5.06 GUSELKUMAB,
Solution for I.V. infusion 200 mg in 20 mL vial,
Injection 100 mg in 1 mL single use pre-filled pen,
Injection 200 mg in 2 mL single use pre-filled pen,
Injection 100 mg in 1 mL single use pre-filled syringe,
Injection 200 mg in 2 mL single use pre-filled syringe,
Tremfya®,
Janssen-Cilag Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested Section 100 (Highly Specialised Drugs Program) and General Schedule Authority Required (in writing) Pharmaceutical Benefits Scheme (PBS) listings of guselkumab (GUS) – for one dose formulation administered via intravenous (IV) infusion and four dose formulations administered via subcutaneous (SC) injection – for the treatment of adults with severe Crohn's disease (CD). If recommended, GUS would be the second interleukin (IL) inhibitor and the sixth treatment option available on the PBS for severe CD.

1.2 Listing was on the basis of cost-utility analysis against all PBS-listed biologic/targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD), which included adalimumab (ADA), infliximab (IFX), upadacitinib (UPA), ustekinumab (UST) and vedolizumab (VDZ).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults with severe Crohn's disease (CD). The requested listing is consistent with the other biologics listed on the PBS for the treatment of severe CD.
Intervention	Induction regimen - Guselkumab 200 mg intravenously (IV) at week 0, 4, and 8, or - Guselkumab 400 mg subcutaneously (SC) at week 0, 4, and 8 Maintenance regimen - Guselkumab 200 mg SC at week 12, and then every 4 weeks, or - Guselkumab 100 mg SC at week 16 and then every 8 weeks
Comparator	All currently PBS listed biologics used in the treatment of severe CD (infliximab, adalimumab, vedolizumab, ustekinumab and upadacitinib)
Outcomes	Primary outcomes: clinical outcomes (clinical response and clinical remission)[a] and safety (any AE, SAEs, serious infection and discontinuation due to AE) Supportive outcomes: endoscopic outcomes (endoscopic response and endoscopic remission)[b]
Clinical claim	On the totality of the evidence presented in the submission: - In the induction phase, guselkumab 200 mg IV is non-inferior to guselkumab 400 mg SC in terms of efficacy and safety. - Guselkumab is superior to infliximab, adalimumab, vedolizumab, ustekinumab and upadacitinib in terms of efficacy. - Guselkumab is superior to infliximab and non-inferior to adalimumab, vedolizumab, ustekinumab and upadacitinib in terms of safety.

Source: Table 1.1, p24 of the submission.

AE=adverse events; CDAI=Crohn's disease Activity Index; SAE=serious adverse events; SES-CD=simplified endoscopic activity score for CD;

a In the GALAXI trials: Clinical response was defined as a CDAI reduction of ≥100 points from baseline; Clinical remission was defined as CDAI points <150

b In the GALAXI trials: Endoscopic response was defined as a ≥50% improvement from baseline in the SES-CD or SES-CD score≤2; Endoscopic remission was defined as SES-CD ≤ 4 and a ≥2-point reduction from baseline and no subscore >1 in any individual component

2 Background

Registration status

2.1 ***TGA status at time of PBAC consideration****:* not registered. The submission was made under the Therapeutic Goods Administration (TGA) and PBAC parallel process for the treatment of CD. The proposed TGA indication is as follows: "TREMFYA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment." The TGA clinical evaluation report (CER) and Delegate's overview were available at the time of the evaluation, which indicated that the magnitude of the treatment benefit, across a range of efficacy endpoints, indicated that GUS treatment, in both the induction and maintenance phases, were generally comparable to other Australia approved anti-interleukin-23 (IL-23) inhibitors [e.g. UST] for the treatment of adults with moderately to severely CD (TGA CER first round 09 January 2025, TGA Delegate's overview 5 May 2025).

2.2 GUS is currently TGA approved for the treatment of psoriatic arthritis and psoriasis. The submission noted that TGA approval was also concurrently sought for the treatment of ulcerative colitis, but this submission did not request PBS listing for that indication.

Previous PBAC consideration

2.3 The PBAC has not previously considered GUS for severe CD. GUS is currently listed on the PBS for treatment of chronic plaque psoriasis and psoriatic arthritis.

3 Requested listing

3.1 An abbreviated version of the requested restrictions for initial and continuing treatment is presented below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
GUSELKUMAB					
Initial treatment 200 mg / 20 mL, solution for IV infusion	Published: $3,452.89 (public); $3,501.56 (private) Effective: $[redacted] (public); $[redacted] (private)	1	1	2	TREMFYA® Janssen-Cilag Pty Ltd
Initial treatment 200 mg / 2 mL, solution for injection in pre-filled pen (Ypsomate® 2mL)	Published: $7,068.53 Effective: $[redacted][a]	1	2	2	
Initial treatment 200 mg / 2 mL, solution for injection in pre-filled syringe (Ultrasafe® 2mL)	Published: $7,068.53 Effective: $[redacted][a]	1	2	2	
Continuing 100 mg / 1 mL, solution for injection in pre-filled pen (One Press® 1mL)	Published: $3,615.49 Effective: $[redacted]	1	1	2	
Continuing 100 mg / 1 mL, solution for injection in pre-filled syringe (Ultrasafe® 1mL)	Published: $3,615.49 Effective: $[redacted]	1	1	2	
Continuing 200 mg / 2 mL, solution for injection in pre-filled pen (Ypsomate® 2mL)	Published: $3,615.49 Effective: $[redacted]	1	1	5	
Continuing 200 mg / 2 mL, solution for injection in pre-filled syringe (Ultrasafe® 2mL)	Published: $3,615.49 Effective: $[redacted]	1	1	5	
Category / Program: Section 100 - Highly Specialised Drugs (public/private), IV infusion Section 85 – General Schedule, SC injection					
Restriction type: ☒Authority Required (in writing)					
Indication: Severe Crohn disease					
Treatment Phase: Initial 1 (new patient)					
Clinical criteria:					
Patient must have confirmed severe Crohn disease					
AND					
Patient must have failed to achieve an adequate response to prior systemic therapy (corticosteroids and at least 3 months of immunosuppressive therapy)					
AND					
Patient must have severity of disease activity with CDAI ≥300; OR CDAI ≥220 with extensive small intestine disease					
AND					
Evidence of intestinal inflammation; OR in high faecal output state; OR require surgery or total parenteral nutrition as the next therapeutic option					
AND					

The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction
Treatment criteria:
Must be treated by a gastroenterologist or consultant physician [specialising in gastroenterology]
Population criteria:
Patient must be aged 18 years or older
Treatment Phase: Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
Clinical criteria:
Patient must have received prior PBS-subsidised treatment with a 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 a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction
Treatment Phase: Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
Clinical criteria:
Patient must have received treatment with this drug for this PBS indication prior to [PBS listing date]
AND
Patient must have confirmed severe Crohn disease
AND
Patient must have, prior to initiating treatment with this drug for this condition, failed to achieve an adequate response to prior systemic therapy (corticosteroids and at least 3 months of immunosuppressive therapy)
AND
Patient must have had, prior to initiating treatment with this drug for this condition, severity of disease activity with CDAI ≥300; OR CDAI ≥220 with extensive small intestine disease
AND
Evidence of intestinal inflammation; OR in high faecal output state; OR require surgery or total parenteral nutrition as the next therapeutic option
AND
The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction
Category / Program: Section 85 – General Schedule, SC injection
Restriction type: ☒Authority Required (in writing)
Indication: Severe Crohn disease
Treatment Phase: Continuing
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Patient must have shown adequate response as CDAI <150; OR show an improvement of intestinal inflammation/ reversal of high faecal output state/avoidance of TPN
AND
Patient must not receive >24 weeks of treatment
Prescribing Instructions:
An application for continuing treatment with this drug must include a measurement of response to the most recent course of PBS-subsidised therapy. This assessment must be conducted no later than 4 weeks from the cessation of that treatment course. If the application is the first application for continuing treatment with this drug, it must be accompanied by an assessment of response to a minimum of 12 weeks of treatment with the initial treatment course.

Category / Program: Section 100 - Highly Specialised Drugs (public/private), IV infusion Section 85 – General Schedule, SC injection
Treatment Phase: Grandfather
Clinical criteria:
Patient must have confirmed severe Crohn disease
AND
Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [LISTING DATE]
AND
Patient must be receiving treatment with this drug for this condition at the time of application
AND
Patient must have had a severity of disease activity with CDAI ≥300; OR CDAI ≥220 with extensive small intestine disease
AND
Evidence of intestinal inflammation; OR in high faecal output state; OR require surgery or total parenteral nutrition as the next therapeutic option
AND
(for maintenance) Patient must have shown adequate response as CDAI <150; OR show an improvement of intestinal inflammation/ reversal of high faecal output state/avoidance of TPN from previous non-PBS-subsidised treatment with this drug for this condition
Category / Program: Section 100 - Highly Specialised Drugs (public/private), IV infusion Section 85 – General Schedule, SC injection
Treatment Phase: Balance of supply
Clinical criteria:
Patient must have received insufficient therapy with this drug for this condition under the Initial 1, 2 or 3 restriction to complete the 3 doses (the initial infusion regimen at 0, 4 and 8 weeks); or Patient must have received insufficient therapy with this drug under the Continuing treatment restriction to complete 24 weeks of treatment
AND
The treatment must provide no more than the balance of up to 12 weeks therapy available under Initial 1, 2 or 3 treatment; or The treatment must provide no more than the balance of up to 24 weeks treatment available under Continuing treatment

Source: Table 1.7, p50, Tables 1.8 to 1.11, pp52-54 of the submission.

a Calculated during the based on the requested effective AEMP of $[redacted] for the 200 mg PFS/PFP (two in one pack); the essential elements table presented in the submission calculated an effective DPMQ for the 200 mg PFS/PFP (two in one pack) of $[redacted] based on an effective AEMP of $[redacted] (2*$[redacted]).

3.2 The submission requested (i) Section 100 (Highly Specialised Drugs Program) listing of GUS 200 mg in 20 mL vial for IV infusion, and (ii) General Schedule Authority Required (in writing) listing of GUS 100 mg and 200 mg pre-filled syringe (PFS) and GUS 100 mg and 200 mg SC pre-filled pen (PFP) for SC injection. The 100 mg and 200 mg PFS formulations use the UltraSafe™ Plus Needle Guard; the 100 mg PFP formulation uses the One-Press® Patient-controlled Injector; and the 200 mg PFP formulation uses the YpsoMate™ Autoinjector. The GUS 100 mg PFS with the UltraSafe™ Plus Needle Guard formulation is listed on the PBS for psoriasis and psoriatic arthritis, and the GUS 100 mg PFP with the One-Press® Patient-controlled Injector formulation is listed on the PBS for psoriatic arthritis.

3.3 For initial treatment with either 200 mg IV or 400 mg (2 x 200 mg) SC, the maximum quantity with two repeats (total three doses) allows for up to a maximum 12 weeks of treatment. This provides all patients with the recommended three doses of induction treatment at Weeks 0, 4 and 8. Patients who demonstrate an adequate response to therapy after at least 12 weeks of induction could switch to either 100 mg SC every eight weeks (Q8W) starting from Week 16 or 200 mg SC every four weeks (Q4W) starting from Week 12. For continuing patients, the requested maximum quantity of 100 mg SC or 200 mg SC with five repeats (total six doses) allows for 24 weeks of maintenance treatment at the recommended dose. The Secretariat noted that if a patient loses response to maintenance treatment at the lower dose (100mg Q8W), this would be deemed as treatment failure, consistent with other PBS listings with a similar lower dose schedule.

3.4 The submission requested a Special Pricing Arrangement (SPA). The proposed published ex-manufacturer price (AEMP) of $[redacted] for all dose forms (GUS 200 mg / 20 mL vial, 200 mg PFS/PFP, and 100 mg PFS/PFP) would maintain the same published AEMP of GUS 100 mg in other PBS-listed indications. Table 2 presents the proposed effective AEMPs of GUS for severe CD.

Table 2: Proposed effective AEMP of GUS for severe CD

GUS	Treatment phase	Proposed effective AEMP
GUS 200 mg / 20 mL IV (one vial per pack)	Initial	$[redacted]
GUS 200 mg PFS/PFP SC (two injections per pack)	Initial	$[redacted]
GUS 100 mg PFS/PFP SC (one injection per pack)	Continuing	$[redacted]
GUS 200 mg PFS/PFP SC (one injection per one pack)	Continuing	$[redacted]

Source: Table 1.7, p50 of the submission.
GUS=guselkumab; IV=intravenous; PFP=pre-filled pen; PFS=pre-filled syringe; SC=subcutaneous

3.5 At the requested effective AEMPs: the cost of the 12-week induction period is the same irrespective of route of administration after accounting for administration costs ($[redacted]) and the cost of the 24-week maintenance period is the same irrespective of dosing regimen ($[redacted]); however, the average cost per patient differs over time for the two maintenance regimens due to the different starting points (Week 12 for GUS 200 mg and Week 16 for GUS 100 mg). For maintenance therapy, the proposed effective AEMP of GUS 200 mg PFS/PFP (one in one pack) is half the effective AEMP of GUS 100 mg SC (one in one pack) because the recommended dosing frequency with the 200 mg dose (Q4W) is half as frequent as the 100 mg dose (Q8W).

3.6 The submission requested equivalent restriction criteria for GUS to other PBS-listed b/tsDMARDs for initial and continuing treatment of severe CD; as well as a grandfather restriction to allow patients receiving GUS from the GALAXI trials (22 patients) and an anticipated early access program (approximately 463 patients) to transition onto PBS treatment. The early access program was planned to commence three months prior to PBS listing of GUS. The key difference in the PBS restriction across the different b/tsDMARDs was the maximum number of weeks of initial/induction treatment (GUS and UPA: 12 weeks; IFX: 12-14 weeks; ADA and UST: 16 weeks; VDZ: 14-18 weeks). The Secretariat noted that it may be appropriate to have separate initial and

continuing Grandfather restrictions as there is some variation across the clinical criteria and dosing forms for patients transitioning through induction vs maintenance. Additionally, the Secretariat considered it may be appropriate to add clinical criteria to ensure grandfathered patients had previously failed prior therapies.

3.7 The Secretariat proposed the addition of a number of Prescribing Instructions and amendments to some clinical criteria to ensure consistency with other PBS-listed b/tsDMARDs for severe CD.

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

4 Population and disease

4.1 CD is an incurable, progressive inflammatory bowel disease (IBD) characterised by chronic transmural inflammation of the gastrointestinal tract, most commonly affecting any portion of the gastrointestinal tract from the mouth to the perianal area. Symptoms of CD include chronic diarrhoea, abdominal pain, rectal bleeding, weight loss and fatigue. Symptom burden increases as disease severity increases from mild to moderate or severe active disease. CD runs a relapsing and remitting course. Although inflammation subsides during periods of remission, the disease is progressive and evolves over time from luminal inflammation to fibrostenotic structuring or penetrating lesions (fistula or abscesses), resulting in structural bowel damage. Some patients who develop complications require surgery, such as surgical resection.

4.2 Crohn's disease activity index (CDAI) score is commonly used to assess the severity of CD and response to treatment in clinical trials and routine practice. CDAI is a weighted index comprising eight clinical and laboratory items (weight, gender, hematocrit, number of loose stools, degree of pain, general well-being, use of anti-diarrheal medication, presence of abdominal mass, and extra-intestinal findings or complications) to calculate the severity of disease activity as mild, moderate or severe disease. For induction treatment with a b/tsDMARD on the PBS, patients must have a CDAI score ≥300 or CDAI ≥220 with extensive small intestine disease. For maintenance treatment with a b/tsDMARD on the PBS, patients must achieve and maintain (following induction treatment) a CDAI <150 or an improvement of intestinal inflammation/ reversal of high faecal output state/avoidance of total parenteral nutrition.

4.3 Endoscopic outcomes (evaluating the severity of mucosal inflammation) are increasingly used in the management of CD and clinical trials alongside clinical outcomes such as CDAI, which evaluates severity of symptoms but may be poorly correlated with findings of intestinal inflammation. The most common endoscopic scoring systems in CD are the CD Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for CD (SES-CD). The SES-CD evaluates four key endoscopic items: ulcer size, proportion of ulcerated surface, proportion of affected surface, and the presence and type of stenosis. The US Food and Drug Administration (FDA) guidance

2022 on the development of drug therapies in CD has recommended clinical remission and endoscopic remission as co-primary endpoints of the treatment effect on signs, symptoms and mucosal inflammation at the end of the induction and maintenance period. In practice, endoscopy may form part of routine monitoring in patients with CD to monitor disease activity, check for complications and manage treatment. Patients may undergo endoscopy once a year to once every five years. The frequency and type of endoscopy depends on the disease location, other associated diseases and the patient's risk of colorectal cancer (Crohn's & Colitis Australia[1]).

4.4 Initial treatment for patients diagnosed with CD, includes conventional therapies such as 5-ASA, oral corticosteroids and immunomodulators (azathioprine, 6-mercaptopurine and methotrexate). Patients who fail to achieve adequate response or have intolerance to conventional therapies would initiate treatment with a b/tsDMARD. The proposed clinical management algorithm presented in the submission positioned GUS as an alternative treatment to other b/tsDMARDs available on the PBS for the treatment of severe CD.

4.5 Current guidelines offer limited guidance on the positioning of therapies (i.e. first- and second-line) in the management of severe CD. Guidelines suggest early use or first-line treatment include biologics (especially with tumour necrosis factor inhibitor (TNFi) agents) rather than delaying until after failure of conventional therapy (AGA 2021[2], GESA 2018[3]). Patients who failed to respond to TNFi treatment may benefit from switching to another biologic class. Recent systematic reviews and network meta-analysis by Singh 2021[4] and Attauabi 2025[5] highlighted IFX and ADA as effective for inducing and maintaining clinical remission over other biologics (including GUS) in moderate to severe CD and IL-23 inhibitor (e.g. UST) or Janis-associated kinase (JAK) inhibitor (e.g. UPA) as potentially more effective in TNFi-experienced patients. However, no specific agent was identified as superior in maintaining remission or reducing the risk of adverse events (AEs).

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[1] Crohn's & Colitis Australia (CCA). 2025. Remission. Available from: https://crohnsandcolitis.org.au/living-with-crohns-colitis/medical/remission/#:~:text=How%20often%20you%20have%20an,your%20personal%20and%20family%20history. [accessed on 07/05/2025].

[2]Feuerstein JD, Ho EH, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, Terdiman JP on behalf of American Gastroenterological Association Institute Clinical Guidelines Committee. 2021. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology 160(7):2496-2508.

[3] Gastroenterological Society of Australia (GESA). 2018. Clinical update for general practitioners and physicians : Inflammatory Bowel Disease Gastroenterological Society of Australia.

[4] Singh S, Murad MH, Fumery M, Sedano R, Jairath V, Panaccione R, Sandborn WJ, Ma C. Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2021 Dec;6(12):1002-1014.

[5] Attauabi M, Steenholdt C, Poulsen A, Gubatan J, Burisch J, Nielsen OH, Seidelin JB. Network meta-analysis: Comparative onset of early effect of biologics and small molecules in moderately to severely active luminal Crohn's disease. Aliment Pharmacol Ther. 2024 Jul;60(2):124-143.

4.6 GUS is a fully human anti-interleukin (IL)-23 monoclonal antibody that neutralises inflammation at the source of IL-23 production. IL-23 is a pro-inflammatory cytokine and key driver of IBD pathology as it contributes to the production of a gamut of proinflammatory cytokines (i.e., IL-17A, IL-22, and interferon gamma [IFNγ]), while concurrently limiting regulatory T cell (Treg) activation, which drives inflammation and tissue damage in the intestine. The recommended induction dose is GUS 200 mg IV infusion or 400 (2x200) mg SC injection at Weeks 0, 4 and 8. The recommended maintenance dose is GUS 200 mg Q4W SC injection starting at Week 12 or 100 mg Q8W SC injection starting at Week 16. Based on expert advice, the submission stated the GUS 200 mg Q4W SC dosing regimen may be prescribed more frequently for patients with severe CD, given it was numerically more effective than GUS 100 mg Q8W SC. See Comparative effectiveness.

4.7 The Pre-Sub-Committee Response (PSCR) noted that GUS is an IL-23 inhibitor as opposed to an IL-12/23 inhibitor like ustekinumab and thus represents a distinct mechanism of action (MOA) with a distinct efficacy and safety profile. The PSCR noted biologics are effective therapies for patients with CD; however, patients may not respond to a particular biologic (primary non-response), may lose response after having initially responded (secondary loss of response) or may develop toxicity which requires patients to stop treatment. The PSCR stated that over time, patients will progress through multiple treatment options and eventually patients, who under the biologic treatment cycle can fail three biologics are left without any further effective treatment options.

5 Comparator

5.1 The submission nominated all current PBS-listed b/tsDMARDs for severe CD as the main comparators given GUS could substitute for any of the b/tsDMARDs in practice. This included two TNFi (ADA, IFX), one IL-12/23 inhibitor (UST), one JAK inhibitor (UPA) and one integrin inhibitor (VDZ).

5.2 The nomination of all current PBS-listed b/tsDMARDs as comparators was reasonable; however, GUS may be more likely to substitute for UST, which currently accounts for 40% of the market (measured in patient-weeks of treatment) and has a similar mechanism of action (both are interleukin inhibitors). The PBAC had previously considered all currently listed (or recommended) b/tsDMARDs for CD as comparators were reasonable (paragraph 7.4, upadacitinib PSD July 2023 PBAC meeting).

5.3 The submission requested a considerable price premium for GUS over the nominated comparators, based on a claim of superior effectiveness (versus all comparators) and a modelled economic evaluation suggesting acceptable value for money at the requested price. The ESC noted the recommended dose for CD (see Table 1) was higher than the recommended dose for CPP and PsA (100 mg at week 0, week 4 and then every 8 weeks).

5.4 Table 3 summarises the cost of treatment with GUS and other PBS-listed b/tsDMARDs, assuming patients remain on treatment for two years, costed at the 'estimated'

effective prices assumed in the submission's modelled economic evaluation. 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. Of note, the PBAC has recommended a number of UST biosimilars in March 2025, November 2024 and March 2024[6].

5.5 The PSCR noted that prices for CD bDMARDs have undergone significant value erosion due to price disclosure price reductions of F2 formulary medicines (infliximab, adalimumab) and the impact of the reference pricing flow on reductions when upadacitinib was listed on a cost minimisation basis to the lowest cost alternative therapy. The PSCR stated the sponsor strongly believed that the current prices of bDMARDs used in CD are not reflective of the clinical value represented by a new innovative treatment such as GUS. The PSCR stated that should the PBAC not accept the clinical claims are adequately supported and recommend on a lowest cost comparator basis or cost-minimisation to any of the currently listed bDMARDs, the sponsor would not be able to proceed to listing, because the price level is prohibitively low.

[6] PBS Medicine Status Website. Available from: https://www.pbs.gov.au/medicinestatus/search.html?question=USTEKINUMAB&sort=-psproperty-meeting-date

Table 3: Comparison of treatment costs over the first two years for GUS and PBS-listed comparator biologics for severe CD using the submission's effective AEMP

Drug	Dosing	Estimated effective AEMP	Doses over two years	Cost over two years
GUS	200 mg IV wk 0, 4, 8 induction -> 200 mg SC Q4W maintenance	200 mg IV: $[redacted]	3 IV + 23 SC	$[redacted]
	200 mg IV wk 0, 4, 8 induction -> 100 mg SC Q8W maintenance	100 mg SC: $[redacted]	3 IV + 11 SC	$[redacted]
	2x200 mg SC wk 0, 4, 8 induction -> 200 mg SC Q4W maintenance	200 mg SC: $[redacted]	3 SC + 23 SC	$[redacted]
	2x200 mg SC wk 0, 4, 8 induction -> 100 mg SC Q8W maintenance	2 x 200 mg SC: $[redacted]	3 SC + 11 SC	$[redacted]
Other biologics				
IFX IV	5 mg/kg IV wk 0, 2, *6* induction -> 5 mg/kg IV Q8W maintenance	100 mg IV: $186.16[a]	14.3 IV infusions (57 vials)[d]	$10,611.12 $11,968.19[e]
IFX IV/SC	5 mg/kg IV wk 0, 2 and 120 mg SC wk 6, 8, 10, 12 induction -> 120 mg SC Q2W	100 mg IV: $186.16 120 mg SC (PFP): $252.40[a]	2 IV (8 vials) + 49 SC	$13,856.88 $14,046.68[e]
UST Q12W	130 mg IV weight-based[c] wk 0, and 90 mg SC wk 8 induction -> 90 mg SC Q12W maintenance	130 mg IV: $[redacted]45 mg SC: $[redacted]	1 IV (3 vials) + 8.3 SC	$10,542.47[redacted] $[redacted][e]
ADA	160 mg (2 x 80 mg) SC wk 0 and 80 mg SC wk 2, then 40 mg SC Q2W wk 4, 6, 8, 10, 12, 14 induction -> 40 mg SC Q2W maintenance	3 x 80 mg SC: $618.90[a]	1	$11,908.49
		40 mg SC: $505.95[a]	6	
		40 mg SC: $444.17[ab]	44	
UST Q8W	130 mg IV weight-based[c] wk 0, and 90 mg SC wk 8 induction -> 90 mg SC Q8W maintenance	130 mg IV: $[redacted]45 mg SC: $[redacted]	1 IV (3 vials) + 12 SC	$[redacted] $[redacted][e]
VDZ IV/SC	300 mg IV wk 0, 2, then 108 mg SC wk 6, 8, 10, 12, 14, 16 induction -> 108mg SC Q2W maintenance	300 mg IV: $[redacted][g] 2 x 108 mg SC: $[redacted][g]	2 IV + 49 SC	$[redacted] $[redacted][e]
VDZ IV	300 mg IV wk 0, 2, 6, induction -> 300 mg IV Q8W maintenance	300 mg IV: $[redacted][g]	14.25 IV	$[redacted] $[redacted][e]
UPA	45 mg D induction -> 30 mg D maintenance	45 mg oral (28 tablets): $[redacted][h]	26	$[redacted]
		30 mg oral (28 tablets): $[redacted][h]	26	$[redacted]
	45 mg D induction -> 15 mg D maintenance	15 mg oral (28 tablets): $[redacted][h]	26	$[redacted]

Source: constructed during the evaluation based on Attachment 3.1 Guselkumab CD Economic Model.xlsx.

ADA=adalimumab; PFP=pre-filled pen; PFS=pre-filled syringe; GUS=guselkumab; IFX=infliximab; IV=intravenous; SC=subcutaneous; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; D=daily; QxW=every x week;

a As IFX and ADA are on F2 formulary, their effective prices are assumed to be the published prices.

b PBS Continuing.

c UST infusion solution composed of number of 130 mg vials by patient body weight: ≤55kg at dose 260 mg (2 vials x 130 mg UST), >55 kg to ≤85 kg at 390 mg (3 vials x 130 mg UST) and >85 kg at 520 mg (4 vials x 130 mg UST).

d The submission assumed an average of 4 IFX IV vials dispensed per script, which equates to average patient weight of 80 kg.

e Drug cost plus administration cost (MBS item 14245 $94.90 fee).

f The effective price of UST was known to the sponsor (same sponsor as GUS).

g The submission estimated the effective price of VDZ using a cost-minimisation approach versus UPA.

h The effective price of UPA was made known to the sponsor in March 2024 in relation to a flow on reference price reduction for UST on 1 June 2024.

5.6 The pre-PBAC response noted that the cost-effective cost per patient over 2 years for infliximab and ustekinumab at the time of initial listing for CD was $44,199 and $31,990, respectively.

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 hearing was in the form of a written statement from three experienced Australian Gastroenterologists who treat CD patients. The statement noted the significant health, economic and social burden of IBD in Australia. The statement noted the importance of improved access to novel therapies for IBD and noted two medicines (risankizumab and mirikizumab) are not available on the PBS for IBD despite receiving positive recommendations from the PBAC. The statement noted the importance of having access to an IL23-p19 therapy for patients with IBD.

6.2 The statement noted that multiple studies have shown that endoscopic mucosal healing is associated with prognostic benefit in Crohn's disease, reducing risk of surgery, hospitalisation, and morbidity. Moreover, endoscopic mucosal healing leads to improved patient quality of life and gains in occupational and social function. The statement concluded that if a novel therapy shows significant benefit in achieving endoscopic mucosal response/improvement compared to an existing therapy, this is likely to be highly impactful for patients.

Consumer comments

6.3 The PBAC noted and welcomed the input from individuals (1), health care professionals (17) and organisations (3) via the Consumer Comments facility on the PBS website. Input was provided by clinicians with considerable experience treating CD. Input described an unmet need regarding effective and durable treatments for moderate to severe CD, with current treatment options noted as moderately effective with high rates of loss of response. The comments noted this was in the context of a condition that potentially requires management over 60 to 70 years. Comments highlighted GUS's potential to treat the significant proportion of individuals who have exhausted all other treatment options and preventing the need for invasive surgical interventions. Input described the favourable safety profile of guselkumab, with low risks of serious adverse events demonstrated in clinical trials. Comments outlined the lack of access to p19 inhibitors as a therapeutic option in Australia, despite their utilisation in other countries. Comments noted that the subcutaneous administration of GUS resulted in a reduced treatment burden, particularly for remote and regional areas with limited access to infusion clinics. Input described significant and chronic morbidity associated with CD, leading to impaired quality of life. One contributor noted the increased prevalence of mental health issues among individuals with Crohn

disease, pointing to the emotional toll of chronic pain, invasive treatments such as bowel alteration and inability to perform daily tasks or work. An individual with severe CD noted they had exhausted all treatment options except bowl removal by the age of 25 and access to GUS through a clinical trial resulted in full remission of disease. The individual described the positive impacts of guselkumab treatment, including ability to enjoy life and return to work. The individual noted the inequitable opportunity for improved clinical and quality of life outcomes, due to current lack of access to guselkumab outside of clinical trials.

6.4 Input was received from GESA, Inflammatory Bowel Disease Sydney and Crohn's & Colitis Australia (CCA). All organised emphasised the very significant impact CD has on patients and their families and the importance of having access to additional treatment options. GESA noted that therapeutic needs in CD are unmet by available therapies due to issues associated with access to infusions centres, contraindications/ tolerability, route of administration and efficacy/ persistence. The benefits of having a SC medicine available and dosing every second month was noted. CCA provided testimony from a number of patients living with inflammatory bowel disease including CD. Comments noted the wide-ranging disruption to life of having uncontrolled CD including pain, bleeding, inability to work or study, social isolation, fatigue, anxiety and incontinence. Patients noted the high cost of using medications that are not listed on the PBS. IBD Sydney noted there is a need for new classes of therapies for the management of CD as remission rates remain suboptimal with currently available agents.

Clinical trials

6.5 The submission was based on three head-to-head randomised trials comparing GUS to UST and placebo (PBO) for induction and maintenance treatment: GALAXI 1, GALAXI 2 and GALAXI 3. In addition, the submission presented indirect evidence comparing GUS versus other b/tsDMARD comparators (IFX, ADA, VDZ, UPA) for induction and maintenance treatment. The indirect evidence consisted of indirect treatment comparisons (ITCs) and a network meta-analysis (NMA) based on data from a total of 23 PBO or active-control RCTs.

6.6 The indirect evidence for induction treatment was based on the three head-to-head RCTs (GALAXI 1, GALAXI 2, GALAXI 3) and data from a total of 16 comparator RCTs:

- One RCT comparing GUS SC induction vs PBO: GRAVATI.
- One RCT comparing IFX vs PBO: T16.
- Four RCTs comparing ADA vs PBO: CLASSIC I, GAIN, Watanabe 2012, Chen 2020.
- One RCT comparing ADA vs UST: SEAVUE.
- Four RCTs comparing VDZ vs PBO: GEMINI II, GEMINI III, Watanabe 2020, NCT03234907.
- Two RCTs comparing UPA vs PBO: U-EXCEL, U-EXCEED.
- Three RCTs comparing UST vs PBO: UNITI-1, UNITI-2, CERTIFI.

6.7 The indirect evidence for maintenance treatment was based on the three head-to-head RCTs (GALAXI 1, GALAXI 2, GALAXI 3) and data from a total of seven comparator RCTs:

- One RCT comparing IFX vs PBO: ACCENT.
- Two RCTs comparing ADA vs PBO: Watanabe 2012, CHARM.
- One RCT comparing ADA vs UST: SEAVUE.
- One RCT comparing VDZ vs PBO: GEMINI II.
- One RCT comparing UPA vs PBO: U-ENDURE.
- One RCT comparing UST vs PBO: IM-UNITI.

6.8 Details of the trials presented in the submission are provided in Table 4.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Guselkumab vs placebo and ustekinumab trials		
GALAXI 1 (NCT03466411)	A Phase 2/3, Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease - 48-WeekClinical Study Report (GALAXI 1; Phase 2). Sandborn et al. (2022). Guselkumab for the Treatment of Crohn's Disease: Induction Results From the Phase 2 GALAXI-1 Study. Silvio Danese et al. (2024). Efficacy and safety of 48 weeks of guselkumab for patients with Crohn's disease: maintenance results from the phase 2, randomised, double-blind GALAXI-1 trial.	20 October 2023 Gastroenterology, 162:1650-1664 e8 Lancet Gastroenterol Hepatol, 9: 133-146
GALAXI 2 (NCT03466411)	A Phase 2/3, Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease GALAXI - 48-WeekClinical Study Report (GALAXI2; Phase 3). Remo Panaccione, Danese, et al. (2024). Efficacy and safety of guselkumab therapy in patients with moderately to severely active Chron's Disease: Results of the GALAXI 2 2 & 3 Phase 3 Studies.	19 March 2024 Gastroenterology, 166:5, Supplement (1057b-1057b2)
GALAXI 3 (NCT03466411)	A Phase 2/3, Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Multicenter Protocol to Evaluate the Efficacy and Safety of Guselkumab in Participants with Moderately to Severely Active Crohn's Disease GALAXI - 48-WeekClinical Study Report (GALAXI3; Phase 3). Remo Panaccione, Danese, et al. (2024). Efficacy and safety of guselkumab therapy in patients with moderately to severely active Chron's Disease: Results of the GALAXI 2 2 & 3 Phase 3 Studies.	18 March 2024 Gastroenterology, 166:5, Supplement (1057b-1057b2)
Guselkumab vs placebo trial		
GRAVITI (NCT05197049)	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Guselkumab Subcutaneous Induction Therapy in Participants with Moderately to Severely Active Crohn's Disease - 48-WeekClinical Study Report (GRAVITI)	7 June 2024
Infliximab vs placebo trials		
T16 (NCT00269854)	Targan et al. (1997). A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group.	N Engl J Med, 337(15):1029-1035
ACCENT I (NCT00207662)	Hanauer et al. (2002). Maintenance infliximab for Crohn's disease: the ACCENT 1 randomised trial.	Lancet, 359(9317):1541-1549
Adalimumab vs placebo trials		
CLASSIC I (NCT00055523)	Hanauer et al. (2006). Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC I trial.	Gastroenterology, 130(2):323-333

Trial ID	Protocol title/ Publication title	Publication citation
GAIN (NCT00105300)	Sandborn et al. (2007). Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial.	Ann Intern Med, 146(12):829-838
CHARM (NCT00077779)	Colombel et al. (2007). Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial.	Gastroenterology, 132(1):52-65
Watanabe 2012 (NCT00445939, NCT00445432)	Watanabe et al. (2012). Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease.	J Crohns Colitis, 6(2):160-73
Chen 2020 (NCT02499783)	Chen et al. (2020). Efficacy and safety of adalimumab in Chinese patients with moderately to severely active Crohn's disease: results from a randomized trial.	Therap Adv Gastroenterol, 13:1-13
Adalimumab vs ustekinumab trial		
SEAVUE (NCT03464136)	A Phase 3b, Multicenter, Randomized, Blinded, Active-Controlled Study to Compare the Efficacy and Safety of Ustekinumab to that of Adalimumab in the Treatment of Biologic Naïve Subjects with Moderately-to-Severely Active Crohn's Disease. Sands et al. (2022). Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial.	24 March 2022 Lancet, 399:2200-2211
Vedolizumab versus placebo trials		
GEMINI II (NCT00783692)	Sandborn et al. (2013). Vedolizumab as induction and maintenance therapy for Crohn's disease.	N Engl J Med, 369(8):711-21
GEMINI III (NCT01224171)	Sands et al. (2014). Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed.	Gastroenterology, 147(3):618-627 e3
Watanabe 2020 (NCT02038920)	Watanabe et al. (2020). Effects of vedolizumab in Japanese patients with Crohn's disease: a prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses.	J Gastroenterol, 55(3):291-306
NCT03234907	Vedolizumab IV Compared to Placebo in Chinese Subjects With Crohn's Disease (synopsis on clinicaltrials.gov)	23 March 2022
Upadacitinib versus placebo trials		
U-EXCEL (NCT03345849) U-EXCEED (NCT03345836) U-ENDURE (NCT03345823)	Loftus et al. (2023). Upadacitinib Induction and Maintenance Therapy for Crohn's Disease.	N Engl J Med, 388(21):1966-1980
Ustekinumab versus placebo trials		
UNITI-I (NCT01369329)	Feagan et al. (2016). Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease.	New England Journal of Medicine; 375(20):1946-60
UNITI-II (NCT01369342)	Sandborn et al. (2018). Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy.	Aliment Pharmacol Ther; 48(1):65-77
IM-UNITI (NCT01369355)	Hanauer et al. (2020). IM-UNITI: Three-year Efficacy, Safety, and Immunogenicity of Ustekinumab Treatment of Crohn's Disease. Sandborn et al. (2022). Five-Year Efficacy and Safety of Ustekinumab Treatment in Crohn's Disease: The IM-UNITI Trial.	J Crohns Colitis; 14(1):23-32 Clin Gastroenterol Hepatol; 20(3):578-590.e4
CERTIFI (NCT00771667)	Sandborn et al. CERTIFI Study Group. (2012). Ustekinumab induction and maintenance therapy in refractory Crohn's disease.	N Engl J Med; 367(16):1519-28

Blue shading indicates data previously seen by the PBAC.
Source: Table 2.4, pp74-78 of the submission and Attachment 2.3 – NMA technical report.docx.

6.9 The key features of the included trials are summarised in Table 5 for head-to-head trials of induction and maintenance treatment, Table 6 for the indirect evidence of induction treatment and Table 7 for indirect evidence of maintenance treatment.

Table 5: Key features of the included direct head-to-head evidence – induction and maintenance treatment

Trial	N	Design	Bias	Population	Treatment	Outcome(s)	ITC	NMA	S3
GUS vs UST and PBO									
GALAXI 1 [induction + maintenance]	309[f]	P2, MC, R, PC, DB 48 wks / LTE 4y [IP: 12 wks + MP: 36 wks], Type 1+2 TT LTE 2-4y	*Low*	CDAI ≥220 and ≤450; Biologic naïve and experienced (non-responders excluded)	GUS 200mg IV Wk 0, 4, 8 IP -> 200mg SC Q4W MP GUS 600mg IV Wk 0, 4, 8 IP -> 200mg SC Q4W MP GUS 1200mg IV WK 0, 4, 8 IP ->200mg SC Q4W MP UST 6mg/kg IV WK 0 IP -> 90mg SC Q8W MP PBO[a]	1°: CDAI score 2°: clinical remission and response (CDAI)[c], endoscopic remission and response (SES-CD)[d]	✓i[e]	✓i[e]	✓
GALAXI 2 [induction + maintenance]	508	P3, MC, R, PC, DB 48 wks / LTE 4y [IP: 12 wks + MP: 36 wks], Type 1+2 TT LTE 2-4y	*Low*	CDAI ≥220 and ≤450; Biologic naïve and experienced (non-responders excluded)	GUS 200mg IV Wk 0, 4, 8 IP -> 200mg SC Q4W MP GUS 200mg IV Wk 0, 4, 8 IP -> 100mg SC Q8W MP UST 6mg/kg IV Wk 0 -> 90mg SC Q8W MP PBO[a]	1°: clinical response (CDAI), clinical remission (CDAI) and endoscopic response (SES-CD)[b c] 2°: endoscopic remission (SES-CD)[b d]	✓i[e]	✓i[e]	✓
GALAXI 3 [induction + maintenance]	513	P3, MC, R, PC, DB 48 wks / LTE 4y [IP: 12 wks + MP: 36 wks], Type 1+2 TT LTE 2-4y	*Low*	CDAI ≥220 and ≤450; Biologic naïve and experienced (non-responders excluded)	GUS 200mg IV Wk 0, 4, 8 IP -> 200mg SC Q4W MP GUS 200mg IV Wk 0, 4, 8 IP -> 100mg SC Q8W MP UST 6mg/kg IV Wk 0 -> 90mg SC Q8W MP PBO[a]	1°: clinical remission (CDAI)[b c] 2°: endoscopic response (SES-CD)[b d]	✓i[e]	✓i[e]	✓

Source: Table 2.5, pp84-85 of the submission.

CD=Crohn's disease; CDAI=CD activity index; DB=double blind; GUS=guselkumab; IP=induction phase; ITC=indirect treatment comparison; LTE=long-term extension; MC=multi-centre; MP=maintenance phase; NMA=network meta-analysis; OL=open label; PBO=placebo; PC=placebo-controlled; P2=Phase 2 trial; P3=Phase 3 trial; QxW=every x week; R=randomised; SES-CD=Endoscopic Score for Crohn's Disease; TT=treat-through; UST=ustekinumab; S3=section 3 of the submission; wk=week; y=year; i=analysis with imputed data to adjust for trial design;

a At Wk 12, PBO responders continued PBO treatment from Week 12 through Wk 44. PBO non-responders crossed over to receive active treatment with UST IV induction dose at Wk 12 (weight-based) and maintenance UST SC from Wk 20 through Wk 44.

b Region-specific co-primary endpoints were: i) clinical remission at Wk 12 and ii) endoscopic response at Wk 12. Global co-primary endpoints were: i) clinical response at Wk 12 and clinical remission at Wk 48 and ii) clinical response at Wk 12 and endoscopic response at Wk 48.

c clinical remission: CDAI <150 and clinical response: reduction from baseline of ≥100-point in CDAI score or CDAI score <150 (clinical remission).

d Endoscopic remission: SES-CD ≤4 with at least a 2-point reduction from baseline and no subscore greater than 1 in any individual subcomponent (global definition) or SES-CD ≤2 (region-specific definition) and endoscopic response: ≥50% improvement from baseline in the SES-CD or SES-CD score ≤2.

e Type 2 TT trial design (i.e., GALAXI placebo arms) were standardised to a Type 1 TT design by using additional data sources and assumptions to impute data reflective of Type 1 TT trial.

f Primary efficacy analysis set included 309 patients who were randomized and received ≥1 dose of study drug (including partial dose), and whose induction dosing was not discontinued due to treatment pause. Total 360 randomised, of which 51 patients had induction dosing discontinued due to a safety event.

Table 6: Key features of the included indirect evidence - induction treatment

Trial	N	Design	Bias	Population	Treatment	Outcome(s)	ITC	NMA	S3
GUS vs PBO									
GRAVITI [induction + maintenance]	347	P3, MC, R, PC, DB 24 wks / LTE 72 wks [IP: 12 wks + MP: 12 wks], Type 1 TT	Low	CDAI ≥220 and ≤450; Biologic naïve and experienced	GUS 400mg SC Wk 0, 4, 8 IP -> 200mg Q4W MP GUS 400mg SC Wk 0, 4, 8 IP -> 100mg Q8W MP PBO	1°: clinical remission (CDAI)[a], endoscopic response (SES-CD)[b]	✓[k]	-	-
IFX vs PBO									
T16 [induction only]	108	P2/3, MC, R, PC, DB 12 wks [IP: 12 wks]	Low	CDAI ≥220 and ≤400; Biologic (TNFi) naive	IFX 5mg/kg IFX 10mg/kg IFX 20mg/kg PBO	1°: clinical response (CDAI)[c] 2°: clinical remission (CDAI)[a]	✓[m]	-	✓
ADA vs PBO									
CLASSIC I [induction only]	299	P3, MC, R, PC, DB 4 wks [IP: 4 wks]	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naive	ADA 160/80mg SC Wk 0, 2 ADA 80/40mg SC Wk 0, 2 ADA 40/20mg SC Wk 0, 2 PBO	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[c d]	✓	✓	IP: MA
GAIN [induction only]	325	P3, MC, R, PC, DB 4 wks [IP: 4 wks]	Low	CDAI ≥220 and ≤450; Biologic (TNFi) experienced	ADA 160/80mg SC Wk 0, 2 PBO	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[c d]	✓	✓	IP: MA
Watanabe 2012 [induction + maintenance]	IP: 90	P2/3, MC (Japan), R, PC, DB 56 wks [IP: 4 wks + MP: 52 wks], Type 3 RWD	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naïve and experienced (non-responders excluded)	ADA 160/80mg SC Wk 0, 2 IP -> 40mg SC Q2W MP ADA 80/40mg SC Wk 0, 2 IP -> 40mg SC Q2W MP PBO	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[c d]	✓	✓	IP: MA
Chen 2020 [induction + single arm maintenance]	205	P3, MC (China), R, PC, DB 8 wks / OL f-up 18 wk [IP: 4 wks + MP: 18 wks]	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naive	ADA 160/80mg SC Wk 0, 2 and 40mg SC Wk 4, 6 IP -> OL 40mg SC Q2W MP PBO	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[c]	✓	✓	IP: MA
ADA vs UST									

Trial	N	Design	Bias	Population	Treatment	Outcome(s)	ITC	NMA	S3
SEAVUE [induction + maintenance]	386	P3b, MC, R, parallel, DB 56 wks [IP: 4-8 wks + MP: 48-52 wks], Type 1 TT	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naive	ADA 160/80mg SC Wk 0, 2 IP -> 40mg SC Q2W MP UST 6mg/kg IV Wk 0 IP -> 90mg SC Q8W MP	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[e]	✓	✓	IP: MA
VDZ vs PBO									
GEMINI II [induction + maintenance]	368	P3, MC, R, PC, DB 52 wks [IP: 6 wks + MP: 46 wks], Type 3 RWD	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naïve and experienced	VDZ 300mg IV Wk 0, 2, 6 IP -> 300mg Q4W MP VDZ 300mg IV Wk 0, 2, 6 IP -> 300mg Q8W MP PBO	1°: clinical remission (CDAI)[a], clinical response (CDAI)[d]	✓	✓	IP: MA
GEMINI III [induction only]	416 (315[f])	P3, MC, R, PC, DB 10 wks [IP: 10 wks]	Low	CDAI ≥220 and ≤400; Biologic (TNFi) naïve and experienced	VDZ 300mg IV Wk 0, 2, 6 PBO	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[d]	✓	✓	IP: MA
Watanabe 2020 [induction + maintenance]	157	P3, MC (Japan), R, PC, DB 60 wks / OL f-up 94 wks [IP: 14 wks + MP: 46 wks]	Low	CDAI ≥220 and ≤450; Biologic (TNFi) experienced	VDZ 300mg IV Wk 0, 2, 6 IP -> 300mg Q8W MP PBO	1°: clinical response (CDAI)[d] 2°: clinical remission (CDAI)[a]	✓	✓	IP: MA
NCT03234907 [induction + maintenance]	215	P3, MC (China), R, PC, DB 64 wks / safety 18 wks [IP: 10 wks + MP: 50 wks] *Type 2 TT*	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naïve and experienced	VDZ 300mg IV Wk 0, 2, 6 IP -> 300mg Q4W MP VDZ 300mg IV Wk 0, 2, 6 IP -> 300mg Q8W MP PBO	1°: clinical response (CDAI)[d] 2°: clinical remission (CDAI)[a]	✓	-	IP: MA
UPA vs PBO									
U-EXCEL [induction only]	526	P3, MC, R, PC, DB 12 wks [IP: 12 wks]	Low	*Mean CDAI 293;* Biologic naïve and experienced	UPA 45 mg D PBO	1°: clinical remission (CDAI)[a], endoscopic response (SES-CD)[b] 2°: clinical response (CDAI)[d]	✓	✓	IP: MA
U-EXCEED [induction only]	495	P3, MC, R, PC, DB 12 wks / OL 12 wks[g] [IP: 12 wks]	Low	*Mean CDAI 307;* Biologic experienced	UPA 45 mg D PBO	1°: clinical remission (CDAI)[a], endoscopic response (SES-CD)[b] 2°: clinical response (CDAI)[d]	✓	✓	IP: MA
UST vs PBO									
UNITI-1 [induction only]	741	P3, MC, R, PC, DB 8 wks[i] [IP: 8 wks]	Low	CDAI ≥220 and ≤450; Biologic (TNFi) experienced	UST 6mg/kg Wk 0 PBO	1°: clinical response (CDAI)[e] 2°: clinical remission (CDAI)[a]	-[n]	✓	-[p]

Trial	N	Design	Bias	Population	Treatment	Outcome(s)	ITC	NMA	S3
UNITI-2 [induction only]	628	P3, MC, R, PC, DB 8 wks[i] [IP: 8 wks]	Low	CDAI ≥220 and ≤450; Biologic naïve and experienced (non-responders excluded)[h]	UST 6mg/kg Wk 0 PBO	1°: clinical response (CDAI)[e] 2°: clinical remission (CDAI)[a]	-[n]	✓	-[p]
CERTIFI [induction + maintenance]	526	P2b, MC, R, PC, DB 36 wks [IP: 8 wks + MP: 28 wks] *Type 3 RWD*	Low	CDAI ≥220 and ≤450; Biologic (TNFi) experienced	UST 1mg/kg IP -> US 90mg SC Wk 8, 16 UST 3 mg/kg IP -> US 90mg SC Wk 8, 16 UST 6mg/kg IP -> US 90mg SC Wk 8, 16 PBO	1°: clinical response (CDAI)[e] 2°: clinical remission (CDAI)[a]	-	✓	-[p]

Blue shading indicates data previously seen by the PBAC.

Source: Table 2.5, pp84-85 of the submission.

ADA=adalimumab; CD=Crohn's disease; CDAI=CD activity index; DB=double blind; GUS=guselkumab; IFX=infliximab; IP=induction phase; ITC=indirect treatment comparison; IV=intravenous; MC=multi-centre; MP=maintenance phase; NMA=network meta-analysis; OL=open label; PBO=placebo; PC=placebo-controlled; P2=Phase 2 trial; P3=Phase 3 trial; QxW=every x week; R=randomised; RWD=randomised withdrawal design, SC=subcutaneous; SES-CD=Endoscopic Score for Crohn's Disease; TNFi=tumour necrosis factor inhibitor; TT=treat-through; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; S3=section 3 of the submission; D=daily; wk=week;

a Clinical remission: CDAI score <150.

b Endoscopic response: ≥50% improvement from baseline in SES-CD score.

c Clinical response (70-point response): reduction of ≥70 points in CDAI score.

d Clinical response (100-point response): reduction of ≥100 points in CDAI score.

e Clinical response (100-point response): reduction of ≥100 points in CDAI score or a CDAI score <150.

f Primary analysis was in 315 patients with previous TNF antagonist failure (i.e., an inadequate response to, loss of response to, or intolerance of ≥1 TNFi).

g U-EXCEED had an additional 12-week OL, active single-group induction period to allow accrual of sufficient number of patients who had a clinical response while receiving UPA for entry into U-ENDURE.

h Patients in UNITI-2 could have previously received one or more TNFi provided they had not had unacceptable side effects and had not met the criteria for non-response to treatment.

i In UNITI-1 and UNITI-2, follow-up for safety occurred either through Wk 8 in patients who entered the maintenance trial or 20 weeks after the induction dose in patients who did not enter the maintenance trial.

k Comparison of IV vs SC only.

m Included in sensitivity analysis only.

n The submission excluded UNIT-1 and UNITI-2 in the ITC due to available direct evidence.

p The submission's modelled economic evaluation used the pooled GALAXI trials results for UST in induction treatment.

Table 7: Key features of the included indirect evidence - maintenance treatment

Trial	N	Design	Bias	Population	Treatment	Outcome(s)	ITC	NMA	S3
IFX vs PBO									
ACCENT I [maintenance]	MP: 335[f]	P3, MC, R, DB 54 wks [IP: 2 wks + MP[f]: 52 wks], Type 2 TT	Low	CDAI ≥220 and ≤400; Biologic (TNFi) naïve Response to IFX at Wk 2	IFX 5mg/kg Wk0 IP -> 5mg/kg Wk 2, 6, Q8W MP IFX 5mg/kg Wk0 IP -> 5mg/kg Wk 2, 6, 10mg/kg Q8W MP IFX 5mg/kg Wk0 -> PBO	1°: clinical remission (CDAI)[a] | clinical response (CDAI)[c]	✓i	✓i	MP: NMA
ADA vs PBO									
Watanabe 2012 [induction + maintenance]	MP: 50	P2/3, MC (Japan), R, PC, DB 56 wks [IP: 4 wks + MP[g]: 52 wks], Type 3 RWD	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naïve and experienced (non-responders excluded)	ADA 160/80mg SC Wk 0, 2 IP -> 40mg SC Q2W MP ADA 80/40mg SC Wk 0, 2 IP -> 40mg SC Q2W MP PBO	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[c d]	✓i	✓i	MP: NMA
CHARM [maintenance]	MP: 778	P3, MC, R, PC, OL (IP) and DB (MP) 56 wks [IP: 4 wks + MP[g]: 52 wks], Type 3 RWD	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naïve and experienced (non-responders excluded)	ADA 80/40mg SC Wk 0, 2 IP -> 40mg Q2W MP ADA 80/40mg SC Wk 0, 2 IP -> 40mg QW MP ADA 80/40mg SC Wk 0, 2 -> PBO	1°: clinical remission (CDAI)[a] | clinical response (CDAI)[c]	✓i	✓i	MP: NMA
ADA vs UST									
SEAVUE [induction + maintenance]	386	P3b, MC, R, parallel, DB 56 wks [IP: 4-8 wks + MP: 48-52 wks], Type 1 TT		CDAI ≥220 and ≤450; Biologic (TNFi) naive	ADA 160/80mg SC Wk 0, 2 IP -> 40mg SC Q2W MP UST 6mg/kg IV Wk 0 IP -> 90mg SC Q8W MP	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[e]	✓	✓	MP: NMA
VDZ vs PBO									
GEMINI II [induction + maintenance]	368	P3, MC, R, PC, DB 52 wks [IP: 6 wks + MP: 46 wks], Type 3 RWD	Low	CDAI ≥220 and ≤450; Biologic (TNFi) naïve and experienced	VDZ 300mg IV Wk 0, 2, 6 IP -> 300mg Q4W MP VDZ 300mg IV Wk 0, 2, 6 IP -> 300mg Q8W MP VDZ 300mg IV Wk 0, 2, 6 IP -> PBO PBO	1°: clinical remission (CDAI)[a], clinical response (CDAI)[d]	✓i	✓i	MP: NMA
UPA vs PBO									
U-ENDURE	MP: 502	P3, MC, R, PC, DB 52 wks [MP[h]: 52 wks], Type 4 RWD	Low	*Mean CDAI 307;* Biologic naïve and experienced Response to UPA at Wk 12	UPA 15mg D UPA 30mg D PBO	1°: clinical remission (CDAI)[a], endoscopic response (SES-CD)[b] 2°: clinical response (CDAI)[d]	✓i	✓i	MP: NMA
UST vs PBO									

Trial	N	Design	Bias	Population	Treatment	Outcome(s)	ITC	NMA	S3
IM-UNITI	397	P3, MC, R, PC, DB 44 wks / OL LTE 5 y [MP[i]: 44 wks], Type 3 RWD	Low	CDAI ≥220 and ≤450; Biologic (TNFi) experienced Response to UST at Wk 8	UST 90mg SC Q8W UST 90mg SC Q12W PBO	1°: clinical remission (CDAI)[a] 2°: clinical response (CDAI)[e]	-	✓i	-[k]

Blue shading indicates data previously seen by the PBAC.

Source: Table 2.5, pp84-85 of the submission.

ADA=adalimumab; CD=Crohn's disease; CDAI=CD activity index; DB=double blind; IFX=infliximab; IP=induction phase; ITC=indirect treatment comparison; IV=intravenous; MC=multi-centre; MP=maintenance phase; NMA=network meta-analysis; OL=open label; PBO=placebo; PC=placebo-controlled; P2=Phase 2 trial; P3=Phase 3 trial; QxW=every x week; R=randomised; RWD=randomised withdrawal design, SC=subcutaneous; SES-CD=Endoscopic Score for Crohn's Disease; TNFi=tumour necrosis factor inhibitor; TT=treat-through; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; S3=section 3 of the submission; D=daily; wk=week; i=analysis with imputed data to adjust for trial design;

a Clinical remission: CDAI score <150.

b Endoscopic response: ≥50% improvement from baseline in SES-CD score.

c Clinical response (70-point response): reduction of ≥70 points in CDAI score.

d Clinical response (100-point response): reduction of ≥100 points in CDAI score.

e Clinical response (100-point response): reduction of ≥100 points in CDAI score or a CDAI score <150.

f In ACCENT 1, 335 patients were IFX responders at Wk 2 and were randomly assigned to PBO, IFX 5 mg/kg or 10 mg/kg maintenance regimen and included in the predefined primary efficacy analyses. Response was defined as decrease in CDAI score ≥70 points from baseline value and ≥25% reduction in the total score.

g Patients who achieved response (defined as reduction of ≥70 points in CDAI score compared to baseline) were randomised to maintenance therapy.

h Patients who had a clinical response to UPA induction therapy at Wk 12 in U-EXCEL and U-EXCEED were randomly assigned to UPA maintenance therapy in the U-ENDURE for 52 weeks. Response was defined as decrease of ≥30% in average daily frequency of very soft or liquid stools or in the abdominal pain score (range, 0 [no pain] to 3 [severe pain]), with neither worse than baseline.

i Patients who completed the two 8-week induction trials (UNITI-1 or UNITI-2) and had a clinical response to UST could enrol in the IM-UNITI maintenance trial. Response was defined as ≥100 points in CDAI score from baseline.

k The submission's modelled economic evaluation used the pooled GALAXI trials results for UST in maintenance treatment.

6.10 GALAXI 1, GALAXI 2 and GALAXI 3 trials were all multicentre *(*including Australia), randomised, placebo-controlled, double-blind trials with a treat-through design where patients with moderate to severe CD were randomised to GUS, UST or PBO for 48 weeks. In each trial, patients randomised to GUS or UST remained on the same treatment for induction (Weeks 0-12) and maintenance therapy (Weeks 12-48) irrespective of induction response. In contrast, only patients randomised to PBO who achieved clinical response at Week 12 remained on PBO until the end of the trial and patients with non-response at Week 12 crossed over to UST. Patients who completed GALAXI 1, GALAXI 2 and GALAXI 3 may enter long-term extension for additional 4 years of treatment (Week 48 to Week 252). At Week 12, a high number of PBO non-responders crossed over to UST treatment to Week 48: 44 (72.1%) in GALAXI 1, 49 (64.5%) in GALAXI 2 and 49 (68.1%) in GALAXI 3.

6.11 GRAVITI was a multicentre, randomised placebo-controlled, double-blind trial with treat-through design where patients with moderate to severe CD were randomised to GUS 400 mg SC induction followed by either GUS 200 mg or 100 mg maintenance, or PBO. Patients in PBO group could receive rescue treatment with GUS (i.e. GUS 400 mg SC induction then 100 mg Q8W maintenance) from Week 16 onwards if rescue criteria were met. At Week 24, all patients entered a treatment extension phase on the same maintenance dose regimen to Week 96.

6.12 For GUS and the comparator trials, the design of the induction trials / phases was similar in that eligible patients were randomised to active treatment or control (PBO) with response to treatment assessed at Week 4 to 14. In contrast, the maintenance trials / phases differed in terms of trial designs. The submission described four categories of maintenance trial designs:

- Type 1: Treat-through design, where continuing treatment in the trial is not conditional on having response at a pre-defined time point. GALAXI trials (GUS and UST arm) and SEAVUE were Type 1 treat-through designs.
- Type 2: Treat-through design, where continuing treatment in the trial is conditional on an initial response by a defined timepoint (either at induction or after induction). GALAXI trials (PBO arm) and ACCENT-1 trial were Type 2 treat-through designs.
- Type 3: Randomised withdrawal design, where patients who respond to active induction treatment by a given timepoint are randomised or re-randomised to continue either active therapy or PBO (withdrawal) for maintenance treatment. CHARM, Watanabe 2012 and GEMINI II trials were Type 3 randomised withdrawal designs.
- Type 4: Randomised withdrawal design, the same Type 3 above but where patients who do not respond to active induction treatment by the given timepoint remain on active treatment to allow for delayed response (prior to randomisation or re-randomisation to active maintenance or PBO withdrawal). U-ENDURE trial had a Type 4 randomised withdrawal design.

6.13 The baseline characteristics were generally balanced between treatment arms within the included trials but there was a high degree of heterogeneity across the trials with respect to disease duration, prior exposure to conventional and biologic therapy, baseline concomitant therapies and the definition of the clinical response to induction treatment (required for enrolment in the randomised withdrawal trials/phases). The trial populations may also not be completely representative of the proposed PBS population, given the trials generally enrolled patients with less severe disease on average than permitted by the PBS restriction criteria and a number of trials likely enrolled patients with more refractory disease (indicated by time since diagnosis and prior exposure to b/tsDMARDs).

6.14 Overall, the risk of bias within each of the included trials was considered low. In general, discontinuations and loss to follow-up were low across most trials and any differences across treatment arms were unlikely to favour the active treatment due to non-responder imputation assumptions. In GALAXI 1, there was a temporary pause of induction dosing during the study to evaluate an event of toxic hepatitis in a patient treated with GUS. Patients who had their induction treatment paused due to the evaluation of this event were discontinued from the study (n=51). Data from these discontinued patients were included in the safety analyses but were not included in the primary efficacy analysis.

6.15 The risk of bias for the indirect comparisons was considered high due to the numerous differences across the included trials in terms of the enrolled populations, concomitant therapies permitted during the trial periods, outcome definitions and the timing of reported outcomes (see comparative effectiveness). The differences will likely have an impact on the transitivity of the trials included in the indirect comparisons, however the direction of impact is unclear. However, the PBAC had previously used this data to make decisions on the clinical effectiveness and safety claims for severe CD for UPA, UST, VDZ and risankizumab (paragraph 6.12, upadacitinib PSD July 2023 PBAC meeting).

Comparative effectiveness

6.16 The PBAC had previously based recommendations for listing of b/tsDMARDs for the treatment of severe CD on the proportion of patients achieving and maintaining 'clinical response' (≥100 point or ≥70 point reduction in CDAI from baseline, i.e. CR-100 or CR-70) and 'clinical remission' (CDAI<150 points) (see infliximab PSD, March 2007 PBAC meeting and vedolizumab PSD, March 2015 PBAC meeting). This was consistent with the current response criteria on the PBS, requiring patients with severe CD to demonstrate 'clinical remission'. In addition to the clinical response and clinical remission, the submission argued that the PBAC should also consider 'endoscopic response' and 'endoscopic remission' defined by the SES-CD.

6.17 Across the trials, the definition of clinical remission was generally similar (CDAI <150 in all trials and CDAI ≤150 in VDZ trials) but the definition of clinical response varied (CR-100 or CDAI<150 in GUS trials and the ADA vs UST trial (SEAVUE), or CR-70 or CR-100 in all other trials). Further, the clinical response and clinical remission outcomes

were reported at different time points for induction (Week 12 for GUS and UPA trials, Weeks 2-4 for IFX and ADA trials, Weeks 6 to 10 for VDZ, Week 8 for UST trials and Week 16 ADA vs UST trial (SEAVUE)) and maintenance therapy (Week 48 for GUS, Weeks 52-60 for IFX, ADA, UST, UPA and VDZ trials).

6.18 Not all trials reported endoscopic outcomes and there were differences in their definitions across the trials that included them for GUS (GALAXI trials and GRAVITI), ADA vs UST (SEAVUE) and UPA (U-ENDURE). Endoscopic response was defined as a reduction of SES-CD score ≥50% from baseline, or a SES-CD score ≤3, or a SES-CD of 0 if baseline SES-CD =3 in the ADA vs UST (SEAVUE) trial; reduction of SES-CD score ≥50% from baseline, or reduction of ≥2 points from baseline if baseline SES-CD=4 in UPA (U-ENDURE) trial; and reduction of a SES-CD score ≥50% from baseline, or reduction of ≥2 points from baseline in the GUS trials. For endoscopic remission, the GALAXI 2 and GALAXI 3 trials included two definitions based on global-specific (SES-CD ≤4 with at least a 2-point reduction from baseline and no subscore greater than 1 in any individual subcomponent) and region-specific (SES-CD score ≤2) testing modules. Whereas endoscopic remission was defined as SES-CD score ≤3, or SES-CD of 0 for patients with baseline SES-CD of 3 in SEAVUE and SES-CD ≤4, reduction of ≥2 points from baseline and no subscore >1 in any individual subcomponent in U-ENDURE.

6.19 In GALAXI 2 and GALAXI 3, the results between the two testing modules (global' (US FDA guidance) and 'region-specific' (EMA guidance)) were generally consistent except for endoscopic remission outcome, given differences in their outcome definitions. The submission used global-specific outcomes for the meta-analyses, which showed significantly more patients treated with GUS 100 mg Q8W and 200 mg Q4W achieved endoscopic remission compared to UST at Week 48. Whereas the meta-analysis conducted during the evaluation based on region-specific definition indicated no difference with GUS 200 mg Q4W and only GUS 100 mg Q8W was significantly more effective in terms of endoscopic remission compared to UST. See below.

6.20 To estimate the indirect treatment effects between GUS versus all PBS-listed b/tsDMARDs, the submission conducted both (i) ITCs using the Bucher method and (ii) a Bayesian NMA. The submission stated that an 'Australian' NMA was estimated by excluding b/tsDMARDs that are not currently PBS-listed from a 'global' NMA containing data for IFX, ADA, UST, UPA, VDZ and GUS, as well as other treatments with regulatory approval in other countries (such as mirikizumab, risankizumab, certolizumab, natalizumab). The submission did not provide any rationale for excluding non-relevant interventions when estimating the Australian NMA (given data for non-PBS-listed treatments may still improve inferences between PBS-listed treatments) or provide the results of the global NMA for comparison to assess the impact of removing data (Cochrane handbook 2024[7]).

[7] Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Chapter 11: Undertaking network meta-analyses [last updated October 2019]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors).

Head-to-head evidence for induction and maintenance treatment: GUS versus UST

6.21 Table 8 presents the key outcomes of clinical remission, clinical response, endoscopic remission and endoscopic response for induction and maintenance in GALAXI 1, GALAXI 2 and GALAXI 3 comparing GUS to UST. Figure 1 presents the proportion of patients in each trial with clinical remission by study visit to Week 48. The table presents results including and excluding GALAXI 1 from the meta-analysis, as results were inconsistently applied in the modelled economic evaluation. The rationale for excluding GALAXI 1 from the maintenance phase results was due to the different induction doses used (despite no difference in effectiveness observed).

Table 8: Summary of head-to-head evidence: GUS vs UST (GALAXI 1, GALAXI 2 and GALAXI 3)

	GUS	UST	OR	RR	RD
Induction, GUS IV vs UST IV					
Clinical remission (Wk12)					
GALAXI 1, 2, 3 meta-analyses	309/643 (48.1)	166/354 (46.9)	1.08 (0.80, 1.44)	1.04 (0.89, 1.21)	0.02 (-0.05, 0.09)
Clinical response (Wk12)					
GALAXI 1, 2, 3 meta-analysis	406/643 (63.1)	213/354 (60.2)	1.17 (0.89, 1.53)	1.06 (0.96, 1.18)	0.04 (-0.03, 0.1)
Maintenance, GUS 100 vs UST 90					
Clinical remission (Wk48)					
GALAXI 1, 2, 3 meta-analysis	226/347 (65.1)	220/354 (62.1)	1.14 (0.84, 1.55)	1.05 (0.94, 1.17)	0.03 (-0.04, 0.1)
GALAXI 2, 3 meta-analysis	187/286 (65.4)	183/291 (62.9)	1.11 (0.79, 1.57)	1.04 (0.92, 1.17)	0.02 (-0.05,0.10)
Clinical response (Wk48)					
GALAXI 1, 2, 3 meta-analysis	256/347 (73.8)	247/354 (69.8)	1.22 (0.88, 1.69)	1.06 (0.96, 1.16)	0.04 (-0.03, 0.11)
GALAXI 2, 3 meta-analysis	211/286 (73.8)	204/291 (70.1)	1.20 (0.83, 1.72)	1.05 (0.95, 1.16)	0.04 (-0.04, 0.11)
Endoscopic remission (Wk48)					
GALAXI 1, 2, 3 meta-analysis	106/347 (30.5)	76/354 (21.5)	**1.61 (1.14, 2.28)**	**1.40 (1.07, 1.82)**	**0.09 (0.03, 0.16)**
GALAXI 2, 3 meta-analysis	95/286 (33.2)	72/291 (24.7)	**1.51 (1.05, 2.17)**	**1.34 (1.03, 1.74)**	**0.09 (0.01, 0.16)**
GALAXI 2, 3 meta-analysis[a]	72/286 (25.2)	48/291 (16.5)	**1.70 (1.13, 2.56)**	**1.53 (1.10, 2.12)**	**0.09 (0.02, 0.15)**
Endoscopic response (Wk48)					
GALAXI 1, 2, 3 meta-analysis	164/347 (47.3)	127/354 (35.9)	**1.60 (1.18, 2.17)**	**1.31 (1.09, 1.56)**	**0.11 (0.04, 0.19)**
GALAXI 2, 3 meta-analysis	137/286 (47.9)	108/291 (37.1)	**1.59 (1.12, 2.17)**	**1.28 (1.04, 1.58)**	**0.11 (0.03, 0.19)**
Clinical remission (Wk48) | induction remission (Wk12)					
GALAXI 1, 2, 3 meta-analysis	140/171 (81.9)	134/165 (81.2)	1.27 (0.71, 2.28)	1.04 (0.95, 1.15)	0.04 (-0.04, 0.11)
GALAXI 2, 3 meta-analysis	114/133 (85.7)	112/137 (81.8)	1.33 (0.69, 2.56)	1.04 (0.94, 1.16)	0.04 (-0.05, 0.12)
Durable clinical remission[c] (clinical remission Wk12-48)					
GALAXI 1, 2, 3 meta-analysis	169/347 (48.7)	152/354 (42.9)	1.26 (0.94, 1.70)	1.13 (0.96, 1.33)	0.06 (-0.02, 0.13)
GALAXI 2, 3 meta-analysis	138/286 (48.3)	122/291 (41.9)	1.29 (0.87, 1.90)	1.15 (0.93, 1.43)	0.06 (-0.03, 0.16)
Sustained clinical remission[d] (clinical remission Wk12&48)					
GALAXI 1, 2, 3 meta-analysis	140/347 (40.3)	134/354 (37.9)	1.11 (0.82, 1.51)	1.07 (0.89, 1.28)	0.03 (-0.05, 0.10)
GALAXI 2, 3 meta-analysis	114/286 (39.9)	112/291 (38.5)	1.06 (0.76, 1.48)	1.04 (0.85, 1.27)	0.01 (-0.07, 0.09)
Maintenance, GUS 200 vs UST 90					
Clinical remission (Wk48)					
GALAXI 1, 2, 3 meta-analysis	289/420 (68.8)	220/354 (62.1)	**1.38 (1.02, 1.87)**	**1.12 (1.01, 1.24)**	**0.07 (0.01, 0.14)**
GALAXI 2, 3 meta-analysis	208/296 (70.3)	183/291 (62.9)	1.40 (0.99, 1.97)	1.12 (1.00, 1.26)	0.07 (0.00, 0.15)
Clinical response (Wk48)					

Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane, 2024. Available from www.training.cochrane.org/handbook [accessed on 17/04/2025].

GALAXI 1, 2, 3 meta-analysis	319/420 (76.0)	247/354 (69.8)	1.38 (1.00, 1.90)	1.09 (1.00, 1.19)	0.06 (0.00, 0.13)
GALAXI 2, 3 meta-analysis	225/296 (76.0)	204/291 (70.1)	1.35 (0.94, 1.96)	1.09 (0.99, 1.20)	0.06 (-0.01, 0.13)
Endoscopic remission (Wk48)					
GALAXI 1, 2, 3 meta-analysis	141/420 (33.6)	76/354 (21.5)	**2.15 (1.24, 3.7)**	**1.70 (1.14, 2.53)**	**0.14 (0.07, 0.22)**
GALAXI 2, 3 meta-analysis	110/296 (37.2)	72/291 (24.7)	**1.80 (1.18, 2.75)**	**1.51 (1.18, 1.93)**	**0.12 (0.02, 0.23)**
GALAXI 2, 3 meta-analysis[a]	60/296 (20.3)	48/291 (16.5)	1.29 (0.85, 1.96)	1.23 (0.87, 1.73)	0.04 (-0.02, 0.10)
Endoscopic response (Wk48)					
GALAXI 1, 2, 3 meta-analysis	212/420 (50.5)	127/354 (35.9)	**1.90 (1.41, 2.55)**	**1.43 (1.20, 1.69)**	**0.15 (0.09, 0.22)**
GALAXI 2, 3 meta-analysis	156/296 (52.7)	108/291 (37.1)	**1.90 (1.36, 2.64)**	**1.41 (1.18, 1.70)**	**0.16 (0.08, 0.24)**
Clinical remission (Wk48) | induction remission (Wk12)					
GALAXI 1, 2, 3 meta-analysis	177/203 (87.2)	134/165 (81.2)	1.65 (0.92, 2.94)	1.08 (0.98, 1.18)	0.06 (-0.01, 0.14)
GALAXI 2, 3 meta-analysis	124/141 (87.9)	112/137 (81.8)	1.59 (0.81, 3.12)	1.07 (0.97, 1.18)	0.06 (-0.03, 0.14)
Durable clinical remission[c] (clinical remission Wk12-48)					
GALAXI 1, 2, 3 meta-analysis	213/420 (50.7)	152/354 (42.9)	**1.35 (1.01, 1.80)**	1.17 (1.00, 1.36)	0.07 (0.00, 0.15)
GALAXI 2, 3 meta-analysis	149/296 (50.3)	122/291 (41.9)	**1.40 (1.01, 1.95)**	**1.20 (1.01, 1.43)**	0.08 (0.00, 0.16)
Sustained clinical remission[d] (clinical remission Wk12&48)					
GALAXI 1, 2, 3 meta-analysis	177/420 (42.1)	134/354 (37.9)	1.20 (0.90, 1.61)	1.11 (0.93, 1.33)	0.04 (-0.03, 0.11)
GALAXI 2, 3 meta-analysis	124/296 (41.9)	112/291 (38.5)	1.15 (0.83, 1.60)	1.09 (0.89, 1.33)	0.03 (-0.05, 0.11)

bold text indicates statistical significance p<0.05.

Risk statistics calculated using Review Manager (version 5.3).

Source: Tables 2.93 and 2.94, pp205-206, Tables 2.95 and 2.96, pp208-209, Tables 2.133 to 2.135, pp264-268 of the submission. Attachment 2.33 GALAXI GUS vs UST – meta-analysis.xlsx.

GUS=guselkumab; SES-CD=simplified endoscopic activity score for CD; UST=ustekinumab; wk=week;

a region-specific definition of endoscopic remission (SES-CD score ≤2).

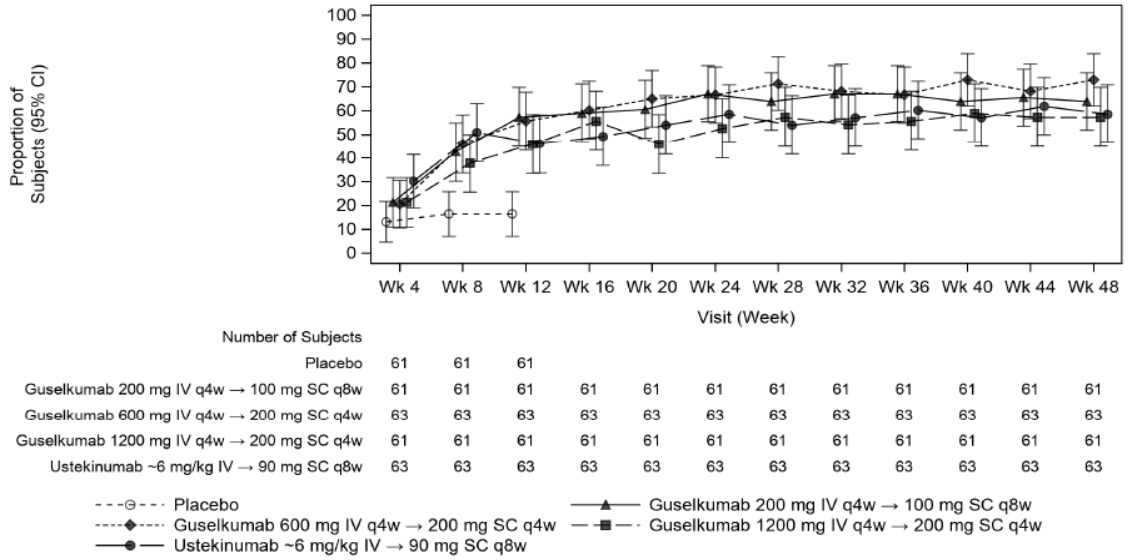
b calculated during the evaluation using RevMan v.5.3.

c Durable clinical remission defined as CDAI <150 for ≥80% of all visits between Week 12 and Week 48 [i.e., at least 8 of 10 visits]), which must include Week 48.

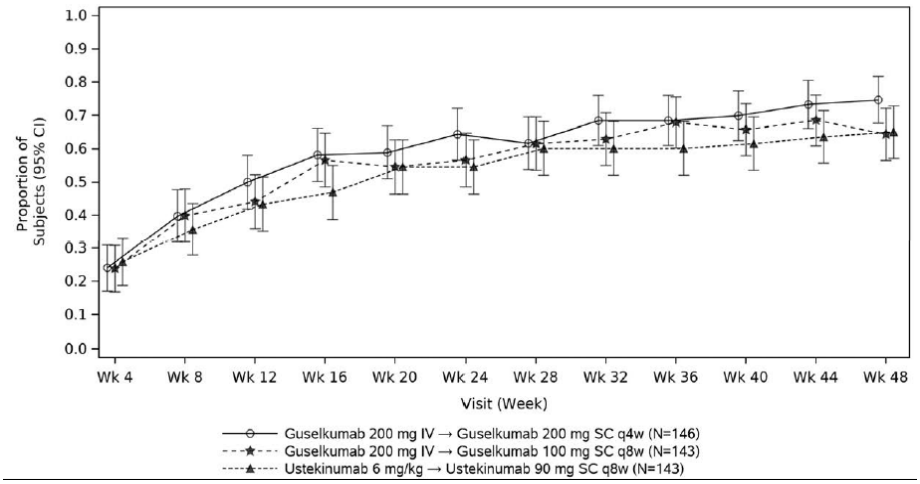
d Sustained clinical remission defined as clinical remission at both Weeks 12 and 48.

Figure 1: Clinical remission by visit through to 48 weeks in GALAXI 1, GALAXI 2 and GALAXI 3.

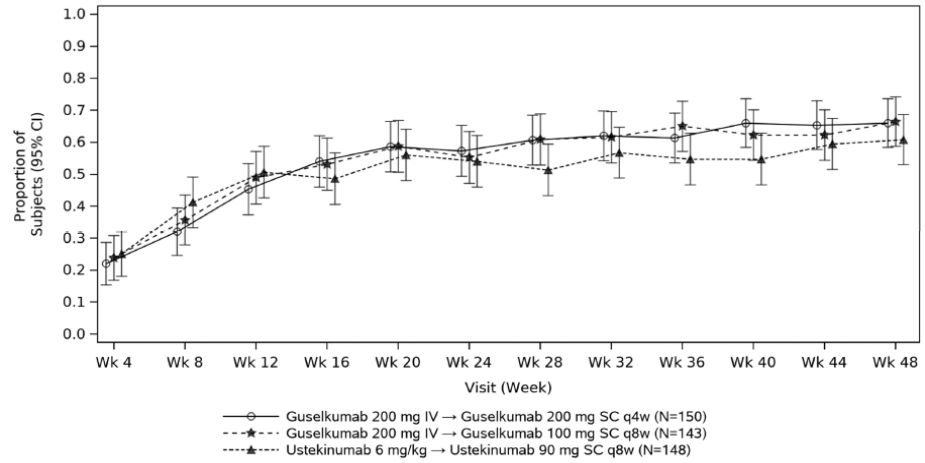
[A] GALAXI 1



[B] GALAXI 2



[C] GALAXI 3



Source: Figure 5, p130 GALAXI 1 CSR; Figure 8, p150 GALAXI 2 CSR; Figure 8, p145 GALAXI 3 CSR

6.22 The head-to-head evidence of GALAXI 1, GALAXI 2 and GALAXI 3 showed:

- For induction treatment (i.e. Week 12), no difference between GUS and UST in terms of clinical remission or clinical response. Comparisons versus PBO (not presented in the table or figure) confirmed that both GUS and UST were more effective than PBO across both outcomes at the same time point.
- For maintenance treatment (i.e. Week 48), generally no difference between GUS 100 mg SC, GUS 200 mg SC and UST in terms of clinical remission and clinical response outcomes, with the exception of a few comparisons that favoured GUS 200 mg SC over UST on maintenance of clinical remission and durable clinical remission. In contrast, GUS 100 mg SC and GUS 200 mg SC were generally more effective than UST in terms of endoscopic remission and endoscopic response outcomes.

6.23 The pre-PBAC response stated the CDAI is a subjective measure of severity and not inflammation and underestimates the efficacy value of treatments by not capturing the long-term benefits of reduced inflammation. It stated patients can have obtained symptomatic CDAI remission but still show signs of inflammation and therefore the continued presence of disease. The pre-PBAC noted that since the listing of infliximab for CD in 2007, endoscopic remission has gained recognition as a key treatment objective in CD. The international clinical guideline STRIDE-II recommends that symptom control (i.e. clinical response and remission) and normalisation of CRP should be the short to intermediate term treatment target for CD and recommends endoscopic healing as a long-term treatment target for patients with CD. As such, since 2022, the US FDA has required that endoscopic remission be included as a co-primary endpoint in combination with clinical remission to be assessed at the end of the trial induction period and at Week 52 for all clinical trials in CD and UC. This recognises that an assessment of the benefits of treatments should cover symptoms (CDAI remission) and degree of inflammation (endoscopic remission).

6.24 The pre-PBAC response noted that 110 patients treated with GUS 200 mg achieved endoscopic remission at 48 weeks and 100 patients achieved deep remission (both clinical remission and endoscopic remission). Therefore, the pre-PBAC response noted the vast majority of patients who achieve endoscopic remission also achieved clinical remission (100/110 [90%]). The pre-PBAC response noted this correlation also existed for UST, with 65 out of 72 patients (90%) who achieved endoscopic remission also achieving clinical remission. The pre-PBAC response noted the relationship between endoscopic score after 52 weeks of treatment and clinical outcomes is supported by an analysis of GUS and UST trial data which demonstrated that patients with endoscopic response at 52 weeks are almost twice as likely to maintain clinical

remission at Year 2 (odds ratio 1.91, 95%CI: 1.11, 3.28)[8]. The PBAC noted this analysis appeared to be conducted using the GALAXI 1 and IM-UNITI trials and limited details regarding the analysis were available.

6.25 The pre-PBAC response stated that attainment of endoscopic outcomes resulted in highly impactful benefits to patients and the health system including increased long term clinical remission, corticosteroid-free remission, reduced risk of hospitalisation and surgery and improved quality of life.

Indirect evidence for induction treatment: GUS versus other b/tsDMARDs

6.26 Table 9 presents a summary of the results from the indirect evidence (ITC and NMA) for induction treatment with GUS 200mg IV versus comparator b/tsDMARDs, in the ITT population (including biologic naïve and experienced patients). The outcomes presented included clinical remission and clinical response at Week 4-16. The table also includes direct results from the head-to-head trials (GALAXI 1, GALAXI 2 and GALAXI 3) extracted during the evaluation for comparison.

[8] Neff-Baro et al (2024). Endoscopic improvement at 1 year and association with long term disease outcome: a pooled clinical trial analysis in Crohn's Disease. Poster presented at UEG. October 12-15 2024

Table 9: Induction treatment: GUS 200mg IV (Wk 12) versus comparators (Wk 4-16) – direct and indirect comparisons (ITC and NMA)

	OR	RR	RD
Clinical remission			
vs GUS 400 mg SC (Wk12)	ITC (PBO): 0.91 (0.48, 1.74)	ITC (PBO): 1.01 (0.63, 1.62)	ITC (PBO): -0.04 (-0.16, 0.08)
vs UST (Wk8-12)	Direct (G1,2,3): 1.08 (0.80, 1.44) ITC (PBO): 1.48 (0.83, 2.61) NMA: 1.14 (0.89,1.46)	Direct (G1,2,3): 1.04 (0.89, 1.21) ITC (PBO): 1.17 (0.76, 1.82) NMA: 1.07 (0.94,1.21)	Direct (G1,2,3): 0.02 (-0.05, 0.09) ITC (PBO): **0.15 (0.04, 0.09)** NMA: 0.03 (-0.03, 0.09)
vs ADA (Wk4-16)	ITC (PBO): 0.98 (0.53,1.84) ITC (UST): 0.95 (0.58,1.57) NMA: 1.05 (0.72,1.51)	ITC (PBO): 0.79 (0.49,1.29) ITC (UST): 0.98 (0.79,1.22) NMA: 1.02 (0.85,1.25)	ITC (PBO): 0.1(-0.02,0.21) ITC (UST): -0.01(-0.13,0.1) NMA: 0.01 (-0.08,0.10)
vs VDZ (Wk6-10)	ITC (PBO): **2.65 (1.45, 4.87)** NMA: **1.99 (1.23,3.25)**	ITC (PBO): **1.73 (1.08, 2.77)** NMA: **1.5 (1.12,2.10)**	ITC (PBO): **0.26 (0.16, 0.35)** NMA: **0.16 (0.05,0.27)**
vs UPA (Wk12)	ITC (PBO): **1.83 (1.07, 3.12)** NMA: **1.55 (1.01,2.33)**	ITC (PBO): **1.52 (1.05, 2.2)** NMA: 1.27 (0.85,1.25)	ITC (PBO): **0.12 (0.02, 0.22)** NMA: 0.11 (0.00,0.20)
vs IFX (Wk4)	ITC (PBO): 0.21 (0.02, 1.83)	ITC (PBO): 0.23 (0.03, 1.68)	ITC (PBO): -0.13 (-0.35,0.09)
Clinical response			
vs GUS 400 mg SC (Wk12)	ITC (PBO): 1.03 (0.56, 1.89)	ITC (PBO): 1.2 (0.83, 1.72)	ITC (PBO): 0 (-0.12, 0.13)
vs UST (Wk8-12)	Direct (G1,2,3): 1.17 (0.89, 1.53) ITC (PBO): **2.16 (1.35, 3.45)** NMA: **1.34 (1.03, 1.72)**	Direct (G1,2,3): 1.06 (0.96, 1.18) ITC (PBO): **1.44 (1.06, 1.97)** NMA: **1.10 (1.01, 1.21)**	Direct (G1,2,3): 0.04 (-0.03, 0.1) ITC (PBO): **0.20 (0.09, 0.31)** NMA: **0.06 (0.01, 0.12)**
vs ADA (Wk4-16)	ITC (PBO): 1.8 (0.92, 3.51) ITC (UST): 1.23 (0.73, 2.07) NMA: **1.48 (1.04, 2.11)**[a]	ITC (PBO): 1.33 (0.93, 1.89) ITC (UST): 1.07 (0.91, 1.26) NMA: **1.15 (1.01, 1.33)**[a]	ITC (PBO): 0.14 (-0.01, 0.3) ITC (UST): 0.05 (-0.06, 0.16) NMA: **0.09 (0.01, 0.17)**[a]
vs VDZ (Wk6-10)	ITC (PBO): **3.93 (2.2, 7.03)** NMA: **2.56 (1.72, 3.85)**	ITC (PBO): **2.01 (1.34, 3.02)** NMA: **1.49 (1.23, 1.85)**	ITC (PBO): **0.33 (0.22, 0.45)** NMA: **0.22 (0.13, 0.32)**
vs UPA (Wk12)	ITC (PBO): **2.37 (1.5, 3.76)** NMA: **1.87 (1.26, 2.76)**	ITC (PBO): **1.61 (1.12, 2.21)** NMA: **1.27 (1.09, 1.53)**	ITC (PBO): **0.19 (0.1, 0.29)** NMA: **0.15 (0.05, 0.24)**
vs IFX (Wk4)	ITC (PBO): 0.26 (0.06, 1.16)	ITC (PBO): 0.54 (0.21, 1.39)	ITC (PBO): **-0.24 (-0.46, -0.02)**

The **bold** text indicates statistical significance p<0.05.
Risk statistics calculated using Review Manager (version 5.3).
Source: Tables 2.104 and 2.105, pp220-221, Tables 2.110 and 2.111, pp226-227, Tables 2.116 and 2.117, pp232-233, Tables 2.118 and 2.119, pp235-236, Tables 2.124 and 2.125, pp242-243, Tables 2.131 and 2.132, p249 of the submission, Attachment 2.34 Induction ITC inputs and results.xlsx.
ADA=adalimumab; GUS=guselkumab; IFX=infliximab; ITC=indirect treatment comparison; IV=intravenous; NMA=network meta-analysis; PBO=placebo; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; wk=week;

6.27 For induction treatment (i.e. Week 4-12), the indirect evidence showed:

- no difference between the GUS IV and GUS SC dosing regimens in terms of clinical remission or clinical response.
- no difference between GUS versus ADA and IFX in terms of clinical remission or clinical response, with one exception: the NMA indicated GUS was more effective than ADA in terms of clinical response, but this finding was not supported by the ITC using either PBO or UST as the common comparator.
- no difference between GUS versus UST in terms of clinical remission but GUS was more effective than UST in terms of clinical response. However, the results of the indirect evidence differed from the direct head-to-head evidence, which showed no difference between GUS versus UST for either outcome. The magnitude of the treatment effects (point estimates) estimated from the direct and indirect

evidence also varied greatly.

- GUS was more effective than VDZ and UPA for both clinical remission and clinical response, with one exception: the NMA generally indicated no difference between GUS versus UPA in terms of clinical remission.

Indirect evidence for maintenance treatment: GUS versus other b/tsDMARDs

6.28 The submission argued that conducting indirect comparisons between GUS versus the other comparators (ADA, IFX, VDZ and UPA) based on the reported results of the maintenance phase trials would be biased against GUS because the PBO arms are not interchangeable due to differences in trial design. Patients in the PBO arm of treat-through trials represented a 'true placebo' comparator whereas patients in the PBO arm of randomised withdrawal trials had 'carry-over' benefits of active induction treatment. Patients who responded to PBO induction treatment and continue PBO in maintenance were also likely to be different from patients who respond to active induction treatment and receive PBO in maintenance in terms of their underlying probability of spontaneous resolution. The submission noted that the PBO response rate in the GALAXI trials at Week 48 (including those who crossed over to UST at Week 12) was higher than the randomised withdrawal comparator trials.

6.29 The PBAC had previously accepted that carry over effects were plausible and would likely bias against active treatment in a randomised withdrawal trial when indirectly compared to active treatment in a Type 1 treat-through trial using PBO as common comparator (paragraph 7.9, ustekinumab PSD July 2022 PBAC meeting). In contrast, this submission argued that active treatment in a Type 2 treat through trial would be biased against when indirectly compared to active treatment in a randomised withdrawal trial using PBO as common comparator. This bias would not be from carry over effects, but rather the fact that patients in the PBO arm in the GALAXI trials received PBO induction followed by PBO or UST maintenance treatment, whereas patients in the PBO arm of the randomised withdrawal trials received active induction followed by PBO maintenance.

6.30 Given the differences in the trial designs, the submission argued that it was appropriate to impute / model all of the trial data to mimic a 'Type 1' treat-through design, using a similar approach presented in the UST July 2022 PBAC submission for ulcerative colitis. This involved modelling the (i) 'missing' PBO data in the GUS trials (given the PBO arm had a Type 2 trial design), and (ii) 'missing' PBO/active data in the comparator trials (Types 2, 3 and 4 trial designs). For Type 3 and Type 4 randomised withdrawal trials (GEMINI II, U-ENDURE and Watanabe 2012), the submission also recalculated the intention-to-treat (ITT) sample sizes for the active treatment arm to replicate the population from induction baseline, as these trials re-randomised patients who achieved response from active treatment at induction. The submission then conducted ITCs and NMA based on the imputed / modelled trial data.

6.31 The results of the 'trial-design-adjusted' ITCs and NMA – based on imputed data - found that GUS was more effective than all other b/tsDMARDs for one or more of the

outcomes presented (clinical remission, clinical response, endoscopic remission, endoscopic response) at Week 48-60. The submission argued that any non-statistically significant findings versus ADA and UPA using the RR statistic were due to the non-symmetric nature of the variance of the log RR, and this comparison became statistically significant using non-responder results.

6.32 The submission did not provide a clear rationale for selecting the many different data sources used to inform the required parameters of the proposed imputation / modelling approach. For example, for the GALAXI trials it was unclear the rationale to impute the proportion of PBO induction non-responders achieving clinical remission and clinical response outcomes in maintenance using the PBO clinical remission rates at induction from the GEMINI II (VDZ) trial. Whereas the same parameter (PBO induction non-responders) achieving endoscopic outcomes was calculated using the pooled PBO clinical response rates from the GALAXI trials (response defined by CDAI) and VIVID-1 (mirikizumab) and FORTIFY (risankizumab) trials (response defined by decrease in stool frequency and/or abdominal pain), which are also non-PBS treatments that have been excluded from the submission's 'Australian' NMA.

6.33 Overall, the submission's approach for adjusting carry over effects was poorly described, not transparent, relied on many assumptions that cannot be validated, ignores the many other differences (transitivity assumptions) across the trials. In general, methods used for treatment effect elicitation should be as simple as possible, and any benefit (i.e. reduction in uncertainty) from using complex methods must be balanced against any loss of transparency, interpretability and validation. The ESC had previously considered that the same or similar modelling approach presented in the ustekinumab submission for ulcerative colitis "introduced additional uncertainties in the indirect comparisons" and "the reliability of the modelled approach to address the issue was uncertain" (paragraph 6.38, ustekinumab PSD July 2022 PBAC meeting).

6.34 The results of the submission's trial-design-adjusted indirect comparisons (ITC and Australian NMA) are considered highly uncertain (noting that the magnitude of the treatment effects varied considerably) and could not be externally validated:

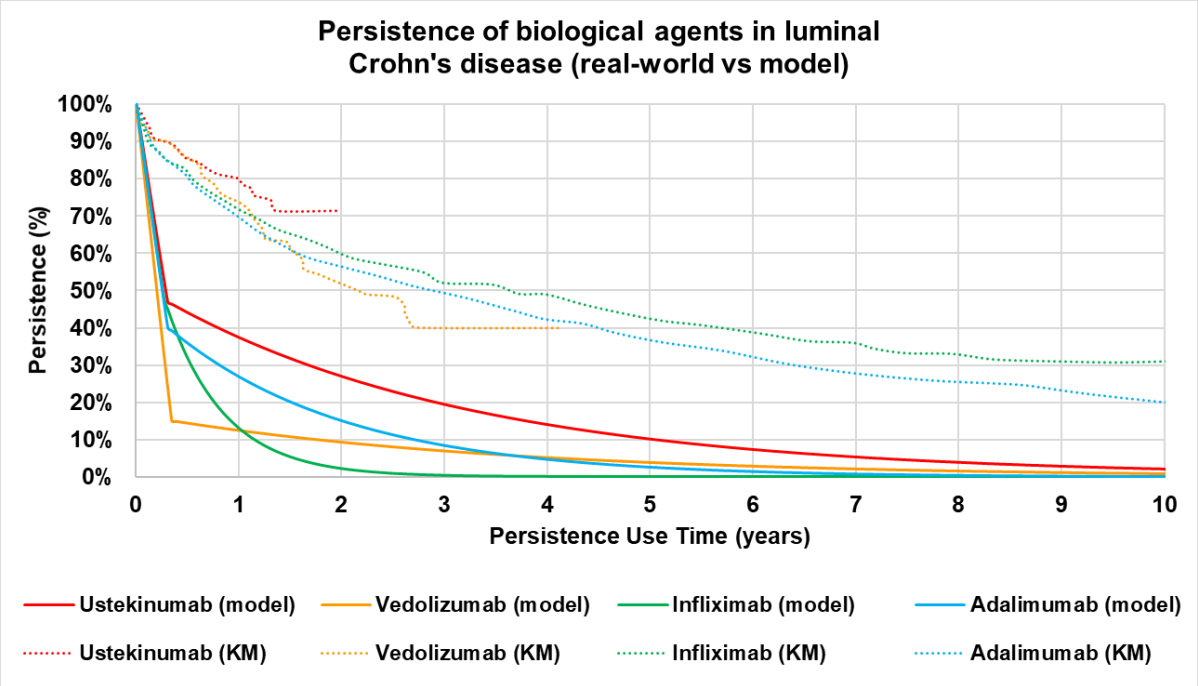
- First, the imputed results for some comparator trials (such as ACCENT 1, Watanabe 2012 and GEMINI II) indicated no difference between active treatment and PBO despite the observed results finding a statistically significant difference favouring active treatment compared to PBO.
- Second, some results of the indirect comparisons between GUS versus UST using the imputed data differed from the direct results between GUS versus UST observed in the head-to-head GALAXI trials (e.g. the NMA found GUS 200 mg SC was superior to UST 90 mg Q8W in terms of clinical remission, but the direct evidence showed no difference).
- Third, the results of the indirect comparisons between GUS versus ADA based on the imputed data (PBO as common comparator) differed from the results of the indirect comparisons between GUS versus ADA based on observed data in the GALAXI trials and SEAVUE (UST as the common comparator), which generally

showed no difference between the treatments. The indirect comparison between GUS and ADA, using UST as the common comparator, without the need for any adjustment/imputation of data, was considered more reliable.

- Finally, the results of the adjusted/imputed analysis implied large differences between the comparator b/tsDMARDs in terms of continuation rates, but real-world data shows no or negligible differences between continuation /persistence rates in practice (see below). In addition, the submission acknowledged (p384 of the submission) that the PBAC had previously determined that the comparators are non-inferior to each other based on data at Week 48.

6.35 Figure 2 illustrates the estimated proportion of patients on treatment in the modelled economic evaluation – based on the proportion of patients with clinical remission estimating using the results of the trial-design-adjusted NMA – was much lower compared to the proportion of patients who remain on treatment in Australian practice, as reported in Ko 2021[9].

Figure 2: Treatment continuation (persistence) in the model compared to real-world evidence (Ko 2021).



Source: generated during the evaluation from Ko 2021 and Attachment 3.1 Guselkumab CD Economic Model.xlsx.

6.36 The PSCR stated that lack of direct head-to-head trials comparing GUS to any treatments other than ustekinumab, as well as variation in patient populations and clinical trial designs (e.g., treat through vs. re-randomization trials), make cross-trial comparison very challenging. The PSCR acknowledged that there is an inherent

[9] Ko Y, Paramsothy S, Yau Y, Leong RW. Superior treatment persistence with ustekinumab in Crohn's disease and vedolizumab in ulcerative colitis compared with anti-TNF biological agents: real-world registry data from the Persistence Australian National IBD Cohort (PANIC) study. Aliment Pharmacol Ther. 2021 Aug;54(3):292-301. doi: 10.1111/apt.16436.

amount of uncertainty associated with such imputation modelling techniques due to the adjusted (imputed) comparator data used in some of the maintenance phase comparisons. However, the PSCR reiterated that comparisons on unadjusted maintenance data would be highly biased against GUS and unreliable for decision-making due to the notable heterogeneities in trial design.

Comparative harms

6.37 Table 10 summarises the AEs reported in the GALAXI trials for induction and maintenance treatment, comparing safety outcomes with GUS and UST.

Table 10: Summary of AEs in the pooled GALAXI 1, GALAXI 2 and GALAXI 3 trials for induction and maintenance treatment with GUS and UST

AEs, n/N (%)	Induction (Week 12)			Maintenance (Week 48)		
	GUS IV	UST	PBO	GUS 100	GUS 200[a]	UST
Any AE	306/655 (46.7)	171/362 (47.2)	113/218 (51.8)	271/359 (75.5)	340/442 (76.9)	289/362 (79.8)
Grade ≥3 AEs	21/655 (3.2)	13/362 (3.6)	9/218 (4.1)	23/359 (6.4)	33/442 (7.5)	32/362 (8.8)
Serious AEs	19/655 (2.9)	20/362 (5.5)	13/218 (6.0)	36/359 (10.0)	31/442 (7.0)	43/362 (11.9)
Discontinuation due to AEs	12/655 (1.8)	8/362 (2.2)	9/218 (4.1)	25/359 (7.0)	27/442 (6.1)	28/362 (7.7)
Serious infection	1/655 (0.2)	*6/362 (1.7)*	0	*3/359 (0.8)*	*5/442 (1.1)*	*13/362 (3.6)*
Death	0	0	0	0	0	0

Source: Table 2.95, p206, Table 2.97, p209, Tables 2.136 and 2.137pp270-272 of the submission, Attachment 2.33 GALAXI GUS vs UST – meta-analyses.xlsx, Attachment 2.34 Induction ITC inputs and results.xlsx.

AE=adverse event; GUS=guselkumab; IV=intravenous; PBO=placebo; UST=ustekinumab; QxW=every x week;

a The submission pooled patients from GALAXI 1, where patients on GUS 200 mg Q4W maintenance received either GUS 600 mg IV or GUS 1200 mg IV as induction, which was inconsistent with the draft TGA PI and induction doses in GALAXI 2 and GALAXI 3 (GUS 200 mg IV).

6.38 Overall, the incidence of AEs was generally similar between GUS, UST and PBO for induction and maintenance therapy across GALAXI 1, GALAXI 2 and GALAXI 3, with few patients experiencing serious or severe AEs. More patients treated with PBO experienced serious AEs or discontinuation due to AEs (mostly attributed to worsening CD) during induction and maintenance. The most commonly reported AEs were infections and gastrointestinal disorders. Safety data reported in the GALAXI trials were consistent with the safety profile of GUS in its approved indications. Based on the direct evidence, the submission claimed that GUS was non-inferior to UST in safety.

6.39 For comparison of safety outcomes versus other b/tsDMARDs (ADA, IFX, UPA and VDZ), the submission presented an ITC (using Bucher method) at Week 4-16 based on safety data reported in the induction phase trials and an unanchored (naïve) ITC at Weeks 48-60 based on safety data reported in the maintenance phase trials. The submission stated that an unanchored (naïve) comparison was used for safety outcomes in maintenance treatment due to the high proportion of induction non-responders in PBO that crossover to UST maintenance treatment, and therefore, the duration of PBO exposure was less than the trial duration follow-up of 48 weeks.

6.40 Overall, the proportions of patients experiencing AEs with GUS appeared to be generally comparable to other b/tsDMARDs for induction and maintenance treatment. The submission noted that the results of the unanchored ITC statistically

favoured GUS over some of the comparator treatment for some outcomes, including versus IFX in terms of serious AEs and AEs leading to discontinuation. These findings were considered uncertain and potentially unreliable, given that the submission's approach does not account for differences between the trials (e.g. populations, concomitant therapies) or the duration of treatment follow-up, and none of the trials were powered to detect differences in safety outcomes. In the July 2023 meeting, the PBAC considered the claim of non-inferior comparative safety of UPA to the nominated comparators (all b/tsDMARDs for CD) was, on balance, likely to be reasonable (paragraph 7.6, upadacitinib PSD July 2023 PBAC meeting).

6.41 The ESC noted the submission claimed superiority to IFX in terms of safety based on an unadjusted (naïve) comparison in the maintenance phase, based on serious AEs and AEs leading to discontinuation. The ESC noted the data for IFX was published in 2002 and most of the AEs were related to infusion reactions. The ESC noted that contemporary evidence demonstrates significantly reduced incidence of infusion reactions with IFX, likely due to improved infusion protocols and greater understanding of infusion reactions with biological medicines.

Benefits/harms

6.42 The indirect nature of the comparisons and exchangeability issues with the clinical trials presented in the submission did not allow for a reliable comparison of the benefits and harms of GUS vs comparators. Overall, on the basis of direct evidence, there were no expected clinically meaningful differences in terms of efficacy or safety between GUS and UST (and by extension to the other nominated comparators, given the PBAC had previously accepted non-inferior effectiveness and safety between all of the nominated comparators), in the treatment of adults with severe CD.

Clinical claim

6.43 In patients with severe CD, the submission described GUS as superior compared to all currently PBS-listed b/tsDMARDs (ADA, IFX, UST, UPA and VDZ) in terms of effectiveness based on maintenance outcomes at Week 48-60. In terms of safety, the submission described GUS as superior compared to IFX and non-inferior compared to ADA, UST, UPA and VDZ. The submission also described GUS IV and GUS SC induction dosing regimens as being non-inferior in terms of efficacy and safety.

6.44 The ESC considered the clinical claim of non-inferior efficacy and safety between the GUS IV and GUS SC induction dosing regimens was reasonably supported by the evidence presented in the submission.

6.45 The ESC considered the clinical claim of superior efficacy versus all PBS-listed b/tsDMARDs (ADA, IFX, UST, UPA and VDZ) was not adequately supported by the evidence presented in the submission:

- First, the submission's claim was based on maintenance outcomes at Week 48-60 for patients who remained (or assumed to remain) on treatment irrespective of response to induction treatment - including clinical remission, clinical response,

endoscopic remission and endoscopic response - which are not the relevant patient outcomes for maintenance treatment on the PBS. As patients can only access maintenance treatment on the PBS after achieving clinical remission following induction treatment, the most relevant outcome for maintenance treatment is clinical response at Week 48 in patients with clinical response at Week 12.

- Second, for comparison between GUS versus UST in the maintenance setting, the submission relied on the results of the head-to-head evidence from the GALAXI trials, which demonstrated no difference between GUS and UST for the patient relevant outcome clinical remission at Week 48 in patients with clinical remission at Week 12. Although, the direct evidence generally showed that GUS was superior to UST in terms of the proportion of patients with endoscopic remission and endoscopic response at Week 48 (in all randomised patients), the PBAC had not previously used these outcomes to establish therapeutic relativities between treatments for CD.
- Third, for comparison between GUS versus ADA, IFX, UPA and VDZ in the maintenance setting, the submission relied on the results of 'trial-design-adjusted' indirect comparisons (ITCs and the Australian NMA), which produced highly uncertain and likely misleading results. The submission's methodological approach for adjusting/imputing/modelling data for each trial - which attempted to mimic results at Week 48-60, assuming patients remained on treatment irrespective of response to induction treatment, was inappropriate and likely increased uncertainty (i.e. not fit-for-purpose). In short, the approach lacked transparency, relied on many assumptions that cannot be validated, and ignored the many other differences across the trials and enrolled populations. The results produced by the trial-design-adjusted indirect comparisons did not align with other unadjusted data sources (refer above) and should not be relied upon to establish clinical superiority.

6.46 The ESC considered the claim of non-inferior safety versus ADA, UST, UPA and VDZ was reasonable, but the submission's claim of superior safety versus IFX was not adequately supported by the evidence presented in the submission. The claim of superior safety versus IFX was based on the results of naïve unanchored indirect comparisons at Week 48-60 that favoured GUS for some safety outcomes (serious AEs, discontinuation due to AEs, infections). Additionally, the ESC noted the understanding and management of the infusion reactions for IFX has evolved over time (see paragraph 6.41). These conclusions should be interpreted with caution given that the unanchored comparisons do not account for differences between the trials, patient populations, or duration of treatment follow-up; and none of the trials were powered to detect differences in safety outcomes (based on small numbers). Overall, the proportions of patients experiencing AEs with GUS appeared to be generally comparable to other b/tsDMARDs for induction and maintenance treatment.

6.47 The evaluation considered a claim of non-inferior efficacy and safety versus ADA, IFX, UST, UPA and VDZ may be more reasonable given that: direct evidence showed no difference between GUS and UST for induction and maintenance treatment (with the

exception of endoscopic outcomes at Week 48); the indirect evidence without data manipulation showed no difference between GUS versus ADA, IFX, UPA and VDZ for induction treatment; and the indirect evidence without data manipulation showed no difference between GUS versus ADA for maintenance treatment. The ESC noted the direct evidence suggested statistically significant improved endoscopic outcomes versus UST but the impact on patient outcomes is unclear.

6.48 The PBAC considered that a claim of superior comparative effectiveness versus UST based on endoscopic outcomes at Week 48 was supported by the clinical trial evidence presented in the submission. However, the clinical relevance of this outcome was uncertain given there was no difference between GUS and UST for the patient relevant outcome of clinical remission at Week 48 in patients with clinical remission at Week 12.

6.49 The PBAC considered that the claim of non-inferior comparative safety versus all other b/tsDMARDs was reasonable but the claim of superior safety to IFX was not adequately supported by the data.

Economic analysis

6.50 The submission presented a cost-utility analysis comparing GUS (GUS 200 mg Q4W and GUS 100 mg Q8W separately) versus a weighted comparator of other b/tsDMARDs, informed by the direct and indirect evidence presented in the submission and parameters from the literature. The main treatment effect in the model was derived from the trial-design-adjusted Australian NMA for maintenance treatment.

6.51 Overall, the ESC considered the modelled economic evaluation presented in the submission was largely uninformative for decision-making, given that the trial-design-adjusted Australian NMA was considered unreliable and the other clinical evidence on balance indicated that GUS was comparable to other b/tsDMARDs in terms of effectiveness. In addition, a major programming error was identified during the evaluation, which miscounted the total number of QALYs for patients in remission on subsequent lines of treatment. After correcting this programming error, the base case ICER for GUS 100 mg increased by [redacted]% (from $25,000 to < $35,000/QALY to $75,000 to < $95,000/QALY) and the base case ICER for GUS 200 mg increased by [redacted]% (from $15,000 to < $25,000/QALY to $55,000 to < $75,000 /QALY).

6.52 Key components of the economic evaluation are summarised in Table 11.

Table 11: Key components of the economic evaluation

<table>
<tr><th>Component</th><th>Summary</th></tr>
<tr><td>Type of analysis</td><td>Cost-utility analysis</td></tr>
<tr><td>Outcomes</td><td>Life years (LYs) gained, quality-adjusted life years (QALYs) gained</td></tr>
<tr><td>Time horizon</td><td>10 years vs 48 weeks in GALAXI trials.</td></tr>
<tr><td>Methods used to generate results</td><td>Induction period: decision-tree.
Maintenance (post-induction) period: Markov model.</td></tr>
<tr><td>Health states</td><td>Clinical remission (CDAI <150), Clinical remission with endoscopic response (CDAI <150 and ≥ 50% improvement from baseline in the SES-CD or SES-CD score ≤ 2), Clinical remission without endoscopic response, Active Crohn's disease (CDAI ≥ 150), and Death.
In general, the health states were consistent with published models in CD, which include health states based on response or non-response and disease activity (mild, moderate-severe). However, none of the models in the literature split the clinical remission health state into those with and without endoscopic response.</td></tr>
<tr><td>Cycle length</td><td>2 weeks</td></tr>
<tr><td>Transition probabilities</td><td>- Proportion of patients with clinical remission at the end of induction treatment, based on an unanchored (naïve)comparison of the active treatment arms in the induction phase trials.
- Loss of clinical remission after the induction period per cycle, calculated assuming an exponential discontinuation rate based on the proportion of patients who maintain clinical remission between the end of induction and Week 48-60. The proportion of patients in clinical remission at Week 48-60, conditional on clinical remission at the end of induction, was estimated from the proportion of patients with sustained clinical remission in the GALAXI trials and results of the trial-design-adjusted NMA in terms of clinical remission at Week 48-60.
- From Week 48, the proportions of patients in sustained remission with and without endoscopic response were derived from post-hoc analysis from GALAXI 2 and GALAXI 3.
- The proportions of patient with loss of clinical remission that move to subsequent treatment with b/tsDMARDs (2L and 3L) or conventional therapy were estimated from the sponsor commissioned analysis of 10% PBS data by Prospection. A number of parameters for subsequent treatments could not be verified from the Prospection report. It was also unclear whether assuming different subsequent treatment options and uptakes was reasonable, given that the assumptions favoured GUS.
- All-cause mortality (life tables)</td></tr>
<tr><td>Utilities</td><td>Health state utilities for remission (before Week 48) and active CD based on AQoL values reported in Gibson 2007. Utilities for clinical remission with/without endoscopic response were calculated using the ratio of EQ-5D values for remission with/without endoscopic remission reported in Danese 2019 to overall EQ-5D value for remission multiplied by the AQoL utility for remission and Danese 2019.
<table>
<tr><th>Health State</th><th>Modelled utility values</th></tr>
<tr><td>Remission (before Week 48)</td><td>0.766</td></tr>
<tr><td>Remission with endoscopic response (after Week 48)</td><td>0.820</td></tr>
<tr><td>Remission without endoscopic response (after Week 48)</td><td>0.748</td></tr>
<tr><td>Active disease</td><td>0.450</td></tr>
</table>
The ICER was sensitive to alternative utility values. Using the EQ-5D-5L scores from Danese 2019 (remission: 0.85, remission with endoscopic response: 0.91, remission without endoscopic response: 0.83 and active disease: 0.75), increased the ICER by [redacted]% from the corrected base case. The submission did not present the utility values from the GALAXI trials by clinical remission. However, the GALAXI trials indicated that there was no difference between GUS and UST in the change from baseline in EQ-5D-5L index score (all domains) and EQ-5D-VAS at Week 12 and Week 48.</td></tr>
</table>

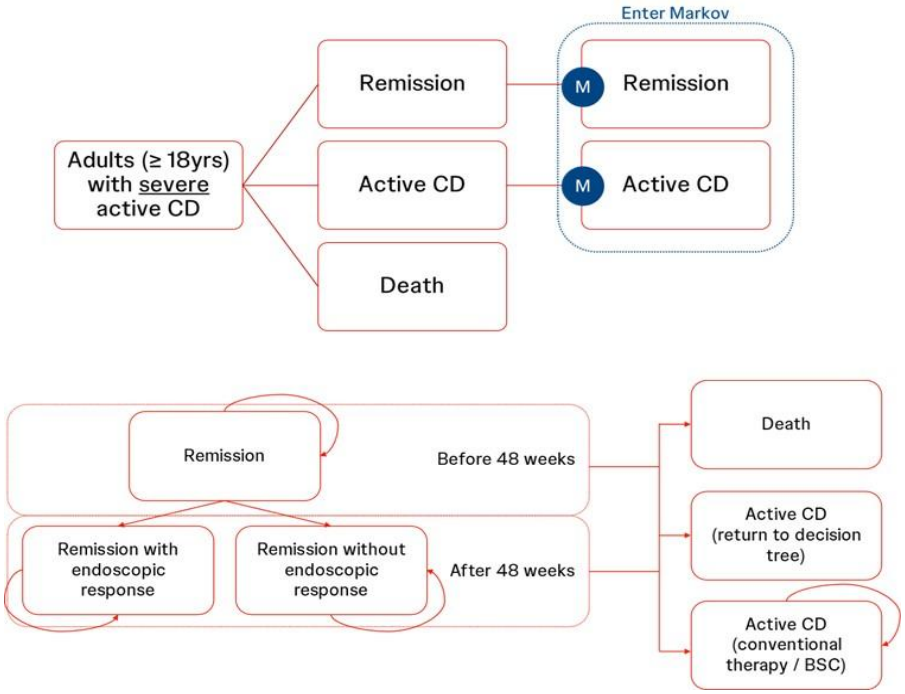
Component	Summary
Costs	The model included drug costs for GUS and comparator b/tsDMARDs (ADA, IFX, UPA, UST and VDZ), drug costs for conventional therapy (azathioprine, 6-mercaptopurine, methotrexate, prednisone, budesonide and 5-aminosalicylate), drug (IV) administration cost, medical services (GP, specialist visits, ED and hospitalisation). Some minor inconsistencies were noted between the dosing used in the model, PI, clinical trials and financial estimates. For example, the model included two induction doses of IFX 5 mg/kg IV at Week 0 and 2, whereas the financial estimates included three induction doses of IFX 5 mg/kg IV at Week 0, 2 and 6. Treatment with IFX IV on the PBS is a total of 3 doses to be administered at Weeks 0, 2 and 6. Further, there appeared to be a programming error in the price of VDZ IV per quantity. The submission assumed VDZ IV pricing quantity of 2 (i.e. price per quantity was $[redacted] / 2 = $[redacted]). This error marginally favoured GUS but was not corrected during the evaluation.
Software package	Excel

Source: Table 3.1, p373 of the submission.
ADA=adalimumab; CD=Crohn's disease; CDAI=CD activity index; ED=emergency department; GUS=guselkumab; IFX=infliximab; IV=intravenous; UST=ustekinumab; SC=subcutaneous; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab;

6.53 The submission modelled seven unique scenarios, whereby patients could receive up to three lines of b/tsDMARDs followed by conventional therapy. In the two 'intervention' scenarios, GUS 100 mg Q8W or GUS 200 mg Q4W were modelled as the index treatment, followed by IFX (second-line) and VDZ (third-line). In the other five 'comparator' scenarios, each of the current PBS-listed b/tsDMARDs were modelled as the index treatment followed by other b/tsDMARDs as second- and third-line treatments based on current market trends (refer below). The model was highly sensitive to the assumed treatment sequence of GUS; scenario analyses conducted during the evaluation assuming GUS is used as second-line treatment or third-line treatment increased the ICER by [redacted]-[redacted]%.

6.54 The submission used a hybrid decision tree (for first induction only) and Markov model to evaluate the costs and benefits of the different scenarios. The model included five health states: (i) clinical remission (CDAI <150), (ii) clinical remission with endoscopic response (CDAI <150 and ≥ 50% improvement from baseline in the SES-CD or SES-CD score ≤ 2), (iii) clinical remission without endoscopic response, (iv) active Crohn's disease (CDAI ≥ 150), and (v) dead. Figure 3 presents the structure of the model.

Figure 3: model structure of the economic evaluation.



Source: Figure 3.2, p380 of the submission.
BSC=best supportive care; CD=Crohn's disease;

6.55 All patients entered the model with active CD and received active induction treatment with a b/tsDMARD. Patients who achieve clinical remission following induction treatment transition to the remission health state and remain on maintenance treatment with the same b/tsDMARD until loss of clinical remission or death. Following 48 weeks of sustained clinical remission, the model partitions those in the remission health state into those with endoscopic response and without endoscopic response. Patients who do not achieve clinical remission following induction treatment and patients who stop responding to maintenance treatment, remain in or transition to the active CD health state, and receive either subsequent induction treatment with an alternative b/tsDMARD or conventional therapy. Following induction treatment with a subsequent b/tsDMARD (which is modelled as a tunnel state), patients who achieve clinical remission after the induction period either remain on treatment until loss of remission or death, identical to the first-line treatment pathway. Patients treated with conventional therapy remain on treatment in the active CD health state for the remainder of the model or until dead.

6.56 Table 12 summarises the key transition probabilities applied in the model, with the same transition probabilities applied for each b/tsDMARD irrespective of the line of therapy. The submission estimated treatment differences between the b/tsDMARDs in terms of:

(i) the probability of clinical remission at the end of induction, based on the (unanchored) average rates observed in the induction phase trials.

(ii) the probability of loss of remission per cycle (post induction), based on the GALAXI trials for GUS and UST and the trial-design-adjusted Australian NMA (and other assumptions) for ADA, UPA, IFX, VDZ.

(iii) the probability of clinical remission with/without endoscopic response (post-48 weeks of maintenance), based on a post-hoc analysis of the GALAXI trials.

(iv) the probability of initiating subsequent second-line and third-line b/tsDMARD treatment, based on an analysis of the 10% PBS sample (and other assumptions).

Table 12: Summary of transition probabilities applied in the model

Index (1L)	Probability of remission at the end of induction (Week 12-18)	Probability of loss of remission per cycle (2 weeks) post induction period	Clinical remission with endoscopic response, post-48 weeks of maintenance period	% 1st subsequent therapy (2L)	% 2nd subsequent therapy (3L)
GUS 100	48.06%	0.85%	67.54%	IFX: 80.6%	VDZ: 87.4%
GUS 200	48.06%	0.71%	66.13%	IFX: 80.6%	VDZ: 87.4%
ADA	40.18%	2.18%	56.25%	UST: 80.3%	VDZ: 75.6%
IFX	48.15%	6.63%	56.25%	ADA: 82.8%	UST: 91.1%
UPA	44.36%	3.12%	56.25%	VDZ: 92.2%	UST: 100%
UST	46.89%	1.25%	56.25%	IFX: 79.3%	VDZ: 91.7%
VDZ	15.18%	1.10%	56.25%	UST: 78.1%	ADA: 86.8%

.
Source: Table 3.7, p384 of the submission, Attachment 3.1 Guselkumab CD Economic Model.xlsx.
ADA=adalimumab; GUS=guselkumab; IFX=infliximab; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; 1L=first-line (index) treatment; 2L=second-line treatment; 3L=third-line treatment;

6.57 There were a number of concerns with the derivation of the transition probabilities applied in the model.

- First, the submission did not provide any justification for modelling the observed (unanchored) average rates of clinical remission in the active treatment arms of the induction phase trials without any adjustment for differences between the trials. This assumption favoured GUS compared to either (i) deriving the comparative treatment effects from the induction NMA or (ii) simply assuming no difference between treatments.
- Second, the submission's approach for estimating the loss of clinical remission parameter was considered highly uncertain and was not externally valid – with a much higher proportion of patients remaining on treatment in practice than assumed in the model as well as similar discontinuation rates observed for the comparator b/tsDMARDs (refer to Figure 2). Not only did the submission use the treatment effects derived from the trial-design-adjusted Australian NMA (which was considered unreliable) but also made further assumptions to convert the estimated treatment effects in terms of clinical remission at Weeks 48-60 irrespective of induction response into the required outcome of clinical remission at Weeks 48-60 in patients with clinical remission following induction treatment.

- Third, the proportion of patients who maintained clinical remission with endoscopic response assumed throughout the model was based on a post-hoc analysis at one time point in the GALAXI trials between GUS versus UST and an assumption that the same treatment benefit would also apply to other comparators (in the absence of evidence).
- Finally, the submission provided no clinical rationale for why there would be causal difference in the probability of receiving subsequent treatment with a b/tsDMARD depending on prior b/tsDMARD (and the assumed differences could not be verified from the source material). The model, however, was not particularly sensitive to these assumed differences.

6.58 The key drivers are summarised in the table below.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case (corrected): $ [redacted][1] /QALY gained (GUS 100) $ [redacted][2] /QALY gained (GUS 200)
Loss of remission (treatment discontinuation)	Loss of clinical remission based on naïve clinical remission rate at the end of the induction period in the model (i.e. Week 12-18) and the proportion of patients estimated to maintain clinical remission at Week 48 from the clinical evidence (trial-design-adjusted NMA).	High, favoured GUS
Utilities	AQoL utility values for remission (before Week 48) and active CD (Gibson 2007), and EQ-5D-5L utility values from remission with/without remission (Danese 2019) 'adjusted' to AQoL utilities for remission from Gibson 2007 for the modelled remission with/without response (after Week 48).	Moderate, favoured GUS
b/tsDMARD sequence	Base case: 1L (index) GUS, 2L IFX, 3L VDZ)	High, favoured GUS
Time horizon	10 years	Moderate, favoured GUS

Source: compiled during the evaluation.
GUS=guselkumab; IFX=infliximab; QALY=Quality Adjusted Life Year; 1L=first-line (index) treatment; 2L=second-line treatment; 3L=third-line treatment; VDZ=vedolizumab;
The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*
[2] *$55,000 to < $75,000*

6.59 Table 14 summarises the results of the economic evaluation based on the estimated effective prices presented in the submission. The table includes the submission's base case (as presented in the submission), the submission's base case (after correcting for the programming error), and scenario analyses assuming the use of GUS in the second- and third-line settings (after correcting for the programming error).

Table 14: **Results of the economic evaluation (discounted 5%)**

Component	GUS 100 vs weighted comparator			GUS 200 vs weighted comparator		
	GUS 100	Comparator[a]	Increment	GUS 200	Comparator[a]	Increment
Base case ([redacted], 2L IFX, 3L VDZ[b] vs weighted comparator; submission's base case)						
Costs	$[redacted]	$182,627	$[redacted]	$[redacted]	$182,627	$[redacted]
QALYs	4.048	3.555	0.493	4.116	3.555	0.561
Incremental cost/QALY gained	$[redacted][1]			$[redacted][2]		
Base case ([redacted], 2L IFX, 3L VDZ[b] vs weighted comparator; programming error corrected)						
Costs	$[redacted]	$182,627	$[redacted]	$[redacted]	$182,627	$[redacted]
QALYs	4.249	4.095	0.154	4.310	4.095	0.215
Incremental cost/QALY gained	$[redacted][3]			$[redacted][4]		
Scenario analysis (1L IFX, [redacted], 3L VDZ[b] vs weighted comparator; programming error corrected)						
Costs	$[redacted]	$182,627	$[redacted]	$[redacted]	$182,627	$[redacted]
QALYs	4.160	4.095	0.065	4.208	4.095	0.113
Incremental cost/QALY gained	$[redacted][5]			$[redacted][6]		
Scenario analysis (1L IFX, 2L VDZ[b], [redacted] vs weighted comparator; programming error corrected)						
Costs	$[redacted]	$182,627	$[redacted]	$[redacted]	$182,627	$[redacted]
QALYs	4.108	4.095	0.012	4.147	4.095	0.051
Incremental cost/QALY gained	$[redacted][7]			$[redacted][5]		

Source: Table 2.38, pp405-406 of the submission and Attachment 3.1 Guselkumab CD Economic Model.xlsx.

ADA=adalimumab; GUS=guselkumab; IFX=infliximab; QALY=Quality Adjusted Life Year; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; 1L=first-line (index) treatment; 2L=second-line treatment; 3L=third-line treatment;

a comparators (ADA, IFX, UPA, UST and VDZ) weighted by market share

b The submission incorrectly derived the VDZ IV unit price assuming a pricing quantity of 2 instead of 1 (i.e. price per quantity was $[redacted] / 2 = $[redacted]). The error marginally favoured GUS but was not corrected during the evaluation.

The redacted values correspond to the following ranges:

[1] *$25,000 to < $35,000*

[2] *$15,000 to < $25,000*

[3] *$75,000 to < $95,000*

[4] *$55,000 to < $75,000*

[5] *$155,000 to < $255,000*

[6] *$95,000 to < $115,000*

[7] *$855,000 to < $955,000*

6.60 Based on the uncorrected base case analysis, the submission stated that GUS was cost-effective compared to the nominated comparators for severe CD given the ICERs were less than $25,000 to < $35,000/QALY gained. After correcting for the programming error identified during the evaluation, the base case ICERs increased substantially above the nominated $25,000 to < $35,000/QALY threshold. Similarly, assuming second-line or third-line use of GUS also further substantially increased the ICER.

6.61 Table 15 presents the results of key sensitivity analyses conducted during the evaluation, illustrating the incremental effect on the ICER of the modelled treatment effects. The multivariate analysis illustrates that the ICER was driven by the modelled differences in the loss of remission parameter, as well as the combined effects of other parameter differences favouring GUS. The base case analysis was also sensitive to the time horizon, health state utilities and health service costs (the results are not presented in the table).

Table 15: Results of sensitivity analyses on corrected base case – GUS 100 and GUS 200 vs comparator (weighted)

	GUS 100 vs weighted comparator[ah]			GUS 200 vs weighted comparator[aj]		
Analyses	**Incremental cost**	**Incremental QALY**	**ICER**	**Incremental cost**	**Incremental QALY**	**ICER**
Base case (1L GUS; programming error corrected)	$[redacted]	**0.154**	$[redacted][1]	$[redacted]	**0.215**	$[redacted][2]
Univariate sensitivity analysis						
(A) Induction remission parameter: % achieving clinical remission set to GUS (48.06%) for all b/tsDMARDs[b]	$[redacted]	0.157	$[redacted][1]	$[redacted]	0.213	$[redacted][2]
(B) Loss of remission input 1: % with clinical remission at Week 48 set to GUS for all b/tsDMARDs[c]	$[redacted]	0.076	$[redacted][3]	$[redacted]	0.080	$[redacted][3]
(C) Loss of remission input 2: loss of response time period set to GUS (36 weeks) for all b/tsDMARDs[f]	$[redacted]	0.114	$[redacted][4]	$[redacted]	0.175	$[redacted][1]
(D) Subsequent conventional therapy 2L parameter: set to GUS (19.4%) for all b/tsDMARDs[d]	$[redacted]	0.155	$[redacted][1]	$[redacted]	0.216	$[redacted][2]
(E) Subsequent conventional therapy 3L parameter: set to GUS (12.6%) for all b/tsDMARDs[e]	$[redacted]	0.144	$[redacted][5]	$[redacted]	0.205	$[redacted][2]
(F) Endoscopic response parameter: set to GUS for all b/tsDMARDs[g]	$[redacted]	0.146	$[redacted][1]	$[redacted]	0.208	$[redacted][2]
Multivariate analyses						
(A)+(B)	$[redacted]	0.059	$[redacted][6]	$[redacted]	0.060	$[redacted][6]
(A)+(B)+(C)	$[redacted]	0.022	$[redacted][7]	$[redacted]	0.023	$[redacted][7]
(A)+(B)+(C) +(D)	$[redacted]	0.022	$[redacted][7]	$[redacted]	0.022	$[redacted][8]
(A)+(B)+(C) +(D)+(E)	$[redacted]	0.011	$[redacted][9]	$[redacted]	0.011	$[redacted][9]
(A)+(B)+(C) +(D)+(E)+(F)	$[redacted]	0.000	N/A	$[redacted]	0.000	N/A

Italics indicate results generated during the evaluation.

Source: constructed during the evaluation from Attachment 3.1 Guselkumab CD Economic Model.xlsx.

ADA=adalimumab; GUS=guselkumab; IFX=infliximab; QALY=Quality Adjusted Life Year; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; 1L=first-line (index) treatment; 2L=second-line treatment; 3L=third-line treatment;

a comparators (ADA, IFX, UPA, UST and VDZ) weighted by market share

b cells E21:E27 in Clinical Inputs worksheet

c cells E32:E38 in Clinical Inputs worksheet i) GUS 100: 85.7% and ii) GUS 200: 87.9%.

d cells D54:D60 in Clinical Inputs worksheet

e cells E54:E60 in Clinical Inputs worksheet

f cells D9: D15 in Clinical Inputs worksheet

g cells E43:E49 in Clinical Inputs worksheet i) GUS 100: 67.5% and ii) GUS 200: 66.1%.

h cells K17:K19 in Results worksheet

j cells K22:K24 in Results worksheet

The redacted values correspond to the following ranges:

[1] *$75,000 to < $95,000*

[2] *$55,000 to < $75,000*

[3] *$155,000 to < $255,000*

[4] *$115,000 to < $135,000*

[5] *$95,000 to < $115,000*

[6] *$255,000 to < $355,000*

[7] *$755,000 to < $855,000*

[8] *$855,000 to < $955,000*

[9] *> $1,055,000*

6.62 Overall, the ESC considered the modelled economic evaluation uninformative because:

- The model included benefits for GUS associated with clinical remission following induction. Based on the head to head trial vs UST, a difference in this outcome was not demonstrated.
- The model included benefits for GUS associated with maintenance of clinical remission. Based on the head to head trial vs UST, a difference in this outcome was not demonstrated (with the exception of a few comparisons that favoured GUS 200 mg SC over UST on maintenance of clinical remission and durable clinical remission). Further the approach used resulted in a much lower proportion of patients remaining on treatment than expected in clinical practice.
- The model included benefits for GUS associated with endoscopic remission. Based on the head to head trial vs UST, a statistically significant difference in this outcome was demonstrated. Incorporating only this benefit in the economic model resulted in ICERs that exceed $1 million/QALY gained (see multivariate analysis (A)+(B)+(C)+(D)+(E) in Table 15).
- The model assumed GUS would be used first line. If GUS is used second line the ICERs increased to >$95,000 to < $115,000 /QALY (see scenario analysis Table 14). If GUS is used third line the ICERs increases to >$155,000 to < $255,000/QALY (see scenario analysis Table 14).

Drug cost/patient/year

6.63 Based on the proposed effective AEMP for GUS, the cost per patient per year are:

Table 16: Drug cost/patient/year based on proposed effective AEMP for GUS

GUS Dosing	Cost/patient/year	Cost/patient/year (incl. administration[a])
200 mg IV wk 0, 4, 8 induction -> 200 mg SC Q4W maintenance	$[redacted]	$[redacted]
200 mg IV wk 0, 4, 8 induction -> 100 mg SC Q8W maintenance	$[redacted]	$[redacted]
400 mg SC wk 0, 4, 8 induction -> 200 mg SC Q4W maintenance	$[redacted]	$[redacted]
400 mg SC wk 0, 4, 8 induction -> 100 mg SC Q8W maintenance	$[redacted]	$[redacted]

Source: compiled during the evaluation.
GUS=guselkumab; IV=intravenous; SC=subcutaneous; QxW=every x week;
a Drug cost plus administration cost (MBS item 14245 $94.90 fee).

Estimated PBS usage & financial implications

6.64 This submission was not considered by DUSC. The submission applied a market share approach to the financial estimates for the PBS listing of GUS for severe CD. Table 17 summarises the inputs used for the financial estimates.

Table 17: Data sources and parameter values applied in the utilisation and financial estimates

Component	Data source
Market share	
Current market	Usage of ADA, IFX, UST, UPA and VDZ: PBS/RPBS dispensed scripts reported by Services Australia from 2020 to 2024. This was reasonable. Projected script usage for substituted treatments: The submission stated that due to differences in dosing schedules, treated patients fill their scripts at different time intervals depending on the drug they are receiving. Therefore, to accurately analyse the growth of the market and shares of the individual biologics, it was necessary to account for patients who are actively on treatment rather than the number of scripts processed. The submission indicated there was a need for a common unit for comparison across the biologics for the script volumes to be aggregated for analysis and forward estimations. • The script data extracted from the PBS/RPBS Services Australia database were converted to units of patient-weeks on treatment. The conversion was based on the average number of weeks of treatment per script expected to be dispensed to patients who follow the TGA approved and PBS listed dosing schedules for each biologic, for initial and continuing treatment periods . • For extrapolation of the market in terms of the number of patient-weeks on treatment, the submission applied a polynomial trendline, on the basis that it provided the best fit to the historical data points with an R2 value of 0.9939. The submission presented a sensitivity analysis based on a linear trendline (R2=0.993). The submission noted that the extrapolation reflected the growing utilisation of biologics for CD (i.e. compound annual growth rate of 5.8%). It was unclear whether the trendline based on patient-weeks of treatment differed from a trendline based on script data. • Based on the number of patient-weeks on treatment, the submission estimated that the current market was 208,010 scripts in Year 1, increasing to 275,965 scripts in Year 6. The submission's approach to estimate the number of scripts ignored the multi-regimen nature of the b/tsDMARD for CD, where switching is allowed after treatment failure and therefore it is likely that patients could be represented across multiple b/tsDMARD sequence in any given review period. The submission also assumed no difference between S85 and S100 patients. The submission applied the proportional split of PBS/RPBS patient category (calculated using 2024 script volumes) to all 2025 scripts (removing individual differences in each b/tsDMARDs).
Uptake (substitution) rate	Assumed uptake of GUS (substitution rate): The uptake of GUS across the total market was expected to be [redacted]% in Year 1, increasing to [redacted]% in Year 6. The submission assumed a different uptake of GUS in the biologic market for CD with a lower uptake (substitution) rate from UST and IFX compared to ADA, UPA and VDZ. The submission assumed the uptake (substitution) rate of GUS from UST and IFX market was [redacted]% in Year 1, increasing to [redacted]% in Year 6, and from ADA, UPA and VDZ markets was [redacted]% in Year 1, increasing to [redacted]% in Year 6. Based on historical utilisation, UST and IFX remain the two most utilised treatments in CD (34.3% and 29.6% share of patient-weeks on treatment in 2020-2024, respectively). UST and IFX are effective treatments for CD and would continue to be prescribed by clinicians if GUS is listed on the PBS. For other biologics, the submission stated that clinicians considered ADA to be less effective than IFX and UST. UPA was PBS listed in December 2023 and relatively new to the market, and utilisation may be impacted by potential safety concerns with the use of JAK inhibitors, including UPA. The submission stated that clinicians considered VDZ to be less effective than other biologics for CD and is used as later lines treatment, when used. The DUSC analysis 2017 indicated an increasing number of prevalent patients receiving biologic treatment on the PBS for CD. While the submission assumed differences in uptake due to efficacy and safety of PBS-listed biologics, the real-world evidence from Australia (Ko 2021 and DUSC 2017 analysis) shows that treatment persistence/continuation rate remains high for all biologic treatments for severe CD, which contradicts the submission's predictions based on the results from the trial-design-adjusted analysis where treatment persistence/continuation varied and were all worse for comparator biologics versus GUS. Sources of UST scripts: The submission assumed the majority of GUS scripts were from substituting ADA and UST, due to the assumed high substitution rates from ADA and high number of predicted scripts for ADA and UST. Number of scripts: To estimate the number of GUS scripts, first, the submission estimated the reduction in each comparator scripts using the assumed uptake of GUS given the assumed proportional rate of substitution, then estimated the corresponding number of GUS scripts based on script equivalence

<table>
<tr><th>Component</th><th>Data source</th></tr>
<tr><td></td><td>between GUS and the comparators.
Script equivalence: Calculated as the ratio of the number of scripts for GUS and the number of scripts for the substituted biologic treatment over a 104-week period based on their respective script schedules. The script equivalence was estimated based on initiation and continuation scripts of the substituted comparator biologics, given the two dosing regimens for GUS in induction and maintenance. For induction, the submission estimated the number of GUS scripts by IV infusion and SC injection formulation assuming 50%:50% proportional split. For maintenance, the submission estimated the script numbers by the two strengths of GUS 100 mg Q8W and GUS 200 mg Q4W, assuming a [redacted]%:[redacted]% proportional split, given clinical evidence showed numerically improved efficacy with higher dose GUS at maintenance compared to the lower dose GUS. To account for differences in the maintenance dosing frequency, the submission converted the proportion to script numbers. As GUS Q4W have twice the number of scripts in the maintenance phase compared to GUS Q8W, the submission total scripts were weighted by the two dose frequencies: [redacted] scripts ([redacted]% x 2 scripts) for GUS Q4W and [redacted] scripts ([redacted]% x 1 script) for GUS Q8W, totalling [redacted] scripts ([redacted] + [redacted]).
Table: Script equivalence over 104 weeks
<table>
<tr><th></th><th>N initial scripts</th><th>N maintenance scripts</th><th>Total</th><th>Avg scripts/patient/yr (initial)</th><th>Avg scripts/patient/yr (maintenance)</th><th>Avg scripts/patient/yr (total)</th></tr>
<tr><td>GUS 100 Q8W</td><td>3.0</td><td>11.0</td><td>14.0</td><td>1.5</td><td>5.5</td><td>7.0</td></tr>
<tr><td>GUS 200 Q4W</td><td>3.0</td><td>23.0</td><td>26.0</td><td>1.5</td><td>11.5</td><td>13.0</td></tr>
<tr><td>GUS weighted</td><td>3.0</td><td>20.9</td><td>23.9</td><td>1.5</td><td>10.4</td><td>11.9</td></tr>
<tr><td>ADA</td><td>1.0</td><td>25.0</td><td>26.0</td><td>0.5</td><td>12.5</td><td>13.0</td></tr>
<tr><td>IFX IV</td><td>3.0</td><td>11.3</td><td>14.3</td><td>1.5</td><td>5.6</td><td>7.1</td></tr>
<tr><td>IFX SC</td><td>-</td><td>49.0</td><td>49.0</td><td>-</td><td>24.5</td><td>24.5</td></tr>
<tr><td>UPA</td><td>3.0</td><td>23.0</td><td>26.0</td><td>1.5</td><td>11.5</td><td>13.0</td></tr>
<tr><td>UST 130 mg</td><td>2.0</td><td>-</td><td>2.0</td><td>1.0</td><td>0.0</td><td>1.0</td></tr>
<tr><td>UST 45 mg</td><td>-</td><td>11.0</td><td>11.0</td><td>0.0</td><td>5.5</td><td>5.5</td></tr>
<tr><td>VDZ IV</td><td>3.0</td><td>11.3</td><td>14.3</td><td>1.5</td><td>5.6</td><td>7.1</td></tr>
<tr><td>VDZ SC</td><td>2.0</td><td>49.0</td><td>51.0</td><td>1.0</td><td>24.5</td><td>25.5</td></tr>
</table>
The submission incorrectly applied the script equivalence for medicines where the maximum quantity units in the PBS restriction is greater than one. For example, IFX 120 mg SC (Rows 159-161 of Attachment 4.1) is for a maximum quantity of two units and is dosed every two weeks. Consequently, for one dispensing, the supply will last 4 weeks and the number of maintenance scripts for IFX injection 120 mg will be 25 instead of 49.</td></tr>
<tr><td>Number of scripts</td><td>Expected GUS utilisation: The estimated total script numbers for GUS was based on the assumed substitution rates and script equivalence by initial and continuing treatment
Grandfathered patients: The submission stated that the sponsor requested a grandfathering restriction for the expected 22 patients from the GALAXI trials and further 463 patients from an anticipated early access program (EAP) to transition to PBS. The financial estimates accounted for the grandfathered patients in the market share of the total scripts in severe CD.
Substituted scripts: The estimated number of substituted scripts was based on the assumed uptake of GUS and the projected number of scripts for the PBS-listed comparator biologics.</td></tr>
<tr><td colspan="2">Cost of medicines</td></tr>
<tr><td>GUS</td><td>The requested effective prices of GUS for severe CD.</td></tr>
<tr><td>Comparator b/tsDMARDs</td><td>The estimated effective prices of PBS items for comparator biologics in severe CD. The submission incorrectly applied average public/private DPMQs of script to the total of both public and private script volumes. There were also a number of discrepancies between the included DPMQs and max quantity and their current PBS schedule.</td></tr>
<tr><td>Patient co-payment</td><td>PBS: $41.30, RPBS: $6.60
Based on PBS/RPBS script volume for comparator biologics (ADA, IFX, UPA, UST and VDZ) for 2024. The calculated co-payments are inconsistent with current amounts (PBS: $31.60 and RPBS: 7.70).</td></tr>
<tr><td>MBS item</td><td>$116.60
MBS item 14245 administration of intravenous infusion.</td></tr>
</table>

Source: Tables 4.6 to 4.9, pp420-422, Tables 4.10 and 4.11, pp424-425 of the submission, Attachment 4.1 USM Tremfya CD Jul-25 Base (1 of 3).xlsx, Attachment 4.2 USM Tremfya CD Jul-25 Base (2 of 3).xlsx and Attachment 4.3 USM Tremfya CD Jul-25 Base (3 of 3).xlsx.
ADA=adalimumab; b/tsDMARD=biologic/targeted synthetic disease-modifying anti-rheumatic drug; CDAI=Crohn's disease; GUS=guselkumab; IFX=infliximab; IV=intravenous; SC=subcutaneous; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; QxW=every x week;

6.65 Table 18 presents the estimated net financial implications to the PBS/RPBS and health budget for the proposed PBS listing of GUS for the treatment of severe CD over the first six years.

Table 18: Estimated net cost of GUS to the PBS/RPBS and health budget using the submission's effective prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of the use and financial impact of GUS						
GUS scripts[a]	[redacted][1]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][5]	[redacted][6]
Initial	[redacted][7]	[redacted][8]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Continuing	[redacted][1]	[redacted][9]	[redacted][2]	[redacted][10]	[redacted][4]	[redacted][5]
GUS, net cost to PBS/RPBS[b]	$[redacted][11]	$[redacted][12]	$[redacted][13]	$[redacted][14]	$[redacted][14]	$[redacted][14]
Estimation of changes in use and financial impact of other medicines[c]						
Comparator scripts	-[redacted][1]	-[redacted][9]	-[redacted][2]	-[redacted][15]	-[redacted][16]	-[redacted][5]
ADA	-[redacted][8]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][17]	-[redacted][17]
IFX	-[redacted][7]	-[redacted][7]	-[redacted][7]	-[redacted][8]	-[redacted][8]	-[redacted][8]
UPA	-[redacted][7]	-[redacted][7]	-[redacted][8]	-[redacted][8]	-[redacted][1]	-[redacted][1]
UST	-[redacted][7]	-[redacted][8]	-[redacted][8]	-[redacted][8]	-[redacted][1]	-[redacted][1]
VDZ	-[redacted][7]	-[redacted][7]	-[redacted][7]	-[redacted][7]	-[redacted][7]	-[redacted][8]
Comparators, net cost to PBS/RPBS	-$[redacted][18]	-$[redacted][18]	-$[redacted][19]	-$[redacted][11]	-$[redacted][20]	-$[redacted][20]
ADA	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][18]	-$[redacted][18]
IFX	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]
UPA	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][18]
UST	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][18]	-$[redacted][18]	-$[redacted][18]
VDZ	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]
Estimated financial implications for the PBS/RPBS and the health budget						
Net cost to MBS	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]	-$[redacted][21]
Net cost to PBS/RPBS	$[redacted][19]	$[redacted][22]	$[redacted][12]	$[redacted][23]	$[redacted][24]	$[redacted][14]
Net cost to health budget	$[redacted][19]	$[redacted][22]	$[redacted][12]	$[redacted][23]	$[redacted][24]	$[redacted][14]

Source: Table 4.13, p427, Tables 4.15 and 4.16, pp428-430, Table 4.18, p431, Tables 4.20 and 4.21, pp432-433, Tables 4.24 and 4.26, p435 of the submission, Attachment 4.1 USM Tremfya CD Jul-25 Base (1 of 3).xlsx, Attachment 4.2 USM Tremfya CD Jul-25 Base (2 of 3).xlsx and Attachment 4.3 USM Tremfya CD Jul-25 Base (3 of 3).xlsx.
ADA=adalimumab; GUS=guselkumab; IFX=infliximab; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab.

[a] Calculated by adding across all three EXCEL files.

[b] This was derived from row 70 and row 75 of '5. Impact – net' worksheet in EXCEL file 1 of 3, which was calculated by adding across all three EXCEL files.

[c] Derived only from file 1 of 3.

The redacted values correspond to the following ranges:

[1] 10,000 to < 20,000
[2] 30,000 to < 40,000
[3] 40,000 to < 50,000
[4] 50,000 to < 60,000
[5] 70,000 to < 80,000
[6] 80,000 to < 90,000
[7] 500 to < 5,000
[8] 5,000 to < 10,000
[9] 20,000 to < 30,000
[10] 40,000 to < 50,000
[11] $30 million to < $40 million
[12] $50 million to < $60 million
[13] $80 million to < $90 million

[14] *$100 million to < $200 million*
[15] *40,000 to < 50,000*
[16] *60,000 to < 70,000*
[17] *20,000 to < 30,000*
[18] *$10 million to < $20 million*
[19] *$20 million to < $30 million*
[20] *$40 million to < $50 million*
[21] *$0 to < $10 million*
[22] *$40 million to < $50 million*
[23] *$70 million to < $80 million*
[24] *$90 million to < $100 million*

6.66 The net cost to the PBS/RPBS of listing GUS was estimated to be $400 million to < $500 million and a net cost to the MBS - $0 to < $10 million, over the first 6 years of listing. A programming error was identified whereby the additional GUS IV scripts substituting ADA, UPA and VDZ were not included in the total MBS cost. Including these additional costs would increase the net cost to the MBS $0 to < $10 million, over the first 6 years of listing.

6.67 The net cost to the PBS/RPBS and the health budget was driven by the relatively higher cost per patient with GUS compared to the comparator treatments, the assumed uptake/substitution rates assumed for each comparator (given the average cost per patient differs by treatment), and the estimated rate of market growth.

6.68 The ESC noted the submission assumed uptake of GUS across the total market of [redacted]% in Year 1, increasing to [redacted]% in Year 6, and based on this uptake there was a substantial incremental cost to the PBS of listing GUS with an estimated net cost of $400 million to < $500 million over 6 years.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) and General Schedule Authority Required (in writing) Pharmaceutical Benefits Scheme (PBS) listings of guselkumab (GUS) for the treatment of adults with severe Crohn's disease (CD). The PBAC considered that, based on direct evidence, while GUS was non-inferior in terms of effectiveness compared to ustekinumab (UST) for the outcomes of clinical remission and response, it was likely superior in terms of endoscopic outcomes in the maintenance treatment setting. The PBAC considered the economic model was uninformative, noting it included short-term and long-term benefits for clinical remission that were not supported by the available clinical trial data, and the assumed link between endoscopic remission, longer term clinical remission and quality of life was not adequately supported and quantified. Unable to recommend on a cost-effectiveness basis, the PBAC recommended GUS be cost minimised to UST over 2 years.

7.2 The PBAC noted the consumer comments regarding the significant quality of life impact severe CD has on patients and the importance of having additional treatment options available, particularly medicines with different mechanisms of action.

7.3 The PBAC considered the amendments to the restriction criteria proposed by the Secretariat in Section 3 for consistency with other PBS listed biologic/targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARD) were reasonable.

7.4 The PBAC noted the submission nominated all PBS listed b/tsDMARD as comparators: adalimumab (ADA), infliximab (IFX), ustekinumab (UST), upadacitinib (UPA) and vedolizumab (VDZ). The PBAC noted GUS may be more likely to substitute for UST, which currently accounts for 40% of the market (measured in patient-weeks of treatment) and has a similar mechanism of action (both are interleukin inhibitors).

7.5 The PBAC noted the key clinical evidence presented in the submission for GUS was from three head-to-head randomised trials comparing GUS to UST and placebo (PBO) for induction and maintenance treatment. The GALAXI 1 (n=309), GALAXI 2 (n=508) and GALAXI 3 (n=513) trials were all multicentre, randomised, placebo-controlled, double-blind trials where patients with moderate to severe CD were randomised to GUS, UST or PBO for 48 weeks. Each trial used a treat-through design where patients randomised to GUS or UST remained on the same treatment for induction (Weeks 0-12) and maintenance therapy (Weeks 12-48) irrespective of induction response. The PBAC noted that, based on a meta-analysis of the three trials, there were no statistically significant differences between GUS (100 mg and 200 mg) and UST in terms of clinical remission or clinical response at Week 12 (induction) or Week 48 (maintenance), with the exception of the comparison of GUS 200 mg and UST at Week 48 for clinical remission where the difference was statistically significant. The PBAC noted there was a statistically significant difference for endoscopic remission and response for GUS 100 mg SC and GUS 200 SC compared to UST at Week 48; however, the clinical relevance, particularly in the long term, was uncertain.

7.6 The PBAC noted that treatment guidelines for CD refer to the importance of achieving endoscopic healing and in 2022 the FDA implemented a requirement for endoscopic remission as a co-primary endpoint with clinical remission in clinical trials. The PBAC acknowledged the references included in the pre-PBAC response (see paragraphs 6.24 and 6.25) but considered it remained unclear if achieving endoscopic remission (as defined in the GALAXI trials) at Week 48 leads to better longer term outcomes for patients. Given the lack of significant differences in key outcomes for clinical remission, the correlation between endoscopic and clinical remission for GUS versus UST remained uncertain.

7.7 The PBAC noted the submission also presented indirect evidence comparing GUS versus the nominated comparators for induction and maintenance treatment. The PBAC considered these analyses were largely uninformative due to significant transitivity issues (e.g., different trial designs, patient populations, outcome definitions, timing of endpoint assessment) and, in particular, due to the use of imputed data to inform the maintenance analysis.

7.8 The PBAC noted the submission presented a cost utility analysis comparing GUS to the nominated comparators weighted according to market share. The PBAC noted the model included short-term and long-term benefits for clinical remission that were not

supported by the clinical trial data presented. Additionally, the PBAC noted the model assumed a link between endoscopic remission, longer term clinical remission and quality of life that had not been adequately supported or quantified. The PBAC agreed with the ESC that the model was uninformative (as discussed in paragraph 6.62).

7.9 The PBAC considered that, in the absence of an appropriate economic model comparing GUS and UST based on endoscopic outcomes, it was unable to determine the magnitude of price premium for GUS over UST that would be cost effective. The PBAC considered GUS was highly unlikely to be cost effective at the price requested in the submission as the cost per patient over 2 years was more than twice that of UST and the benefit in endoscopic remission observed in the trial was limited to a risk difference of 9% to 14% at 48 weeks. Unable to recommend on a cost-effectiveness basis, the PBAC recommended GUS be cost minimised to UST over 2 years based on the equi-effective doses outlined in the paragraph below.

7.10 The PBAC advised the following equi-effective doses were appropriate:

Guselkumab 200 mg intravenously at week 0, 4, and 8, or guselkumab 400 mg subcutaneously (SC) at week 0, 4, and 8 followed by guselkumab 200 mg SC at week 12, and then every 4 weeks, or guselkumab 100 mg SC at week 16 and then every 8 weeks is equi-effective to ustekinumab 390 mg IV at week 0 and 90 mg SC at week 8 followed by 90 mg SC every 8 weeks or every 12 weeks.

The PBAC considered a split of dosage regimens, as applied in the financial estimates (see Table 17), was reasonable.

7.11 The PBAC noted the utilisation estimates presented in the submission assumed the uptake of GUS across the total market was [redacted]% in Year 1, increasing to [redacted]% in Year 6 and considered this was reasonable. The PBAC noted that, based on the recommendation in paragraph 7.9, there will be an incremental cost to the PBS as GUS may substitute for less costly alternatives. The PBAC noted the utilisation estimates applied incorrect script equivalence for some medicines (as outlined in Table 17) that will need to be corrected.

7.12 The PBAC recalled it had previously advised that guselkumab 100 mg PFP and guselkumab 100 mg PFS should be considered equivalent for the purposes of substitution (i.e., 'a' flagged in the Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purposes of substitution) (paragraph 7.11, guselkumab minutes, May 2025 PBAC meeting). Additionally, the PBAC advised, under Section 101 (4AACD) of the *National Health Act*, that guselkumab 200 mg PFP and guselkumab 200 mg PFS should be considered equivalent for the purposes of substitution (i.e., 'a' flagged in the Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purposes of substitution).

7.13 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for GUS:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative therapies;

b) The treatment is not expected to address a high and urgent unmet clinical need as there are alternative therapies available;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new items:

Proposed Restriction – initial treatment (General Schedule SC injection)
Proposed Restriction – Grandfather arrangements for induction (General Schedule SC injection)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
GUSELKUMAB					
guselkumab 200 mg/2 mL injection, 2 x 2 mL pen devices	NEW	1	2	2	Tremfya
guselkumab 200 mg/2 mL injection, 2 x 2 mL syringes	NEW	1	2	2	Tremfya

Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL - Section 85 General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
Prescribing rule level		**Administrative Advice:** Overarching administrative advice note:
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply
		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Administrative Advice: The prescriber completing this authority application must be a specialist medical practitioner of the type specified in the restriction.

Restriction Summary [new1] / Treatment of Concept: [new1]	
	Indication: Severe Crohn disease
	Treatment Phase: Initial 1 (new patient)
	Clinical criteria:
	Patient must have confirmed severe Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician
	AND
	Clinical criteria:
	Patient must have failed to achieve an adequate response to prior systemic therapy with a tapered course of steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period
	AND
	Clinical criteria:
	Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with azathioprine at a dose of at least 2 mg per kg daily for 3 or more consecutive months; or
	Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more consecutive months; or
	Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with methotrexate at a dose of at least 15 mg weekly for 3 or more consecutive months
	AND
	Clinical criteria:
	Patient must have a Crohn Disease Activity Index (CDAI) Score greater than or equal to 300 as evidence of failure to achieve an adequate response to prior systemic therapy; or
	Patient must have short gut syndrome with diagnostic imaging or surgical evidence, or have had an ileostomy or colostomy; and must have evidence of intestinal inflammation; and must have evidence of failure to achieve an adequate response to prior systemic therapy as specified below; or
	Patient must have extensive intestinal inflammation affecting more than 50 cm of the small intestine as evidenced by radiological imaging; and must have a Crohn Disease Activity Index (CDAI) Score greater than or equal to 220; and must have evidence of failure to achieve an adequate response to prior systemic therapy as specified below
	AND
	Clinical criteria:
	The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction
	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
	Prescribing Instructions: The authority application must be made in writing and must include: (1) details of the proposed prescription; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

	Prescribing Instructions: Evidence of failure to achieve an adequate response to prior therapy must include at least one of the following: (a) patient must have evidence of intestinal inflammation; (b) patient must be assessed clinically as being in a high faecal output state; (c) patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient. Evidence of intestinal inflammation includes: (i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or (ii) faeces: higher than normal lactoferrin or calprotectin level; or (iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery.
	Prescribing Instructions: All assessments, pathology tests and diagnostic imaging studies must be made within 4 weeks of the date of application and should be performed preferably whilst still on conventional treatment, but no longer than 4 weeks following cessation of the most recent prior treatment.
	Prescribing Instructions: If treatment with any of the specified prior conventional drugs is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application.
	Prescribing Instructions: If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application.
	Prescribing Instructions: Details of the accepted toxicities including severity can be found on the Services Australia website.
	Prescribing Instructions: Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS subsidised therapy
	Prescribing Instructions: A maximum quantity and number of repeats to provide for an initial course of this drug consisting of two pre-filled subcutaneous injections of 200 mg per dose (400mg in total), administered at weeks 0, 4 and 8, will be authorised. **(FOR HSD LISTING: A maximum quantity and number of repeats to provide for an initial course of this drug consisting of a single 200 mg dose (via IV infusion) administered at weeks 0, 4 and 8, will be authorised)**
	Prescribing Instructions: If fewer than 2 repeats are requested at the time of the application, authority approvals for sufficient repeats to complete the 3 doses of this drug may be requested by telephone and authorised through the Balance of Supply treatment phase PBS restriction. Under no circumstances will telephone approvals be granted for initial authority applications, or for treatment that would otherwise extend the initial treatment period.
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted up to 12 weeks of therapy and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.

	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
Restriction Summary [new2] / Treatment of Concept: [new2]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL – Section 85 General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
	Indication: Severe Crohn Disease
	Treatment Phase: Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle
	AND
	Clinical criteria:
	The treatment must not have on a previous occasion failed to provide the patient with an adequate response during the current treatment cycle
	AND
	Clinical criteria:
	The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction
	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
	Prescribing Instructions: The authority application must be made in writing and must include: (1) details of the proposed prescription; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: In relation to the biological medicine prescribed immediately before this one, provide at least one of the following which is not more than 4 weeks from the last administered dose: (i) the Crohn Disease Activity Index (CDAI) score, including the date the score was calculated on; or (ii) the unique serial/identifying number and date(s) of pathology or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; or (iii) confirmation that a severe intolerance occurred that resulted in the cessation of treatment.

Restriction Summary [new3] / Treatment of Concept: [new3]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL – Section 85 General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
	Indication: Severe Crohn Disease
	Treatment Phase: Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition
	AND
	Clinical criteria:
	Patient must have a break in treatment of 5 years or more from the most recently approved PBS-subsided biological medicine for this condition
	AND
	Clinical criteria:
	Patient must have confirmed severe Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician
	AND
	Clinical criteria:
	Patient must have a Crohn Disease Activity Index (CDAI) Score of greater than or equal to 300 that is no more than 4 weeks old at the time of application; or
	Patient must have a documented history of intestinal inflammation and have diagnostic imaging or surgical evidence of short gut syndrome if affected by the syndrome or has an ileostomy or colostomy; or
	Patient must have a documented history and radiological evidence of intestinal inflammation if the patient has extensive small intestinal disease affecting more than 50 cm of the small intestine, together with a Crohn Disease Activity Index (CDAI) Score greater than or equal to 220 and that is no more than 4 weeks old at the time of application
	AND
	Clinical criteria:
	Patient must have evidence of intestinal inflammation; or
	Patient must be assessed clinically as being in a high faecal output state; or
	Patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient
	AND
	Clinical criteria:
	The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction
	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
	Prescribing Instructions: The authority application must be made in writing and must include: (1) details of the proposed prescription; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: Provide at least one of the following: (i) the current Crohn Disease Activity Index (CDAI) score, including the date this score was calculated on; (ii) confirmation that there is a documented history of intestinal inflammation plus diagnostic imaging/surgical evidence of at least one of: (a) short gut syndrome, (b) ileostomy, (c) colostomy; (iii) confirmation that there is a documented history and radiological evidence of intestinal inflammation from extensive small intestinal disease affecting more than 50 cm of the small intestine where the CDAI score is at least 220, but below 300
	Prescribing Instructions: Evidence of intestinal inflammation includes: (i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or (ii) faeces: higher than normal lactoferrin or calprotectin level; or (iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery.
	Prescribing Instructions: Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS subsidised therapy.
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted up to 12 weeks of therapy and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition *within this treatment cycle*. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsided biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.
Restriction Summary [new4] / Treatment of Concept: [new4]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
	Indication: Severe Crohn disease

	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements *(for patients transitioning through induction doses)*
	Clinical Criteria:
	Patient must have a documented history of severe Crohn disease
	AND
	Clinical criteria:
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [redacted]
	AND
	Clinical criteria:
	Patient must be receiving treatment with this drug for this condition at the time of application
	AND
	Clinical criteria:
	Patient must have had a Crohn Disease Activity Index (CDAI) Score of greater than or equal to 300 prior to commencing treatment with this drug; or
	Patient must have had short gut syndrome with diagnostic imaging or surgical evidence, or have had an ileostomy or colostomy; and must have had evidence of intestinal inflammation; and must have had evidence of failure to achieve an adequate response to prior systemic therapy as specified below prior to commencing treatment with this drug; or
	Patient must have had extensive intestinal inflammation affecting more than 50 cm of the small intestine as evidenced by radiological imaging; and must have had a Crohn Disease Activity Index (CDAI) Score greater than or equal to 220; and must have had evidence of failure to achieve an adequate response to prior systemic therapy as specified below prior to commencing treatment with this drug
	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
	Prescribing Instructions: The authority application must be made in writing and must include: (1) details of the proposed prescription; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: The authority application must include the following:, (i) the completed Crohn Disease Activity Index (CDAI) Score including the date of the assessment of the patient's condition, if relevant; or, (ii) the unique serial/identifying number and dates of the pathology test or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant;
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted up to 12 weeks of therapy and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.

	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: The prescriber should request sufficient quantity and repeats to provide for the balance to complete 12 weeks of induction therapy only
	Prescribing Instructions: Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.
	Prescribing Instructions: A Grandfathered patient 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.
	Prescribing Instructions: Evidence of failure to achieve an adequate response to prior therapy must include at least one of the following: (a) patient must have evidence of intestinal inflammation; (b) patient must be assessed clinically as being in a high faecal output state; (c) patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient. Evidence of intestinal inflammation includes: (i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or (ii) faeces: higher than normal lactoferrin or calprotectin level; or (iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery.
	Prescribing Instructions: All assessments, pathology tests and diagnostic imaging studies were to have been within 4 weeks leading up to commencing the non-PBS subsidised supply of this drug and should have been performed preferably whilst still on conventional treatment, but no longer than 4 weeks following the last dose of conventional treatment**.**
	Prescribing Instructions: If treatment with any of the specified prior conventional drugs is contraindicated according to the relevant TGA approved Product Information, please provide details at the time of application.
	Prescribing Instructions: If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application.
	Prescribing Instructions: Details of the accepted toxicities including severity can be found on the Services Australia website.
	Prescribing Instructions: Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS-subsidised therapy.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.

	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

Proposed Restriction – Continuing treatment (General Schedule SC injection)
Proposed Restriction – Grandfather arrangements for maintenance (General Schedule SC injection)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
GUSELKUMAB					
guselkumab 100 mg/1mL injection, 1 x 1 mL pen device	NEW	1	1	2	Tremfya
guselkumab 100 mg/1mL injection, 1 x 1 mL syringe	NEW	1	1	2	Tremfya
guselkumab 200 mg/2 mL injection, 2 mL pen device	NEW	1	1	5	Tremfya
guselkumab 200 mg/2 mL injection, 2 mL syringe	NEW	1	1	5	Tremfya

Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL – Section 85 General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload)
Prescribing rule level		**Administrative Advice:** Overarching administrative advice note:
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply
		Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Administrative Advice: The prescriber completing this authority application must be a specialist medical practitioner of the type specified in the restriction.
Restriction Summary [new6] / Treatment of Concept: [new6]		
		Indication: Severe Crohn disease
		Treatment Phase: Continuing treatment
		Clinical criteria:
		Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition
		AND
		Clinical criteria:
		Patient must have an adequate response to this drug defined as a reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; or

	Patient must have an adequate response to this drug defined as (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C-reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient
	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this restriction
	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
	Prescribing Instructions: Applications for authorisation must be made in writing and must include:, (a) details of the proposed prescription form; and, { *(b) 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).* *In relation to the immediately preceding supply of this biological medicine, provide at least one of the following which is not more than 4 weeks from the last administered dose:* *(i) the Crohn Disease Activity Index (CDAI) score, including the date the score was calculated on; or* *(ii) the unique serial/identifying number and date(s) of pathology or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant .*
	Prescribing Instructions: All assessments, pathology tests, and diagnostic imaging studies must be made within 1 month of the date of application.
	Prescribing Instructions: *An application for the continuing treatment must be accompanied with the assessment of response conducted up to 12 weeks of therapy and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.*
	Prescribing Instructions: Where an assessment is not submitted within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response, to treatment with this drug.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.

	Prescribing Instructions: Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response
Restriction Summary [new7] / Treatment of Concept: [new7]	
	Indication: Severe Crohn disease
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements *(for patients transitioning through maintenance doses)*
	Clinical Criteria:
	Patient must have a documented history of severe Crohn disease
	AND
	Clinical criteria:
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [redacted]
	AND
	Clinical criteria:
	Patient must be receiving treatment with this drug for this condition at the time of application
	AND
	Clinical criteria:
	Patient must have had a Crohn Disease Activity Index (CDAI) Score of greater than or equal to 300 prior to commencing treatment with this drug; or
	Patient must have had short gut syndrome with diagnostic imaging or surgical evidence, or have had an ileostomy or colostomy; and must have had evidence of intestinal inflammation; and must have had evidence of failure to achieve an adequate response to prior systemic therapy as specified below prior to commencing treatment with this drug; or
	Patient must have had extensive intestinal inflammation affecting more than 50 cm of the small intestine as evidenced by radiological imaging; and must have had a Crohn Disease Activity Index (CDAI) Score greater than or equal to 220; and must have had evidence of failure to achieve an adequate response to prior systemic therapy as specified below prior to commencing treatment with this drug
	AND
	Clinical criteria:
	Patient must have an adequate response to this drug defined as a reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; or
	Patient must have an adequate response to this drug defined as (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C-reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient
	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
	Prescribing Instructions: *The authority application must be made in writing and must include:* *(1) details of the proposed prescription; and* *(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
	Prescribing Instructions: The authority application must include the following:, (i) the completed Crohn Disease Activity Index (CDAI) Score calculation sheet including the date of the assessment of the patient's condition, if relevant; or, (ii) the reports and dates of the pathology test or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; and, (iii) the date of most recent clinical assessment.
	Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response conducted up to 12 weeks of therapy and no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.
	Prescribing Instructions: Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.
	Prescribing Instructions: A Grandfathered patient 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.
	Prescribing Instructions: Evidence of failure to achieve an adequate response to prior therapy must include at least one of the following: (a) patient must have evidence of intestinal inflammation; (b) patient must be assessed clinically as being in a high faecal output state; (c) patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient. Evidence of intestinal inflammation includes: (i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or (ii) faeces: higher than normal lactoferrin or calprotectin level; or (iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery.

	Prescribing Instructions: All assessments, pathology tests and diagnostic imaging studies were to have been within 4 weeks leading up to commencing the non-PBS subsidised supply of this drug and should have been performed preferably whilst still on conventional treatment, but no longer than 4 weeks following the last dose of conventional treatment.
	Prescribing Instructions: If treatment with any of the specified prior conventional drugs is contraindicated according to the relevant TGA approved Product Information, please provide details at the time of application.
	Prescribing Instructions: If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application.
	Prescribing Instructions: Details of the accepted toxicities including severity can be found on the Services Australia website.
	Prescribing Instructions: Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS-subsidised therapy.
	Prescribing Instructions: Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria

Proposed Restriction – Balance of Supply (General Schedule SC injection)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
GUSELKUMAB					
guselkumab 200 mg/2 mL injection, 2 mL pen device	NEW	2	2	2	Tremfya
guselkumab 200 mg/2 mL injection, 2 mL syringe	NEW	2	2	2	Tremfya

Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL -Section 85 General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (telephone/electronic)
Prescribing rule level		**Administrative Advice:** Overarching administrative advice note:
		Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply
		Administrative Advice: 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).
		Administrative Advice: The prescriber completing this authority application must be a specialist medical practitioner of the type specified in the restriction.
Restriction Summary [new5] / Treatment of Concept: [new5]		
		Indication: Severe Crohn disease
		Treatment Phase: Initial 1 (new patient), Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years), or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) - balance of supply
		Clinical criteria:
		Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (new patient) restriction to complete the 3 doses (the initial infusion regimen at 0, 4 and 8 weeks); 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 in biological medicine of less than 5 years) restriction to complete the 3 doses (the initial infusion regimen at 0, 4 and 8 weeks); or
		Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete the 3 doses (the initial infusion regimen at 0, 4 and 8 weeks); or
		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 12 weeks therapy available under Initial 1, 2 or 3 treatment or
		The treatment must provide no more than the balance of up to 24 weeks treatment available under Continuing treatment
		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

Proposed Restrictions
Initial treatment 1,2, 3, Grandfather Arrangements (Initial) & Balance of Supply (HSD IV Infusion)
Abridged version of restrictions (to mirror General Schedule restrictions)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
GUSELKUMAB					
guselkumab 200 mg/20 mL injection, 20 mL vial	NEW (public)	1	1	2	Tremfya
guselkumab 200 mg/20 mL injection, 20 mL vial	NEW (private)	1	1	2	Tremfya

Concept ID (for internal Dept. use)	**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (FULL assessment) in writing only via post/HPOS upload) *[for balance of supply - Authority Required (telephone/electronic)]*
	Authority ☒ Complex Authority Required (CAR)
Restriction Summary [new] / Treatment of Concept: [new]	
	Indication: Severe Crohn disease
	Treatment Phase: Initial 1 (new patient)
Restriction Summary [new] / Treatment of Concept: [new]	
	Indication: Severe Crohn disease
	Treatment Phase: Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
Restriction Summary [new] / Treatment of Concept: [new]	
	Indication: Severe Crohn disease
	Treatment Phase: Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
Restriction Summary [new] / Treatment of Concept: [new]	
	Indication: Severe Crohn disease
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements *(for patients transitioning through induction doses)*
Restriction Summary [new] / Treatment of Concept: [new]	
	Indication: Severe Crohn disease
	Treatment Phase: Initial 1 (new patient), Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years), or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) - balance of supply

Overarching Administrative Advice

	Administrative Advice: SEVERE CROHN DISEASE - TREATMENT PHASES AND CYCLES The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of benefits that contain the words: 'severe Crohn disease' in the stated PBS indication. Some of these benefits are not biological medicines, but are small molecules (e.g. a Janus-kinase inhibitor). Where the term 'biological medicine' appears in the restriction, it includes such benefits for PBS administrative purposes. A patient is eligible for PBS-subsidised treatment with only one PBS-subsidised biological medicine at any one time. Treatment cycle: A treatment cycle begins when an authority application is approved under an Initial 1 or Initial 3 type restriction. Once commenced, where biological medicine fails to provide the patient with an adequate response on 3 occasions, the current treatment cycle ends and there must be an absence of PBS-subsidy for a period of 5 years. The 5 year break is measured from the date of the last approval for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with a biological medicine under the new treatment cycle. An exception to this 5 year break clause applies where: (i) since the commencement of the break, an additional biological medicine has since become PBS-listed with a different pharmacological mechanism of action (i.e. the newly listed biological medicine) relative to those available on the PBS at the time of commencing the 5 year break; and (ii) the patient has never been prescribed the newly listed biological medicine; and (iii) the prescribed biological medicine is the newly listed biological medicine. Prescribing of the newly listed biological medicine is to occur through the 'Initial 2' treatment phase listing and the patient will not be in a new treatment cycle (i.e. where this newly listed biological medicine fails to provide an adequate response, the current treatment cycle ends and there must be an absence of PBS-subsidised biological medicine for a period of 5 years unless the exception outlined above is triggered again). Within the same treatment cycle, the same PBS-subsidised biological medicine cannot continue to be subsidised where it has resulted in an inadequate response. An inadequate response is one which does not meet the minimum improvements in disease measures stated in the Continuing treatment restriction. A serious adverse reaction leading to treatment discontinuation will be exempted from being counted as an inadequate response. There is no limit to the number of treatment cycles a patient may undertake in their lifetime. Treatment phases: (a) Initial 1 Apply through this treatment phase where the patient has never been treated with PBS-subsidised biological medicine for this indication. (b) Initial 2 Apply through this treatment phase where the prescribed treatment is changing (other than dose/form), or, where there has been a break in therapy of less than 5 years and treatment is resuming; authority applications through this treatment phase do not require prior response to conventional therapies to be re-established and do not require baseline disease activity to be re-demonstrated. An assessment of response to the preceding supply must be provided - where it is not, it will be assumed that the preceding supply provided an inadequate response. (c) Initial 3 Apply through this treatment phase where treatment is resuming after an absence of PBS-subsidy for at least 5 years; authority applications through this treatment phase do not require a re-trial of conventional therapies. (d) Continuing treatment Apply through this treatment phase where an adequate response to the preceding supply is observed (or where the dose is increasing where multiple strengths exist). It is recommended that a patient be reviewed in the 4 weeks prior to exhausting the current supply to ensure uninterrupted supply. Continuing treatment authority applications are not to be made on the same day as Initial treatment authority applications. (e) Balance of supply

	Apply through this type of treatment phase only where the benefit was not requested in the full amount available in the preceding supply - this may be because the maximum quantity was not prescribed and/or the full number of repeat prescriptions was not prescribed. The intent of this treatment phase listing is to: (i) provide the balance of what could have been obtained had the full quantity and number of repeats been prescribed in the preceding authority application, (ii) allow further time for an adequate response to treatment to be demonstrated where it may not have already, and (iii) provide more immediate access to PBS-subsidy via a telephone/online authority application relative to an 'in-writing only' application where the preceding supply was obtained through such.

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.