AEMP $[redacted]; syringe AEMP $[redacted]), based on the distribution of 2024 PBS scripts for the SC formulations (PBS items 13055D & 13072B).

[b] For adalimumab, the number of PBS 'units per 104 weeks' (26 packs) reflects dispensing patterns, not the number of injections. Each 40 mg pack contains 2 injections and covers 4 weeks of treatment. This means that although 26 packs are dispensed, the patient receives 52 injections over 104 weeks: 1 injection at Week 0, followed by 51 injections every 2 weeks from Week 2 to Week 104.

[c] The submission presented separate 104-week drug costs for ustekinumab Q8W and Q12W regimens. For presentation purposes, these have been combined using the utilisation previously accepted by the PBAC: 88% Q8W and 12% Q12W (July 2023 ustekinumab PSD). The reported ustekinumab (Q8W + Q12W combined) drug cost represents this weighted average of the regimen specific IV and SC components.

[d] IV admin cost (MBS item, 14245, $114,30). The submission also assumed 10% of patients receiving SC treatment would require injection assistance (Amended in PSCR to MBS item 23).

[e] 26 upadacitinib packs were requested in the submission over 104 weeks (3 initial- 45 mg; 23 continuous- 15 mg, 4- weekly dosing).

[f] Cost-minimised AEMPs were estimated by dividing each comparator's total 104-week cost by the number of upadacitinib scripts required over the same period (i.e., 26 packs). For example, infliximab IV only= $[redacted] / 26= $[redacted].
[g] The combined infliximab cost-minimised AEMP of $[redacted] was calculated by weighting the regimen-specific cost-minimised prices according to the estimated utilisation split of 94% IV-only and 6% IV+SC (based on 2024 PBS script volumes for infliximab).

6.36 Two key issues were identified in the submission's cost-minimisation results. First, while the use of MBS item 14245 ($114.30) for IV administration of ustekinumab and infliximab was appropriate, the submission incorrectly applied the same IV infusion item to the 10% of patients assumed to require assistance with SC injections, which would ordinarily attract a standard GP or nurse attendance item (e.g. MBS item 23, $43.90, or MBS item 3, $20.05, not an IV infusion item). The PSCR acknowledged this error and provided an updated CMA for UPA, with a resultant effective AEMP of $[redacted]. The ESC noted SC administration costs were not included in the recent PBAC consideration of ustekinumab for complex refractory FCD (paragraph 6.38, ustekinumab PSD, July 2023 PBAC meeting).

6.37 The second issue was that the submission cost-minimised upadacitinib to a utilisation-weighted average of comparator AEMPs rather than to the least costly alternative therapy. The Pre-PBAC Response argued comparator selection should consider market utilisation and mode of administration where no pharmacological analogue exists, and further argued the lower use of ustekinumab made it an inappropriate sole comparator, and that the weighted CMA approach proposed in the submission represented a balanced approach.

Drug cost/patient/year

6.38 Based on the proposed effective weighted AEMP of $[redacted], the submission estimated an annual drug cost of $[redacted] ($[redacted] x 13) per patient for upadacitinib, calculated using the assumptions outlined in Table 7.

Estimated PBS usage & financial implications

6.39 This submission was not considered by DUSC. The submission used a market share approach for the financial estimates. Table 8 summarises the key inputs used for the financial estimates. Several computational issues with the financial estimates were identified during the evaluation, with many addressed in the PSCR and noted (where relevant) in the table below. Revised financial estimates were also provided alongside the PSCR.

Table 8: Key inputs for financial estimates

<table>
<tr><th>Parameter</th><th>Value applied, source and comment</th></tr>
<tr><td>Current market and market shares</td><td>The submission used script data for adalimumab and infliximab extracted from the PBS/RPBS Services Australia database (2020 to 2024) to describe historical utilisation and market shares.

Table: Scripts dispensed for FCD and corresponding market shares
<table>
<tr><th></th><th>2020</th><th>2021</th><th>2022</th><th>2023</th><th>2024</th></tr>
<tr><td>Scripts
ADA
IFX
UST [a]</td><td>22,910
12,880
10,030
-</td><td>30,355
19,277
11,078
-</td><td>30,229
18,125
12,104
-</td><td>35,739
21,297
14,442
-</td><td>36,510
18,069
17,366
1,075</td></tr>
<tr><td>Market share
ADA</td><td>100%
56.2%</td><td>100%
63.5%</td><td>100%
60.0%</td><td>100%
59.6%</td><td>100%
49.0%</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Value applied, source and comment</th></tr>
<tr><td></td><td>
<table>
<tr><td>IFX
UST [a]</td><td>43.8%
-</td><td>36.5%
-</td><td>40.0%
-</td><td>40.4%
-</td><td>48.0%
3.0%</td></tr>
</table>
Source: Tables 4-4 and 4-5, pp130-131 of the submission. Italicised text was added during the evaluation.
ADA = adalimumab; FCD = Fistulising Crohn's disease = IFX, infliximab; UST = ustekinumab.
[a] Ustekinumab was PBS-listed for fistulising Crohn's disease in January 2024. It was not available for most of the historical period (2020-2023); therefore, the submission did not report ustekinumab scripts.
</td></tr>
<tr><td>Market growth</td><td>For market projection of comparator usage, the submission fitted linear trend lines to 2020-2024 PBS script volumes for infliximab (all items combined) and adalimumab (80 mg initiation, 40 mg initiation, and continuing items estimated separately). Ustekinumab was listed for FCD only in 2024; therefore, its projected usage was based on the historical growth pattern observed in severe Crohn's disease. Discrepancies were identified between the linear trendlines provided in the financial model and those derived from the calculations provided. This was addressed in the PSCR.
Also, the submission assumed that the introduction of upadacitinib would not alter underlying market growth. This assumption was uncertain as sequential treatment will likely increase the overall number of scripts dispensed per patient.</td></tr>
<tr><td>Forecast market and market shares, without upadacitinib</td><td>The submission first estimated script volumes for 2025 using the linear model and then extended the trend forward to 2031 (Year 6). Simplifications were applied by grouping multiple PBS item numbers for each comparator, and ustekinumab projections were based on growth trends from severe Crohn's disease, given recent FCD listing (p130 of the submission). These projected comparator scripts formed the basis for estimating upadacitinib substitution volumes and financial impact.

Table: Projected usage of comparator treatments, FCD indication without upadacitinib
<table>
<tr><th></th><th>2026 (Yr1)</th><th>2027 (Yr2)</th><th>2028 (Yr3)</th><th>2029 (Yr4)</th><th>2030 (Yr5)</th><th>2031 (Yr6)</th></tr>
<tr><td>Comparator scripts
ADA
IFX
UST</td><td>44,554
23,133
20,065
1,356</td><td>47,696
24,359
21,840
1,497</td><td>50,838
25,585
23,616
1,637</td><td>53,980
26,811
25,391
1,778</td><td>57,122
28,037
27,166
1,918</td><td>60,264
29,263
28,942
2,059</td></tr>
<tr><td>
ADA
IFX
UST</td><td>100%
52%
45%
3%</td><td>100%
51%
46%
3%</td><td>100%
50%
46%
3%</td><td>100%
50%
47%
3%</td><td>100%
49%
48%
3%</td><td>100%
49%
48%
3%</td></tr>
</table>
Source: Table 4-7, p132 of the submission; Attachment 4 worksheet titled 'data for graphs'. Text in italics was added during the evaluation.
ADA = adalimumab; FCD = Fistulising Crohn's disease; IFX = infliximab; UST = ustekinumab.

The market share estimates applied the financial estimates differed from those used to calculate the weighted AEMP in the CMA (adalimumab = 39.9%, infliximab = 37.9%, ustekinumab = 22.2%). In particular, the financial model forecasts assumed substantially higher shares for adalimumab and infliximab, and a much lower share for ustekinumab (approximately 3% across all years), which was inconsistent with the weighting applied in the CMA.</td></tr>
<tr><td>Uptake rate</td><td>The submission assumed that upadacitinib uptake would be modest and gradual, with substitution rates increasing uniformly from [redacted]% in Year 1 to [redacted]% in Year 6, applied equally across ustekinumab, adalimumab and infliximab. This does not seem reasonable because this simplifying assumption treated all comparators as equally likely to be displaced, regardless of their current market shares. Because adalimumab and infliximab accounted for the majority of biologic use in FCD, applying equal substitution proportions effectively resulted in a disproportionate shift away from these agents relative to ustekinumab. Also, no clinical rationale was provided for why all 3 comparators would be displaced at the same rate, and the resulting projections may either over- or under-estimate upadacitinib uptake depending on how clinicians actually sequence therapies over time.

For instance, the 2023 ustekinumab submission assumed that the majority of ustekinumab scripts would be sourced from substituting adalimumab (30% in Year 1, increasing to 50% in Year 6) compared to infliximab (10% in Year 1, increasing to 15% in Year 6), arguing that ustekinumab would be more likely to replace adalimumab as a second-line treatment after infliximab (paragraph 6.42, ustekinumab, PSD, July 2023 PBAC meeting). The PSCR argued the uptake of upadacitinib</td></tr>
</table>

<table>
<tr><th>Parameter</th><th>Value applied, source and comment</th></tr>
<tr><td></td><td>was expected to be modest and gradual, reflecting the established nature of the FCD biologic market.</td></tr>
<tr><td>Script equivalence</td><td>The submission derived script-equivalence ratios by mapping the PBS-funded dosing intervals and maximum-quantity rules for each comparator to upadacitinib's PBS scripting pattern (3 scripts over 12-week initiation and 13 scripts per 12-month maintenance period). For each comparator, the number of PBS scripts required to cover the induction and continuation dosing schedules was calculated directly from the PBS pack sizes, maximum quantities, repeats and dosing frequency specified in the current listings and Product Information. For ustekinumab, the submission applied the 88% Q8W and 12% Q12W maintenance split; for infliximab, separate IV-only and IV+SC regimens were modelled using the utilisation-based proportions (94% and 6%). These script counts were then expressed relative to the corresponding number of upadacitinib scripts to produce the script-equivalence ratios shown in the Table.

Table: Estimated script equivalence between upadacitinib and comparators
<table>
<tr><th>Comparator</th><th>Script equivalence to UPA, initial</th><th>Script equivalence to UPA, continuing</th></tr>
<tr><td>ADA</td><td>1:1 – 80mg ADA script vs UPA 45mg
1:1 – 40mg ADA script vs UPA 45mg
(PSCR adjusted)</td><td>13:13</td></tr>
<tr><td>IFX IV</td><td>2.94:2.89 [a]</td><td>6.5:13
1:2 (1st cont., PSCR adjusted)</td></tr>
<tr><td>IFX SC</td><td>2: 2 - 120mg SC IFX vs UPA 45mg</td><td>13:13</td></tr>
<tr><td>UST</td><td>1:2 – UST IV vs UPA 45mg
1:1 – UST SC vs UPA 45mg</td><td>6.24:13</td></tr>
</table>
Source: Tables 4-12 and 4-13, pp138-139 of the submission. Changes in PSCR estimates noted where relevant.
ADA = adalimumab; Cont. = continuing; FCD = Fistulising Crohn's Disease; IFX = infliximab; IV = intravenous; SC = subcutaneous; UPA = upadacitinib; UST = ustekinumab; vs = versus.
Note: The submission assumed (p138) a split of 30mg vs 15mg UPA to be 77.5%:22.5%.
[a] 100mg IV IFX vs UPA 45mg (weighting 94% 'IV only' regimen and 6% 'IV & SC' regimen).

For initial dosing, the submission assumed a single script equivalence ratio of 1:0.67 between adalimumab 40 mg and upadacitinib 45 mg by grouping all adalimumab 40 mg initiating items together including items with different quantities (quantity 6 and quantity 2). However, in the financial estimates, quantity 6 items had a script equivalence of 1:1, whereas the quantity 2 items had a script equivalence of 1:0.67. Grouping these items therefore applied an inappropriate equivalence to initial dosing. The PSCR calculated adalimumab forms with a different pack quantity separately.
For continuing dosing, the financial model assumed a script equivalence ratio of 1:1 between infliximab 100 mg (first continuing) and upadacitinib 30/15 mg, however a single infliximab IV script lasts for 8 weeks, implying a script equivalence of 1:2. This was addressed in the PSCR.</td></tr>
<tr><td>MBS costs</td><td>The submission applied MBS item 14245 ($114.30; IV infusion ≥2 hours) for all IV administrations of infliximab and ustekinumab. For SC biologics, the submission assumed that 10% of administrations require professional assistance and also costed these using MBS item 14245. Applying MBS item 14245 to SC administrations was not appropriate, as item 14245 is specific to IV infusions of ≥2 hours' duration. Assisted SC injections would ordinarily attract a standard GP or nurse attendance (e.g., MBS item 3 or 23), not an IV infusion item. The PSCR amended MBS costs for SC items to MBS item 23 (standard GP consult) for 10% of these injections.

The ESC noted that MBS items for general practice are typically not accepted in estimated financial implications as these costs/savings to Government will not be realised in clinical practice (paragraph 6.63, cabotegravir + rilpivirine PSD, November 2021 PBAC meeting). The Pre-PBAC Response argued the supporting documentation for the Department-provided utilisation and cost model (UCM) require the estimation and inclusion of all net changes in MBS items and related financial impacts over a 6 year period.</td></tr>
</table>

Parameter	Value applied, source and comment
	No differential monitoring or AE management costs between treatments were presented in the financial analysis of the submission. This was consistent with previous CMAs considered by the PBAC for this indication (see paragraph 6.33 for discussion).

Source: Tables 4-1 to 4-18, pp126-141 of the submission. *Text in italics was added during the evaluation*.
ADA = adalimumab; AE = adverse event; AEMP = Approved Ex-Manufacturer Price; CMA = cost minimisation approach; DPMQ = Dispensed Price for Maximum Quantity; FCD = Fistulising Crohn's disease; IFX = infliximab; IV = intravenous; MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = Public Summary Document; Q8W = every 8 weeks; Q12W = every 12 weeks; RPBS = Repatriation Pharmaceutical Benefits Scheme; SC = subcutaneous; UST = ustekinumab.

6.40 Table 9 presents the estimated net financial implications to the PBS/RPBS, updated based on revised figures in the PSCR, for the proposed listing of upadacitinib in complex refractory FCD over the first 6 years.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of upadacitinib						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for comparators						
Cost to PBS/RPBS less copayments	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to MBS	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net cost to Australian Govt.	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Tables 4-19 to 4-26, pp142-145 of the submission and financial table submitted alongside PSCR (Impact – net).
ADA = adalimumab; IFX = infliximab; Govt. = Government; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriations Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Scheme; UST = ustekinumab.
The redacted values correspond to the following ranges:
[1] *5,000 to < 10,000*
[2] *10,000 to < 20,000*
[3] *$0 to < $10 million*
[4] *net cost saving*

6.41 Based on updated figures in the PSCR, the total cost to the PBS/RPBS of listing upadacitinib was estimated to be $0 to < $10 million in Year 6, and the net cost to the Australian Government in the first 6 years of listing was approximately $0 to < $10 million.

6.42 Whilst most issues specific to the financial estimates were addressed in the PSCR, the net cost estimates presented in the submission remained uncertain because they relied on the utilisation-weighted approach used to estimate the proposed upadacitinib price, which may have led to an over-estimation of cost offsets and a higher proposed price for upadacitinib. Overall, if listed on a cost-minimisation to the least costly alternative therapy, upadacitinib would be expected to be approximately cost-neutral to the health budget, or potentially cost saving, as substitution would occur from therapies of equivalent or higher cost and upadacitinib does not incur administration costs. The Pre-PBAC Response argued the incremental cost associated with upadacitinib based on the weighted CMA approach proposed in the submission

does not result in a substantial financial impact to the health system and reiterated its proposed approach was reasonable.

6.43 Additional sources of uncertainty included comparator utilisation and uptake. The submission assumed equal substitution across ustekinumab, infliximab and adalimumab despite differing current market usage and sequencing, and the market-share proportions in the financial analysis differed from those used in the economic analysis to derive the weighted AEMP. Also, linear extrapolation of 2020-2024 script data may not reflect future biologic utilisation patterns, given ustekinumab's recent listing for FCD and evolving clinical practice.

Quality Use of Medicines

6.44 The submission indicated that an Australian risk management plan was provided to the TGA and that a patient support program will be available; no other quality use of medicines initiatives were described. Although upadacitinib is already PBS-listed for Crohn's disease, its use in complex refractory FCD involves a clinically high-risk population, and the recognised risk of serious infection remains an important consideration. No information was presented on vaccination guidance, which may be relevant in this group, and the potential for drug interactions due to CYP3A4 (and CYP2D6) metabolism also warrants prescriber attention. Clear education for prescribers and patients would support safe and appropriate use in the requested indication.

6.45 The PBAC noted upadacitinib is classified as Pregnancy Category D with the Product information (page 20) advising that contraception should be used whilst on treatment and for four weeks following the final dose.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of upadacitinib for the treatment of complex refractory fistulising Crohn's disease (FCD). The PBAC's recommendation was based on, among other matters, its assessment that the cost effectiveness of upadacitinib would be acceptable if it were cost minimised to the least costly alternative therapy of infliximab, adalimumab or ustekinumab.

7.2 The PBAC considered the equi-effective doses of upadacitinib and the alternative therapies are:

- Upadacitinib 45 mg once daily for 12 weeks, followed by upadacitinib 15 mg or 30 mg once daily for maintenance therapy;
- Infliximab (IV): 5 mg/kg at Weeks 0, 2 and 6, then every 8 weeks thereafter, with an average of 4.36 × 100 mg vials per infusion based on the 2024-2025 PBS/RPBS utilisation;

- Infliximab (IV + SC): 5 mg/kg IV at Weeks 0 and 2, followed by 120 mg SC every 2 weeks from Week 6;
- Adalimumab: 160 mg at Week 0, 80 mg at Week 2, then 40 mg every 2 weeks; and
- Ustekinumab: weight based intravenous (IV) dose at Week 0 (estimated at 3.3 × 130 mg vials based on 2024-2025 PBS/RPBS utilisation), followed by 90 mg subcutaneous (SC) at Week 8, then 90 mg SC every 8 weeks (88%) or 12 weeks (12%) thereafter.

7.3 The PBAC acknowledged FCD is a severe and debilitating complication of Crohn's disease caused by the formation of abscesses and fistulas that drain either internally or externally, often requiring surgery if untreated. The Committee acknowledged the consumer input supported the listing and considered there was a clinical need for additional effective therapies for FCD, particularly options with different mechanisms of action, with upadacitinib being the first Janus kinase (JAK) inhibitor for this indication. The PBAC also noted that while FCD is a manifestation of Crohn's disease, the nature of the Crohn's disease activity index (CDAI) scale means patients with severe and debilitating disease due to fistula impacts may otherwise not be eligible for treatment under the severe Crohn's disease listings on the PBS, thus necessitating the separate listings.

7.4 With respect to the requested restriction, the PBAC considered the listing should be aligned with that of the other therapies listed for FCD in terms of the criteria, but also recommended the following changes, including:

- That the authority level for initial and continuing therapy for upadacitinib for FCD should be Authority Required (telephone/Online Immediate Assessment). The PBAC noted this change would align the authority levels recommended as part of the administrative restriction amendments for inflammatory bowel diseases that was discussed at the same meeting.
- The listing should be age agnostic, consistent with current listings for FCD.
- An additional listing for upadacitinib 30 mg should be added for induction therapy for patients with Stage 4 renal impairment (as the 45 mg dose is not suitable for these patients), which should also be added for the other inflammatory bowel disease indications (including severe Crohn’s disease and ulcerative colitis) for which upadacitinib 45 mg is the standard induction dose.
- The restriction should allow for an extended induction period for an additional 12 weeks at the 30 mg dose for patients who do not demonstrate an adequate response within the first 12 weeks of treatment.

7.5 The PBAC noted a grandfather restriction was requested in the Pre-PBAC Response and considered that this was reasonable and should remain in place for 12 months from the date of listing, per standard policy.

7.6 The PBAC noted the submission nominated infliximab as the main comparator and

adalimumab and ustekinumab as additional comparators and considered this was reasonable. The Committee considered all of these are alternative therapies for FCD.

7.7 The PBAC noted no head-to-head trials were available comparing upadacitinib and any of the comparators and the submission relied on indirect treatment comparisons (ITCs) from pooled evidence from multiple trials, all of which it had previously considered in support of either the upadacitinib submission for severe Crohn's disease or the comparator trials for FCD. The Committee noted the evidence for upadacitinib and the comparators were largely based on small subgroup analyses from larger Crohn's disease trials (except infliximab) and there were notable differences between the trials including variations in baseline characteristics, disease severity, prior exposure to biologic agents and timing of response measurements. The PBAC considered the evidence base to be inherently uncertain, however acknowledged it had relied upon similarly limited evidence to inform the claims for the comparator submissions. Overall, the PBAC considered the evidence presented was adequate for informing the clinical claims.

7.8 The Committee noted the results of the upadacitinib FCD subgroup analyses versus placebo were statistically significant favouring upadacitinib for the outcomes of induction fistula response (OR 6.33, 95%CI 1.64, 24.52) and fistula remission (OR 9.13, 95%CI 1.90, 43.86) at 12 weeks (Table 4), but not for the same outcomes in maintenance therapy (OR 3.12, 95%CI 0.15, 64.25 for both outcomes) at 52 weeks (Table 5), although acknowledged interpretation of the results was difficult as 0/8 patients in the placebo arm achieved the maintenance therapy outcomes.

7.9 The PBAC noted the results of the ITCs versus the comparators were variable, with induction comparisons favouring upadacitinib over adalimumab for fistula response (OR 12.74, 95%CI 1.88, 86.34) and remission (OR 24.87, 95%CI 1.97, 314.11), and over ustekinumab for fistula response (OR 3.88, 95%CI 0.70, 21.32), but found no difference versus infliximab (Table 4). The Committee also noted the results of the ITCs in maintenance therapy tended to numerically favour the comparators, but the confidence intervals were wide and it was difficult to draw meaningful conclusions (Table 5). Overall, the PBAC considered the evidence presented suggested upadacitinib was likely to be non-inferior to the comparators for comparative effectiveness for induction, and further considered that whilst uncertain, on balance it may be reasonable to accept a claim of non-inferior comparative effectiveness in maintenance therapy.

7.10 With respect to comparative safety, the PBAC noted the available evidence suggested a higher incidence of adverse events for upadacitinib over adalimumab, but no consistent differences versus ustekinumab (Table 6). In addition, the PBAC also noted the adverse event rates for upadacitinib appeared to be consistent over time, and recalled in its consideration of ustekinumab for FCD that it was concluded that there is no reason to expect a difference in safety between severe Crohn's disease and FCD (paragraph 7.10, ustekinumab PSD, July 2023 PBAC meeting) and considered a similar conclusion should be applied to upadacitinib. On that basis, noting the available

evidence and its previously established view that upadacitinib was likely of non-inferior safety to the comparators in severe Crohn's disease (Paragraph 7.6, upadacitinib PSD, July 2023 PBAC meeting) the PBAC considered the claim of non-inferior comparative safety to the comparators was likely to be reasonable.

7.11 Given its view that upadacitinib does not provide a significant improvement in effectiveness or reduction in toxicity compared to the alternative therapies, the PBAC considered that a listing based on a cost minimisation approach (CMA) with costs over two years to the least costly alternative, consistent with the approach previously used for ustekinumab for FCD, was appropriate to determine the cost minimised price of upadacitinib. The PBAC considered the CMA proposed in the submission, which was based on weighted proportions of the three nominated comparators, was inconsistent with recent recommendations for FCD and severe Crohn's disease. The PBAC also considered the claimed offsets for MBS costs for 10% of the population receiving a subcutaneous injection to be administered by a clinician was unlikely to be reflective of how these treatments are administered in practice and was therefore not reasonable.

7.12 The PBAC noted the financial estimates were based on a price for upadacitinib derived from the weighted CMA proposed in the submission and considered that, if listed on a cost minimisation basis with the least costly alternative, the listing would likely be cost neutral or modestly cost saving to the PBS 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 upadacitinib 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 item:

Initial

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
UPADACITINIB					
upadacitinib 45 mg oral tablet, 28	NEW	1	28	2	Rinvoq

upadacitinib 30 mg oral tablet, 28	NEW	1	28	2	

Concept ID		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required (Telephone/Online PBS Authorities System)
Prescribing rule level		**Administrative Advice:** TREATMENT OF COMPLEX REFRACTORY FISTULISING CROHN DISEASE See below for overarching AA
		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: 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).
		Indication: Complex refractory fistulising Crohn disease
		Treatment Phase: Initial treatment – Initial 1 (new patient or recommencement of treatment after a break in targeted therapy 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; OR
		Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR
		Must be treated by a consultant physician [general medicine specialising in gastroenterology].
		Prescribing Instructions: The number of externally draining complex fistulae, fistula symptom grading scores (discharge/pain/induration) and the date of assessment of the patient's condition must be provided by the prescriber at the time of application and documented in the patient's medical records. All information should, where possible, be no more than 4 weeks old at the time of application.
		Prescribing Instructions: Where a response assessment is not conducted, the patient will be deemed to have not responded 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.
		Indication: Complex refractory fistulising Crohn disease
		Treatment Phase: Initial treatment - Initial 2 (change or recommencement of treatment after *a* break in targeted therapy of less than 5 years)
		Clinical criteria:
		Patient must have received prior PBS-subsidised treatment with a targeted therapy for this condition in this treatment cycle; OR
		Patient must have been eligible for prior PBS-subsidised treatment with a targeted therapy for this condition in this treatment cycle
		AND

	Clinical criteria:
	Patient must have either: (i) not previously received this drug for this condition in the current treatment cycle, (ii) previously received this drug and demonstrated/maintained an adequate clinical response
	Treatment criteria:
	Must be treated by a gastroenterologist; OR
	Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR
	Must be treated by a consultant physician [general medicine specialising in gastroenterology].
	Prescribing Instructions: The following information must be provided by the prescriber at the time of application and documented in the patient's medical records: a. current number of externally draining complex fistulae, fistula symptom grading scores (discharge/pain/induration) and the date of assessment of the patient's condition; and b. details of prior targeted therapies treatment in the current treatment cycle, including the dates and duration of treatment All information should, where possible, be no more than 4 weeks old at the time of application.
	Prescribing Instructions: If a patient was eligible for prior PBS-subsidised treatment with a targeted therapy for this condition but did not receive PBS-subsidised treatment at the time, the application must also provide details of the baseline scores of the prior eligibility requirements, including the number of externally draining complex fistulae, fistula symptom grading scores (discharge/pain/induration) and the date of assessment.
	Prescribing Instructions: Where a response assessment is not conducted, the patient will be deemed to have not responded 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.
	Indication: Complex refractory fistulising Crohn disease
	Treatment Phase: Balance of Supply - Initial 1 (new patient or recommencement of treatment after a break in targeted therapy of more than 5 years), Initial 2 (change or recommencement of treatment after a break in targeted therapy of less than 5 years)
	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 12 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 12 weeks treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance available under the treatment phase from which the immediately preceding supply was obtained under.
	Treatment criteria:
	Must be treated by a gastroenterologist; OR
	Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR
	Must be treated by a consultant physician [general medicine specialising in gastroenterology].
	Prescribing Instruction: Initial (induction) treatment phases and 'Extended induction' treatment phases for this benefit aim to provide 12 weeks treatment duration.

Initial 2 – for 15 mg only:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
UPADACITINIB					
upadacitinib 15 mg oral tablet, 28	NEW	1	28	2	Rinvoq

Concept ID		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required (Telephone/Online PBS Authorities System)
Prescribing rule level		**Administrative Advice:** TREATMENT OF COMPLEX REFRACTORY FISTULISING CROHN DISEASE See below for overarching AA
		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: 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).
		Indication: Complex refractory fistulising Crohn disease
		Treatment Phase: Initial treatment - Initial 2 (change or recommencement of treatment after *a* break in targeted therapy of less than 5 years)
		Clinical criteria:
		Patient must have received prior PBS-subsidised treatment with a targeted therapy for this condition in this treatment cycle; OR
		Patient must have been eligible for prior PBS-subsidised treatment with a targeted therapy for this condition in this treatment cycle
		AND
		Clinical criteria:
		Patient must have either: (i) not previously received this drug for this condition in the current treatment cycle, (ii) previously received this drug and demonstrated/maintained an adequate clinical response
		Treatment criteria:
		Must be treated by a gastroenterologist; OR
		Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR
		Must be treated by a consultant physician [general medicine specialising in gastroenterology].
		Prescribing Instructions: The following information must be provided by the prescriber at the time of application and documented in the patient's medical records: a. current number of externally draining complex fistulae, fistula symptom grading scores (discharge/pain/induration) and the date of assessment of the patient's condition; and b. details of prior targeted therapies treatment in the current treatment cycle, including the dates and duration of treatment All information should, where possible, be no more than 4 weeks old at the time of application.
		Prescribing Instructions: If a patient was eligible for prior PBS-subsidised treatment with a targeted therapy for this condition but did not receive PBS-subsidised treatment at the time, the application must also provide details of the baseline scores of the prior eligibility requirements including the number of externally draining complex fistulae, fistula symptom grading scores (discharge/pain/induration) and the date of assessment.

	Prescribing Instructions: Where a response assessment is not conducted, the patient will be deemed to have not responded 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.

Optional extended induction period

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
UPADACITINIB					
upadacitinib 30 mg oral tablet, 28	NEW	1	28	2	Rinvoq

Concept ID		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required (Telephone/Online PBS Authorities System)
Prescribing rule level		**Administrative Advice:** TREATMENT OF COMPLEX REFRACTORY FISTULISING CROHN DISEASE See below for overarching AA
		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: 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).
		Indication: Complex refractory fistulising Crohn disease
		Treatment Phase: Extended induction period (optional) from weeks 12 to 24
		Clinical criteria:
		Patient must have experienced an inadequate therapeutic benefit following initial 12-week induction period
		Treatment criteria:
		Must be treated by a gastroenterologist; OR
		Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR
		Must be treated by a consultant physician [general medicine specialising in gastroenterology].

Continuing

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
UPADACITINIB					
upadacitinib 30 mg oral tablet, 28	NEW	1	28	5	Rinvoq
upadacitinib 15 mg oral tablet, 28	NEW	1	28	5	

Concept ID		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required (Telephone/Online PBS Authorities System)
Prescribing rule level		**Administrative Advice:** TREATMENT OF COMPLEX REFRACTORY FISTULISING CROHN DISEASE See below for overarching AA
		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: 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).
		Indication: Complex refractory fistulising Crohn disease
		Treatment Phase: Continuing treatment
		Clinical criteria:
		Patient must have received this drug as their most recent course of PBS-subsidised targeted therapy treatment for this condition in this treatment cycle
		AND
		Clinical criteria:
		Patient must have demonstrated an adequate response to treatment with this drug; OR
		The condition must have not met the improvements specified below due to the prescribed dose being too low - this authority approval seeks higher dosing.
		Treatment criteria:
		Must be treated by a gastroenterologist; OR
		Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR
		Must be treated by a consultant physician [general medicine specialising in gastroenterology].
		Prescribing Instruction: 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 current number of externally draining complex fistulae, fistula symptom grading scores (discharge/pain/induration) and the date of assessment of the patient's condition must be provided by the prescriber at the time of application and documented in the patient's medical records. All information should, where possible, be no more than 4 weeks old at the time of application.
		Prescribing Instructions: To demonstrate a response to treatment, the application should, where possible, be accompanied with the assessment of response, conducted no later than 4 weeks from cessation of the most recent course of targeted therapy.

	Prescribing Instructions: Where a response assessment is not conducted, the patient will be deemed to have not responded 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: Where fewer than 5 repeats are prescribed, sufficient repeats to complete a maximum of 24 weeks of treatment with this drug may be requested through the balance of supply restriction.
	Indication: Complex refractory fistulising Crohn disease
	Treatment Phase: Balance of supply - continuing treatment
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the continuing treatment restriction to complete 24 weeks of treatment.
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction
	Treatment criteria:
	Must be treated by a gastroenterologist; OR
	Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR
	Must be treated by a consultant physician [general medicine specialising in gastroenterology].

Grandfather

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
UPADACITINIB					
upadacitinib 30 mg oral tablet, 28	NEW	1	28	5	Rinvoq
upadacitinib 15 mg oral tablet, 28	NEW	1	28	5	

Concept ID		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required (Telephone/Online PBS Authorities System)
Prescribing rule level		**Administrative Advice:** TREATMENT OF COMPLEX REFRACTORY FISTULISING CROHN DISEASE See below for overarching AA
		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: 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).
		Indication: Complex refractory fistulising Crohn disease
		Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfather arrangements
		Clinical criteria:
		Patient must have received non-PBS-subsidised treatment with this drug for this PBS indication prior to [LISTING DATE]

	AND
	Clinical criteria:
	Patient must have, prior to initiating treatment with this drug for this condition, 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/have had an externally draining enterocutaneous or rectovaginal fistula
	AND
	Clinical criteria:
	Patient must have demonstrated an adequate response to treatment with this drug
	Treatment criteria:
	Must be treated by a gastroenterologist; OR
	Must be treated by a consultant physician [internal medicine specialising in gastroenterology]; OR
	Must be treated by a consultant physician [general medicine specialising in gastroenterology].
	Prescribing Instructions: The baseline and current number of externally draining complex fistulae, fistula symptom grading scores (discharge/pain/induration) and the date of assessment of the patient's condition must be provided by the prescriber at the time of application and documented in the patient's medical records. All information for current results should, where possible, be no more than 4 weeks old at the time of application.
	Prescribing Instruction: 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: To demonstrate a response to treatment, the application should, where possible, be accompanied with the assessment of response, conducted no later than 4 weeks from cessation of the most recent course of targeted therapy.
	Prescribing Instructions: Where a response assessment is not conducted, the patient will be deemed to have not responded 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.
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

8.2 Flow-on changes to update the overarching administrative advice for adalimumab, infliximab and ustekinumab for FCD:

Overarching administrative advice note:

	Administrative Advice: **TREATMENT OF COMPLEX REFRACTORY FISTULISING CROHN DISEASE** The following information applies to the prescribing of targeted therapies under the Pharmaceutical Benefits Scheme (PBS) for benefits with a stated indication of 'complex refractory fistulising Crohn disease'. For PBS administration, the term targeted therapy includes biological and targeted synthetic disease modifying anti-rheumatic drugs. A patient is eligible for PBS-subsidised treatment with only one targeted therapy for this condition at any one time. Treatment cycle: A treatment cycle begins when an authority application is approved under the Initial 1 restriction. Treatment must not continue with the same targeted therapy if it has not provided an adequate response as defined in the continuing treatment phase. A patient may trial different targeted therapies within a cycle; however, if 3 separate targeted therapies do not provide an adequate response, the treatment cycle ends and a 5-year PBS exclusion period applies. The 5-year break is measured from the date of the last PBS approval for a targeted therapy in the most recent cycle to the date of first initial treatment application under the next treatment cycle. If a new targeted therapy with a different pharmacological mechanism of action becomes available on the PBS during a 5-year break, a patient may be prescribed the newly listed targeted therapy, through the initial 2 treatment phase, if they have never received that medicine previously. If the newly listed targeted therapy does not provide an adequate response, the treatment cycle ends and the 5-year break recommences. This will not be considered a new treatment phase. There is no limit to the number of treatment cycles a patient may undertake in their lifetime. Treatment phases: Initial treatment authorisations will be limited to provide for a maximum of 16 weeks of therapy for adalimumab and ustekinumab, 12 weeks of therapy for upadacitinib and 14 weeks of therapy for infliximab. 1. Initial 1 – use when the patient has never received a targeted therapy for this indication or if the patient has had a break in targeted therapy of at least 5 years. Patients who have had a break in treatment of at least 5 years must requalify for treatment with respect to the indices of disease severity. 2. Initial 2 – use when: • an alternative targeted therapy is prescribed for this indication, or • the patient has previously been treated with this targeted therapy, or • treatment is resuming after a break of less than 5 years. Baseline disease activity does not need to be re-demonstrated; however, an assessment of response to the preceding supply must be provided if a response has been demonstrated. Continuing treatment – use when patient has demonstrated an adequate response to the preceding supply. A response to treatment is determined by comparison of current disease activity measurements relative to the baseline measurements. Prescribers may provide new baseline measurements any time that an initial treatment authority application is made within a treatment cycle and eligibility will be assessed against the revised baseline measurements. Continuing treatment authority scripts must not be written on the same day as Initial treatment authority applications.

8.3 Flow-on changes to add a 30 mg dose for induction therapy for severe Crohn disease and ulcerative colitis (additions shown in *italics*):

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
UPADACITINIB					
upadacitinib 45 mg oral tablet, 28	13771T	1	28	2	Rinvoq
upadacitinib 30 mg oral tablet, 28	*NEW*	*1*	*28*	*2*	
	Indication: Severe Crohn disease				

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
UPADACITINIB					
upadacitinib 45 mg oral tablet, 28	13262B	1	28	3	Rinvoq
upadacitinib 30 mg oral tablet, 28	*NEW*	*1*	*28*	*3*	
	Indication: Moderate to severe ulcerative colitis				

These restrictions 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

AbbVie acknowledges the Committee's pragmatic approach to evaluating elements of this submission in the context of the significant unmet need for patients with fistulising Crohn's disease, and the willingness to address inconsistencies in authority requirements across IBD. However, AbbVie considers that the lowest-cost comparator convention applied in this instaance does not reflect upadacitinib's likely use in clinical practice. Notwithstanding this, AbbVie remains committed to working constructively with the Department to progress this listing and maintains that, where comparator prices have been significantly eroded over time, future evaluations should adopt more flexible approaches aligned with current clinical practice in order to support patient access.