

**5.12 RISANKIZUMAB,  
Solution concentrate for I.V. infusion 600 mg in  
10 mL,  
Injection 360 mg in 2.4 mL in pre-filled cartridge,  
Skyrizi<sup>®</sup>,  
AbbVie Pty Ltd.**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested Section 100 (Highly Specialised Drugs Program - for IV forms) and General Schedule (for the SC forms), Authority Required (in writing) listings of risankizumab for the treatment of severe Crohn’s disease (CD) and complex refractory fistulising Crohn’s disease (FCD) under the same restrictions and clinical criteria as the other PBS-listed biologics.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus ustekinumab (for severe CD) and adalimumab (for FCD).

**Table 1: Key components of the clinical issue addressed by the submission – severe Crohn’s disease**

<b>Component</b>	<b>Description</b>
Population	Adults with severe Crohn’s disease, who have failed to achieve an adequate response, or are contraindicated, to prior systemic therapy
Intervention	Induction regimen: risankizumab 600 mg intravenously at Week 0, Week 4, Week 8 Maintenance regimen: risankizumab 360 mg subcutaneously at Week 12, and then every 8 weeks thereafter
Comparator	Ustekinumab – primary comparator Infliximab, adalimumab, vedolizumab – supplementary comparators
Outcomes	Clinical response and clinical remission <sup>a</sup>
Clinical claim	Risankizumab is non-inferior to ustekinumab at achieving clinical response and clinical remission and non-inferior in terms of safety.

Source: Table 1-1, p3 of the submission

<sup>a</sup>Outcomes defined as follows:

Clinical response: CDAI reduction of  $\geq 100$  points from baseline

Clinical remission: CDAI  $< 150$

**Table 2: Key components of the clinical issue addressed by the submission – fistulising Crohn’s disease**

Component	Description
Population	Patients with complex refractory fistulising Crohn’s disease who have externally draining enterocutaneous or rectovaginal fistula
Intervention	Induction regimen: risankizumab 600 mg intravenously at Week 0, Week 4, Week 8 Maintenance regimen: risankizumab 360 mg subcutaneously at Week 12, and then every 8 weeks thereafter
Comparator	Infliximab and adalimumab
Outcomes	Fistula response and fistula remission <sup>a</sup>
Clinical claim	Risankizumab is non-inferior to infliximab and adalimumab at achieving fistula remission and fistula response and non-inferior in terms of safety.

Source: Table 1-1, p3 of the submission

<sup>a</sup>Outcomes defined as follows:

Fistula response: ≥50% closure in patients with fistulae at baseline

Fistula remission: no draining fistula in patients with fistulae at baseline

## 2 Background

### **Registration status**

- 2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the proposed Australian Product Information document and the TGA Clinical Evaluation Report (Round 1) were available. The Delegate’s Overview was not received prior to consideration by the PBAC at its July 2022 meeting.
- 2.2 The indication proposed in the draft Product Information (PI) is as follows:  
‘SKYRIZI is indicated for the treatment of moderate to severe active Crohn's disease in patients 16 years of age and older’
- 2.3 FCD was not proposed as a separate indication in the PI. The submission highlighted that in the recommendation of adalimumab in FCD in 2010, the PBAC noted that FCD is ‘a manifestation of moderate to severe Crohn disease, and that it was reasonable to interpret that the TGA approved indication (moderate to severe CD) includes patients with fistulising disease’ (paragraph 12, Adalimumab Public Summary Document (PSD), Nov 2010). However, in March 2017 when the PBAC did not recommend the listing of ustekinumab for the treatment of FCD, the PBAC noted that ‘[ustekinumab] was not currently TGA registered for the FCD indication’ (ustekinumab PSD, March 2017).

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

## 3 Requested listing

- 3.1 The requested abridged listings for severe CD and FCD are provided below. The proposed listings are consistent with existing biologic listings for CD and FCD.

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Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max Qty (units)	No. of Rpts	DPMQ	AEMP	Proprietary Name and Manufacturer
<b>Initial treatment</b>						
RISANKIZUMAB 600 mg/10.0 mL concentrate solution for infusion in a single-dose vial	1	1	2	\$/ (published)	\$/ (published)	SKYRIZI® AbbVie Pty Ltd
<b>Continuing treatment</b>						
RISANKIZUMAB 360 mg/2.4 mL solution for infusion subcutaneous injection in a pre-filled cartridge	1	1	2	\$/ (published)	\$/ <sup>a</sup> (published)	SKYRIZI® AbbVie Pty Ltd

Abbreviations: AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity

Note: The sponsor proposed a special pricing agreement (SPA)

<sup>a</sup>The AEMP presented in Table 1-7 and the Executive Summary (\$/ ) was not consistent with the AEMP used in the cost-minimisation analysis presented in Section 3 (Table 3-7, p143 of the submission)

<b>Category / Program:</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	Medical Practitioners
<b>Severity:</b>	Severe
<b>Condition:</b>	Crohn disease
<b>PBS Indication:</b>	Severe Crohn disease
<b>Restriction:</b>	Authority Required - In Writing
<b>Treatment criteria:</b>	Must be treated by a gastroenterologist or consultant physician [specialising in gastroenterology]
<b>Population criteria:</b>	Patient must be aged 18 years or older.
<b>Treatment phase</b>	<b>Initial treatment</b>
<b>Clinical criteria</b>	<p>Patient must have confirmed severe Crohn disease; AND</p> <p>Patient must have failed to achieve an adequate response to prior systemic therapy (corticosteroids and at least 3 months of immunosuppressive therapy); AND</p> <p>Patient must have severity of disease activity with CDAI <math>\geq 300</math>; OR CDAI <math>\geq 220</math> with extensive small intestine disease; AND</p> <p>Evidence of intestinal inflammation; OR in high faecal output state; OR require surgery or total parenteral nutrition as the next therapeutic option; AND</p> <p>The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction.</p>
<b>Prescriber instructions</b>	<p>A maximum quantity and number of repeats to provide for an initial 12 week course of this drug will be authorised under this item code. A further 8 week course of treatment can be accessed under the balance of supply criteria.</p> <p>The assessment of the patient's response to this initial course of treatment, including the balance of supply, must be made following a minimum of 16 weeks of therapy so that there is adequate time for a response to be demonstrated.</p> <p>It is recommended that an application for continuing treatment is posted to the Department of Human Services at the time of the 16 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p>

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<b>Category / Program:</b>	Section 85 - General
<b>Prescriber type:</b>	Medical Practitioners
<b>Severity:</b>	Severe
<b>Condition:</b>	Crohn disease
<b>PBS Indication:</b>	Severe Crohn disease
<b>Treatment criteria:</b>	Must be treated by a gastroenterologist or consultant physician [specialising in gastroenterology]
<b>Population criteria:</b>	Patient must be aged 18 years or older.
The above criteria apply to all treatment phases outlined below:	
<b>Treatment phase</b>	<b>Continuing treatment</b>
<b>Clinical criteria</b>	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
<b>Restriction level</b>	Authority Required – Telephone
<b>Prescriber instructions</b>	Each application for subsequent continuing treatment with this drug must include an assessment of the patient's response to the prior course of therapy. 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.

<b>Category / Program:</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	Medical Practitioners
<b>Severity:</b>	Complex refractory
<b>Condition:</b>	Fistulising Crohn disease
<b>PBS Indication:</b>	Complex refractory fistulising Crohn disease
<b>Restriction:</b>	Authority Required - In Writing
<b>Treatment criteria:</b>	Must be treated by a gastroenterologist or consultant physician [specialising in gastroenterology]
<b>Population criteria:</b>	Patient must be aged 18 years or older.
The above criteria apply to all treatment phases outlined below:	
<b>Treatment phase</b>	<b>Initial treatment</b>
<b>Clinical criteria</b>	Patient must have confirmed Crohn disease; AND Must have an externally draining enterocutaneous or rectovaginal fistula; AND The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction.
<b>Prescriber instructions</b>	A maximum quantity and number of repeats to provide for an initial 12 week course of this drug will be authorised under this item code. A further 8 week course of treatment can be accessed under the balance of supply criteria. The assessment of the patient's response to this initial course of treatment, including the balance of supply, must be made following a minimum of 16 weeks of therapy so that there is adequate time for a response to be demonstrated. It is recommended that an application for continuing treatment is posted to the Department of Human Services at the time of the 16 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.

<b>Category / Program:</b>	Section 85 - General
<b>Prescriber type:</b>	Medical Practitioners
<b>Severity:</b>	Complex refractory
<b>Condition:</b>	Fistulising Crohn disease
<b>PBS Indication:</b>	Complex refractory fistulising Crohn disease
<b>Treatment criteria:</b>	Must be treated by a gastroenterologist or consultant physician [specialising in gastroenterology]
<b>Population criteria:</b>	Patient must be aged 18 years or older.
The above criteria apply to all treatment phases outlined below:	
<b>Treatment phase</b>	<b>Continuing treatment</b>
<b>Clinical criteria</b>	Patient must have received this drug as most recent course of PBS biological for this condition; AND Patient must have demonstrated an adequate response to treatment with this drug for this condition as $\geq 50\%$ reduction in draining fistula or marked reduction in drainage and less pain; AND Patient must not receive >24 weeks of treatment
<b>Restriction level</b>	Authority Required – Telephone
<b>Prescriber instructions</b>	Each application for subsequent continuing treatment with this drug must include an assessment of the patient's response to the prior course of therapy. 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.

- 3.2 A Special Pricing Arrangement (SPA) was requested. It is noted that SPAs apply to ustekinumab and vedolizumab in CD.
- 3.3 The requested restrictions population is narrower than the proposed TGA indications in the target age group. The proposed TGA indication for risankizumab is for the treatment of moderate to severe active Crohn's disease in patients 16 years of age and older. The requested PBS restrictions in the submission restrict use to adults over 18 years.
- 3.4 The submission proposed that the Authority level for risankizumab be lowered to Telephone Authority for continuing prescriptions, to align with the restriction level in place for some PBS listings in moderate to severe ulcerative colitis (the other form of IBD). All the other biologic drugs PBS listed for severe CD and/or FCD require Written Authorities. The PBAC recently considered the written authority level of the following medicines for severe Crohn disease (adult): infliximab, ustekinumab, vedolizumab and adalimumab and recommended no change to written authority level (Review of Authority Required (Written) PBS listings Tranche 3, July 2021 PBAC Outcomes).

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

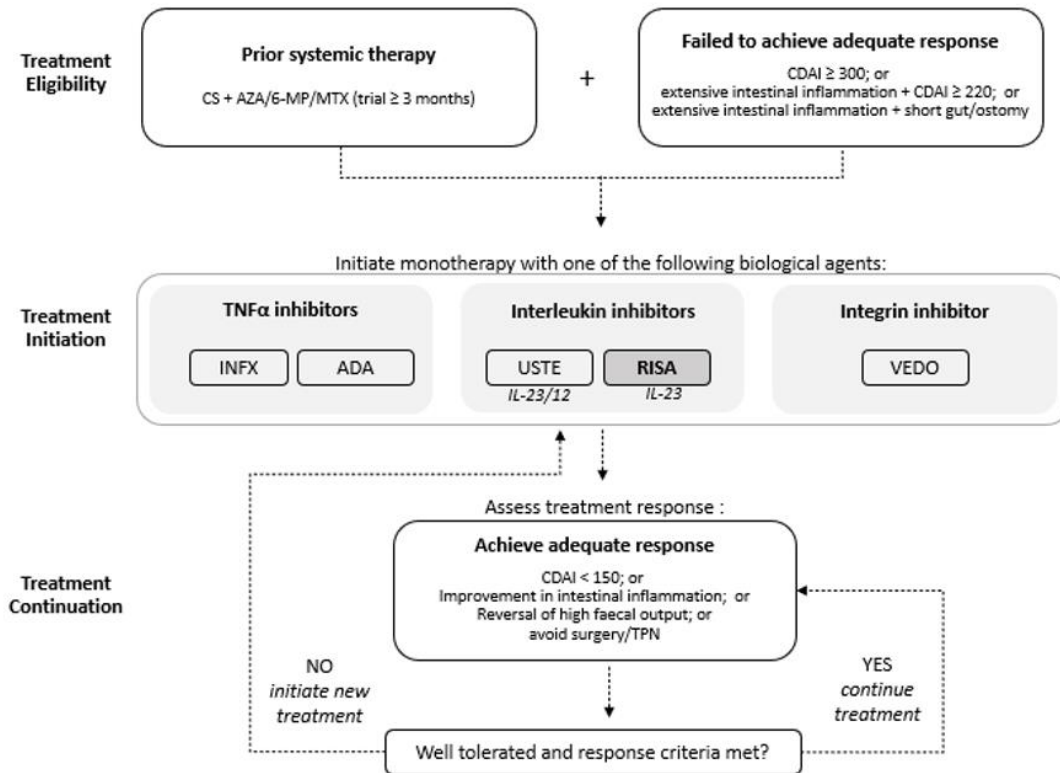
## 4 Population and disease

- 4.1 Crohn's disease is one of the main forms of inflammatory bowel disease (IBD), along with ulcerative colitis. It is an incurable, progressive, inflammatory gastrointestinal disorder that damages the gastrointestinal tract through inappropriate immune

activation and chronic inflammation. Anywhere from the mouth to the anus can be affected. The course of disease is usually episodic with remitting and relapsing symptoms. Damage to the gastrointestinal tract in CD is associated with significant morbidity and has a marked impact on the patient's quality of life as the most common symptoms include debilitating pain, rectal bleeding, diarrhoea, fatigue, and weight loss due to malnutrition. The submission targeted two subgroups of patients with Crohn's disease – severe CD and complex refractory FCD. FCD is characterised by ulceration and development of a sinus tract which penetrates through the bowel wall and connects two epithelial-lined organs such as the intestine to the skin (enterocutaneous) or to the vagina (enterovaginal).

- 4.2 Risankizumab is a selective humanised immunoglobulin G1 antagonistic monoclonal antibody directed against the p19 subunit of IL-23, a cytokine that contributes to gastrointestinal inflammation in CD. IL-23 is elevated in colonic mucosa in Crohn's disease and promotes survival of T helper 17 (Th17) cells, which produce pro-inflammatory downstream cytokines. The submission stated that risankizumab has unique pharmacokinetic and pharmacodynamic properties that give rise to a durable effect of more than 1 year after the final induction dose, which may bias results against risankizumab. The PBAC has acknowledged this in their recommendation of ustekinumab for CD (paragraph 7.6, Ustekinumab PSD, March 2017).
- 4.3 The proposed treatment algorithms for CD and FCD are presented in the figures below.

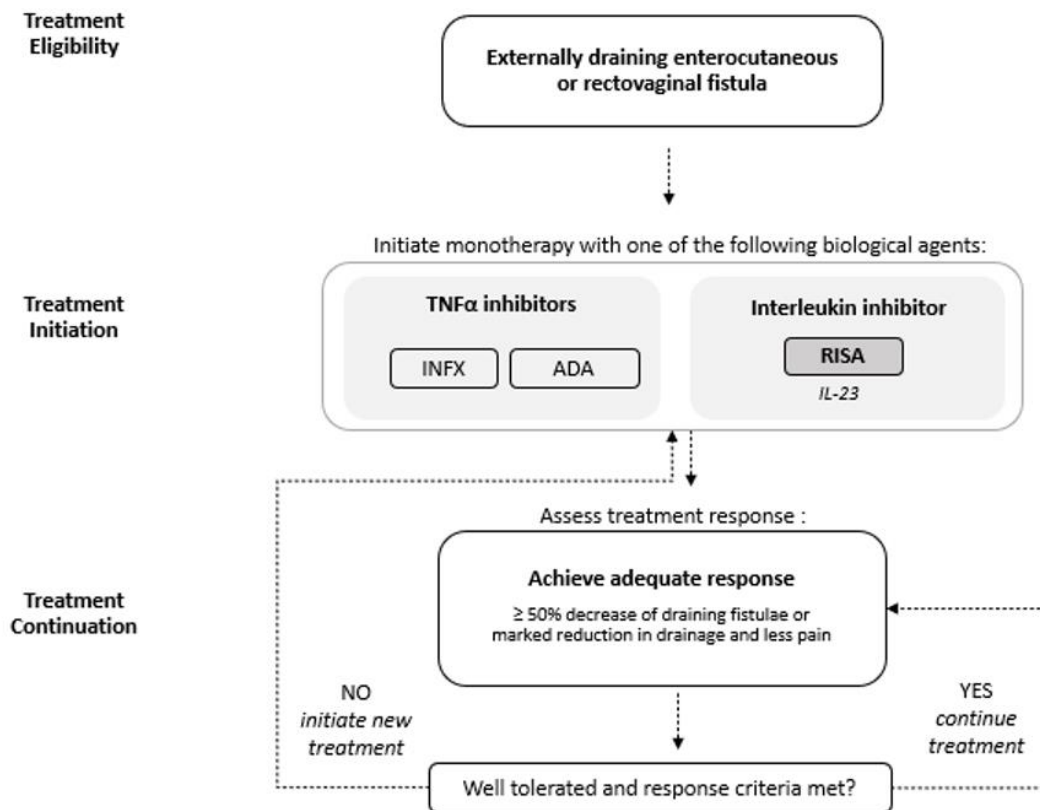
Figure 1: Current and proposed clinical management algorithms – severe CD



Source: Figure 1-5, p41 of the submission

Abbreviations: ADA = adalimumab; CDAI = Crohn’s Disease Activity Index; CS = corticosteroids; IL = interleukin; INFX = infliximab; MP = mercaptopurine; MTX = methotrexate; TPN = total parenteral nutrition; RISA = risankizumab; USTE = ustekinumab; VEDO = vedolizumab.

Figure 2: Current and proposed clinical management algorithms – FCD



Source: Figure 1-6, p42 of the submission

Abbreviations: ADA = adalimumab; IL = interleukin; INFX = infliximab; RISA = risankizumab

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

## 5 Comparator

- 5.1 For severe CD population, the submission nominated ustekinumab as the main comparator because ustekinumab is the closest pharmacological analogue to risankizumab, has a PBS population that is also restricted to use in adults, and has an almost identical manner of administration and dosing regimen. The submission also nominated infliximab, adalimumab and vedolizumab as supplementary comparators.
- 5.2 For FCD population, the submission nominated adalimumab and infliximab as the main comparators as they are the only other treatment options available in the proposed FCD patient population. The submission claimed that adalimumab is the most widely used treatment for FCD, therefore, the most appropriate comparator for risankizumab.
- 5.3 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. Alternative therapies for CD include infliximab, adalimumab, ustekinumab and vedolizumab and for FCD include infliximab and adalimumab.

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

## 6 Consideration of the evidence

- 6.1 In the pre-PBAC response, the sponsor acknowledged that the low patient numbers in clinical trials made it difficult to demonstrate the clinical effectiveness of risankizumab in the treatment of FCD and therefore withdrew their request for a listing RIS for FCD. For completeness, the clinical evaluation and ESC view of the request relating the FCD population have been retained in the PSD .

### ***Sponsor hearing***

- 6.2 There was no hearing for this item.

### ***Consumer comments***

- 6.3 The PBAC noted and welcomed the input from health care professionals (HCPs; 2) and consumer organisation Crohn's & Colitis Australia (CCA) via the Consumer Comments facility on the PBS website.
- 6.4 CCA stated that the SC formulation is an important option for consumers because it would not require infusion in a medical facility, providing flexibility for consumers, avoidance of absence from work for treatment and reduced travel for those particularly in remote or regional areas. CCA noted that risankizumab provides an additional treatment option for consumers who had failed multiple agents.
- 6.5 The HCPs detailed the high morbidity and disability associated with Crohn's Disease and the poor response to existing treatments in up to 50% of patients, thereby creating an unmet need. The comments from HCPs described a range of benefits of treatment with risankizumab including its excellent efficacy, similar safety profile to other biologics, enhanced quality of life and the advantages of the SC administration.

### ***Clinical trials***

- 6.6 There were no head-to-head trials comparing risankizumab with ustekinumab for severe CD or risankizumab with adalimumab and/or infliximab for FCD.
- 6.7 For severe CD, the submission was based on:
- Four trials comparing risankizumab to placebo: M15-993 (N=80), ADVANCE (N=559) and MOTIVATE (N=413) (induction trials) and FORTIFY (N=363)

(maintenance trial). Results from the induction trials were meta-analysed and used in the indirect comparison.

- An indirect comparison to ustekinumab, based on three trials comparing ustekinumab to placebo: UNITI-1 (N=496) and UNITI-2 (N=419) (induction trials) and IM-UNITI (N=265) (maintenance trial). Results from the induction trials were meta-analysed and used in the indirect comparison.
- The submission also presented supplementary analyses of indirect comparisons comparing risankizumab to adalimumab, infliximab, and vedolizumab to support the clinical claim.
- The total patient population (N) included for consideration in the submission were based on patients allocated to placebo and the proposed risankizumab dose (600 mg IV for induction and 360 mg SC for maintenance).
- The results of all comparator trials have previously been considered by the PBAC in the March 2017 submission for ustekinumab.

6.8 For FCD, the submission was based on:

- Subgroup analysis of patients with FCD from three trials comparing risankizumab and placebo: ADVANCE (27/559; 5%) and MOTIVATE (29/413; 7%) (induction trials) and FORTIFY (22/363; 6%) (maintenance trial). These trials reported fistula remission at week 12 in patients with draining fistulae at baseline as a secondary endpoint and fistula response ( $\geq 50\%$  reduction in number of draining fistula from baseline) as a post-hoc subgroup analysis.
- A naïve (unadjusted) comparison to adalimumab based on subgroup analysis of patients with FCD from three trials comparing adalimumab and placebo: CLASSIC-I (18/150; 12%) and GAIN (45/325; 14%) (induction trials) and CHARM (approximately 15%) (maintenance trial) and to infliximab based on two trials with FCD specific populations comparing infliximab and placebo: T20 (N=62) (induction trial) and ACCENT-II (N=195) (maintenance trial). Naïve comparisons limit the ability to determine if any differences noted between the efficacy measures were solely attributable to the treatment.

6.9 Details of the trials presented in the submission are provided in the table below.

**Table 3: Trials and associated reports presented in the submission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Risankizumab</b>		
M15-993 NCT02031276	A Phase 2, Multicenter, Randomized, Double-Blind, Multiple Dose, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Pharmacokinetics, and Safety of BI 655066 (Risankizumab), an IL-23 p19 Antagonist Monoclonal Antibody, in Patients With Moderately to Severely Active Crohn's Disease Who Are Naïve to or Were Previously Treated With Anti-TNF Therapy.  Feagan, Sandborn, W. J., D'Haens, G., Panés, J., Kaser, A., Ferrante, M., Louis, E., Franchimont, D., Dewit, O., Seidler, U., Kim, K.-J., Neurath, M. F., Schreiber, S., Scholl, P., Pamulapati, C., Lalovic, B., Visvanathan, S., Padula, S. J., Herichova, I., ... Böcher, W. O. (2017). Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study.	26 October 2017  The Lancet (British Edition), 389(10080), 1699–1709. <a href="https://doi.org/10.1016/S0140-6736(17)30570-6">https://doi.org/10.1016/S0140-6736(17)30570-6</a> .
M16-066 ADVANCE NCT03105128	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease.	19 December 2019.
M15-991 MOTIVATE NCT03104413	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects with Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment.	19 December 2019.
M16-000 FORTIFY NCT03105102	Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects with Crohn's Disease Who Responded to Induction Treatment in M16-006 or M15-991; or Completed M15-989.	9 April 2020.
<b>Ustekinumab</b>		
UNITI-I UNITI-II IM-UNITI	Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease.	New England Journal of Medicine. 2016;375(20):1946-60
<b>Adalimumab</b>		
CLASSIC-I	Hanauer, S. B., Sandborn, W. J., Rutgeerts, P., Fedorak, R. N., Lukas, M., MacIntosh, D., Panaccione, R., Wolf, D., and Pollack, P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial.	Gastroenterology. 2006 Feb;130(2):323-33
GAIN	Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Colombel, J. F., Panaccione, R., D'Haens, G., Li, J., Rosenfeld, M. R., Kent, J. D., and Pollack, P. F. Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial.	Annals of Internal Medicine 2007; 146 (12): 829-838
CHARM	Colombel, J., Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Panaccione, R., Schreiber, S., Byczkowski, D., Li, J., Kent, J. D., and Pollack, P. F. Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial.	Gastroenterology 2007; 132 (1): 52-65.s
<b>Infliximab</b>		
T20	Present, D. H., Rutgeerts, P., Targan, S., Hanauer, S. B., Mayer, L., Van Hogezaand, R. A., Podolsky, D. K., Sands, B. E., Braakman, T., DeWoody, K. L., Schaible, T. F., and Van Deventer, S. J. Infliximab for the treatment of fistulae in patients with Crohn's disease. The New England Journal of Medicine; 1999; 340: 1398- 1405.	New England Journal of Medicine. 1999;340:1398-1405

ACCENT-II	Sands, B. E., Anderson, F. H., Bernstein, C. N., Chey, W. Y., Feagan, B. G., Fedorak, R. N., Kamm, M. A., Korzenik, J. R., Lashner, B. A., Onken, J. E., Rachmilewitz, D., Rutgeerts, P., Wild, G., Wolf, D. C., Marsters, P. A., Travers, S. B., Blank, M. A., and Van Deventer, S. J. Infliximab maintenance therapy for fistulising Crohn's disease. The New England Journal of Medicine 2004; 350(9): 876-885.	New England Journal of Medicine 2004; 350(9): 876-885
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Source: Table 2.3, pp31-33 of the submission.

6.10 The key features of the randomised trials for severe CD and FCD are summarised in the tables below.

**Table 4: Key features of the included evidence: Severe CD (indirect comparison)**

Trial	N	Design	Duration (Assessment of outcomes)	Risk of bias	Patient population	Outcome(s)
<b>Risankizumab versus placebo</b>						
M15-993	IP: 121	Phase 2, R, DB, PC, MC, IP	IP: 12 weeks	Low	Biological-naïve and experienced patients	CDAI clinical remission <sup>a</sup> * CDAI clinical response <sup>b</sup>
ADVANCE	IP: 931	Phase 3, R, DB, PC, MC, IP	IP: 12 weeks	Low	Biological-naïve and experienced patients	
MOTIVATE	IP: 618	Phase 3, R, DB, PC, MC, IP	IP: 12 weeks	Low	Biological-experienced and inadequate response/intolerant only	
FORTIFY	IP:524 (sub-study 1)	Phase 2, R, DB, PC, MC, IP	MP: 64 weeks#	Low	Responders from ADVANCE and MOTIVATE ( $\geq 30\%$ decrease in SF and/or $\geq 30\%$ decrease in average daily AP score, and both not worse than baseline of induction)	
<b>Ustekinumab versus placebo</b>						
UNITI-1	IP: 741	Phase 3, R, DB, PC, MC, IP	IP: 8 weeks	Low	TNF $\alpha$ refractory	CDAI clinical response <sup>b</sup> * CDAI clinical remission <sup>a</sup>
UNITI-2	IP: 628	Phase 3, R, DB, PC, MC, IP	IP: 8 weeks	Low	TNF naïve and TNF experienced (but non-refractory)	
IM-UNITI	MP: 397	Phase 3, R, DB, PC, MC, MP	MP: 52 weeks#	Low	Patients with response (CR-100) to UST induction at W8 of UNITI-1 or UNITI-2	

Source: Table 2.8, p48-52 of the submission

Abbreviations: AP=abdominal pain; CDAI=Crohn's Disease Activity Index DB=double blind; MC=multicentre, IP= induction phase; MP = maintenance phase; OL=open-label; PC= placebo-controlled; SF= stool frequency; R=randomised; TNF= tumour necrosis factor; CR-100= clinical response as defined by attaining CDAI  $\geq 100$  point reduction from baseline; UST= ustekinumab;

\* denote primary trial outcome

# counted from start of induction therapy

a. CDAI clinical remission was classified as CDAI < 150.

b. CDAI clinical response defined by a CDAI reduction from baseline of at least 100 points or a CDAI < 150.

Table 5: Key features of the included evidence: FCD (naive comparison)

Trial	N (with fistulas)	Design	Duration (Assessment of outcomes)	Risk of bias	Patient population	Outcome(s)
<b>Risankizumab versus placebo</b>						
ADVANCE	IP: 27	Phase 3, R, DB, PC, MC, IP	IP: 12 weeks	Low	Bio-naïve and experienced patients	<u>Fistula remission</u> No draining fistula (wk12) <u>Fistula response</u> <sup>a</sup> ≥50% reduction in number of draining fistulas
MOTIVATE	IP: 29	Phase 3, R, DB, PC, MC, IP	IP: 12 weeks	Low	Bio-experienced and inadequate response/intolerant only	<u>Fistula remission</u> No draining fistula (wk12) <u>Fistula response</u> <sup>a</sup> ≥50% reduction in number of draining fistulas
FORTIFY	IP: 22	Phase 2, R, DB, PC, MC, IP	MP: 64 weeks#	Low	Responders from ADVANCE and MOTIVATE (≥30% decrease in SF and/or ≥30% decrease in average daily AP score, and both not worse than baseline of induction)	<u>Fistula remission</u> No draining fistula (wk64#) <u>Fistula response</u> <sup>a</sup> ≥50% reduction in number of draining fistulas
<b>Adalimumab versus placebo</b>						
CLASSIC I	IP: 18	Phase 3, R, DB, PC, MC, IP	IP: 4 weeks	Low	TNF naïve	<u>Fistula response</u> ≥50% reduction in number of draining fistulas at 2 consecutive visits (wk 2 and 4). <u>Fistula remission</u> Closing of all draining fistulas at 2 consecutive visits (wk 2 and 4)
GAIN	IP: 45	Phase 3, R, DB, PC, MC, IP	IP: 4 weeks	Low	TNF-experienced (infliximab) – intolerant or lost response	<u>Fistula response</u> ≥50% reduction in number of draining fistulas at 2 consecutive visits (wk 2 and 4). <u>Fistula remission</u> Closing of all draining fistulas at 2 consecutive visits (wk 2 and 4)
CHARM	MP: 64	Phase 3, R, DB for MP, PC, MC, MP	(IP: 4 weeks) MP: 56 weeks#	Low	TNF-naïve and TNF-experienced (non-refractory)	<u>Fistula remission</u> Complete closure of all draining fistulas (wk26 and 56#)
<b>Infliximab versus placebo</b>						
T20	IP: 62	Phase 3, R, DB, PC, MC, IP	IP: 18 weeks	Low	Single or multiple draining fistulas > 3 months; TNF naïve	<u>Fistula response</u> ≥50% reduction in number of draining fistulas at >2 consecutive visits. <u>Fistula remission</u> Absence of any draining fistulas at 2 consecutive visits

Trial	N (with fistulas)	Design	Duration (Assessment of outcomes)	Risk of bias	Patient population	Outcome(s)
ACCENT-II	MP: 195	Phase 3, R, DB for MP, PC, MC, MP	(IP: 14 weeks) MP: 54 weeks#	Low	Single or multiple draining fistulas > 3 months; Infliximab naive	<u>Fistula response</u> Time to loss of response* ≥50% reduction in number of draining fistulas at consecutive visits ≥4 weeks apart (at wk 54#). <u>Fistula remission</u> Absence of draining fistulas (wk54#)

Source: Table 2.8, p48-52 of the submission

Abbreviations: AP=abdominal pain; CDAI=Crohn's Disease Activity Index DB=double blind; MC=multicentre, IP= induction phase; MP = maintenance phase; OL=open-label; PC= placebo-controlled; SF= stool frequency; R=randomised; TNF= tumour necrosis factor; wk= week

\* denote primary trial outcome

# counted from start of induction therapy

a. Not an outcome of the trial but was presented as post-hoc subgroup analysis

### **Severe CD**

6.11 All patients included in the trials (M15-993, ADVANCE, MOTIVATE, FORTIFY, UNITI-I, UNITI-II AND IM-UNITI) had moderate to severe CD (CDAI score of  $\geq 220$  and  $\leq 450$ ). The CDAI scores range from 0 to 600, therefore the upper cut-off at 450 may exclude patients with the most severe disease. The proposed PBS listing is for severe CD (CDAI score  $\geq 300$ ), therefore the population included in the trials is likely to include some moderate CD patients not eligible for the proposed PBS indication and exclude some severe CD patients who may be treated with risankizumab under PBS. This issue applies to both the risankizumab and ustekinumab trials. This was also highlighted in the TGA Clinical Evaluation report (Round 1) where TGA has requested for further data to demonstrate the outcomes by disease severity category (moderate Crohn's disease (CDAI score between 220 and 450) and severe Crohn's disease (CDAI score  $>450$ )) or to provide justification for risankizumab treatment in patients with severe CD (p85, Risankizumab TGA Clinical Evaluation Report, March 2022). However, the PBAC has previously considered trials that included moderate to severe CD (CDAI score of  $\geq 220$  and  $\leq 450$ ) to support the clinical and safety claims for severe CD. This included considerations for ustekinumab and vedolizumab. The Pre-Sub-Committee Response (PSCR) argued that PBAC previously considered trials that included moderate to severe CD (CDAI score of  $\geq 220$  and  $\leq 450$ ) in other previously recommended biologic therapies and claimed that the evidence presented in the submission was reasonable to support the clinical and safety claims for severe CD. Additionally, the PSCR claimed that the baseline severity of disease showed no impact on treatment outcomes across the clinical trials.

6.12 Prior treatment eligibility of patients included in the trials used in the indirect comparison differed. The risankizumab trials studied both patients who were biologic-naïve (M15-993) and who were biologic-experienced (ADVANCE, MOTIVATE AND FORTIFY), while the ustekinumab trials (UNITI-I and UNITI-II) included patients who were biologic-experienced (exposure to anti-TNF) but were naïve to interleukin-12 or

interleukin-23 antagonists. While the proposed PBS population can be biologic-naïve or biologic-experienced, all patients are required to have failed to achieve adequate response to prior systemic therapy.

- 6.13 The PBS continuing criteria relies on achieving CDAI clinical remission (CDAI<150 point). This was a primary outcome for the risankizumab trials but was a secondary outcome in the ustekinumab trials (UNITI-I and UNITI-II).
- 6.14 The eligibility criteria for entry into maintenance studies (risankizumab, FORTIFY and ustekinumab, IM-UNITI) differed between trials. Entry into FORTIFY required a SF/APS clinical response, defined as  $\geq 30\%$  decrease in average daily SF and/or  $\geq 30\%$  decrease in APS from baseline, while entry into IM-UNITI required achieved clinical response, defined as a decrease in CDAI score of  $\geq 100$  points. Both these criteria were less stringent than the proposed PBS continuation criteria. The submission contended that the less stringent entry criteria for risankizumab has the potential to bias maintenance results in favour of ustekinumab. The potential for bias in favour of ustekinumab is unclear as subgroup results for clinical remission were not presented.
- 6.15 There were differences in the timing of assessment between risankizumab trials and the comparators, which were likely due to the different dosing regimens. This will have an impact on the transitivity of the trials in the indirect comparison, however the direction of impact is unclear.
- 6.16 There were patients in the risankizumab trials that have been exposed to adalimumab, infliximab, vedolizumab and ustekinumab. The proportions exposed to these prior therapies range from 13.7% to 72.3%. This was balanced between risankizumab and placebo arms. No patients in the ustekinumab trials had been exposed to any of these prior therapies. The proportion of patients on concomitant therapies appears to be higher in the ustekinumab trials – corticosteroids (ranges from 35.7 to 48.5% ustekinumab vs 28.% to 36.4% risankizumab), 5-ASA (ranges from 20.1% to 44.5% ustekinumab vs 15.4% to 33.7% risankizumab) and immunomodulator ranges from 31.3% to 35.3% ustekinumab vs 18.8% to 46.2% risankizumab). This is likely to affect the transitivity of trials, however, the direction of impact is unclear.
- 6.17 Across the trials, there were differences in the protocols on use of concomitant treatments, particularly in the time when tapering or adjustments were allowed. This could impact the comparability between trials, and the direction of impact is unclear.
- 6.18 Although multiple doses of risankizumab were trialled, the submission focused on arms relevant to the proposed registered doses of 600 mg intravenously in the induction period and 360 mg subcutaneously in the maintenance period (p39 of the submission). Similar to the risankizumab trials, multiple doses were trialled in these ustekinumab trials and arms relevant to the proposed registered doses (for example, for ustekinumab 6mg/kg IV for induction and 90mg SC for maintenance) were included.

**FCD**

- 6.19 The number of patients with fistulas in the risankizumab trials was small (N = 11, less than 7% of the total trial population). Therefore, these trials are likely to be underpowered to detect differences in the outcomes proposed.
- 6.20 Apart from the infliximab trial (T20) which was a FCD specific trial with FCD related outcomes as a primary outcome (therefore adequately powered), for all other trials presented in the submission a subgroup of FCD patients were presented. Risankizumab trials relied on post-hoc analysis, therefore the results are uncertain and more prone to bias compared to outcomes assessed as primary or secondary outcomes as presented in the comparator trials.
- 6.21 There were imbalances in some baseline demographics and disease characteristics between treatment arms in the risankizumab trials. This included differences in proportions of males (ADVANCE – 44.4% placebo vs 66.7% risankizumab; MOTIVATE – 60% placebo vs 42.9% risankizumab), duration of disease (ADVANCE – 12 years placebo vs 7.5 years risankizumab) and exposure to prior therapies. Although some differences were expected as the FCD population represent a subgroup from the trials, the observed differences may confound the observed treatment effect. This may be particularly important because a naïve comparison was used to support the clinical claim for the FCD indication, and these differences are likely to have an impact on the robustness of the naïve comparison results.
- 6.22 Across trials, observed differences include mean age (ranges from 33.1 to 35.7 risankizumab, 33.2 to 39 adalimumab, 37 to 41.2 infliximab), baseline disease severity based on mean CDAI score (ranges from 334.8 to 344.7 risankizumab, 295 to 317.8 adalimumab, 184.4 (SD 98.5) infliximab). These differences may impact the transitivity of trials for the naïve comparison.
- 6.23 The definition for fistula response in the risankizumab trials was a decrease in the number of draining fistulae  $\geq 50\%$  from baseline, whereas in the comparator trials, the definition required the demonstration of a decrease for at least 2 consecutive visits. Similarly, in the comparator trials, the definition for fistula remission required a demonstration of closure of draining fistulae at multiple visits (at least 2) where risankizumab trials only required a demonstration of no draining fistulae at week 12 (induction) or 64 (maintenance). The definition of outcomes appeared to be more stringent in the comparator trials compared to risankizumab trials and would likely favour risankizumab.

## Comparative effectiveness

### Severe CD

6.24 Table 4 below presents the results for clinical remission and clinical response outcomes across the trials for the induction and maintenance phases separately. It also includes meta-analysed (pooled) results for the induction trials and results of the indirect comparison between risankizumab and ustekinumab.

**Table 6: Trial and indirect comparison results: risankizumab vs ustekinumab for induction**

Trial type or estimate	Trial ID	DMARD n/N (%)	PBO n/N (%)	OR [95% CI] <sup>a</sup>	RD [95% CI] <sup>b</sup>
<b>Clinical remission (CDAI &lt; 150)</b>					
RISA vs PBO	M15-993	15/41 (36.6)	6/39 (15.4)	<b>3.17 [1.08, 9.32]</b>	<b>0.21 [0.03, 0.40]</b>
	ADVANCE	152/336 (45.2)	43/175 (24.6)	<b>2.54 [1.69, 3.80]</b>	<b>0.21 [0.12, 0.29]</b>
	MOTIVATE	80/191 (41.9)	37/187 (19.8)	<b>2.92 [1.84, 4.63]</b>	<b>0.22 [0.13, 0.31]</b>
	Pooled	247/568 (43.5)	86/401 (21.4)	<b>2.73 [2.04, 3.66]</b> (p < 0.0001)	<b>0.21 [0.16, 0.27]</b> (p < 0.0001)
USTE vs PBO	UNITI I	52/249 (20.9)	18/247 (7.3)	<b>3.36 [1.90, 5.93]</b>	<b>0.14 [0.08, 0.20]</b>
	UNITI II	84/209 (40.2)	41/210 (19.5)	<b>2.77 [1.79, 4.30]</b>	<b>0.21 [0.12, 0.29]</b>
	Pooled	136/458 (29.7)	59/457 (12.9)	<b>2.98 [2.10, 4.21]</b> (p < 0.0001)	<b>0.16 [0.09, 0.24]</b> (p < 0.0001)
ITC result	–	–	–	0.916 [0.582, 1.443] (p = 0.7054)	0.05 [-0.043, 0.143] (p = 0.292)
<b>Clinical response (reduction of &gt;100 points in CDAI score from baseline)</b>					
RISA vs PBO	M15-993	17/41 (41.5)	9/39 (23.1)	2.36 [0.90, 6.23]	0.18 [-0.02, 0.38]
	ADVANCE	201/336 (59.8)	64/175 (36.6)	<b>2.58 [1.77, 3.77]</b>	<b>0.23 [0.14, 0.32]</b>
	MOTIVATE	114/191 (59.7)	56/187 (29.9)	<b>3.46 [2.26, 5.30]</b>	<b>0.30 [0.20, 0.39]</b>
	Pooled	332/568 (58.5)	129/401 (32.2)	<b>2.89 [2.20, 3.79]</b>	<b>0.25 [0.19, 0.32]</b>
USTE vs PBO	UNITI I	94/249 (37.8)	50/247 (20.2)	<b>2.39 [1.60, 3.57]</b>	<b>0.18 [0.10, 0.25]</b>
	UNITI II	121/209 (57.9)	67/210 (31.9)	<b>2.93 [1.97, 4.38]</b>	<b>0.26 [0.17, 0.35]</b>
	Pooled	215/458 (46.9)	117/457 (25.6)	<b>2.65 [2.00, 3.52]</b>	<b>0.21 [0.13, 0.30]</b>
ITC result	–	–	–	1.091 [0.737, 1.614] (p = 0.6649)	0.04 [-0.067, 0.147] (p = 0.4638)

Source: Table 2.39, p118 of the submission

Abbreviations: –, not required; CI, confidence interval; n, number of participants with event; N, total number of participants in group; OR, odds ratio; RD, risk difference; RISA, risankizumab; PBO, placebo; UST, ustekinumab; ITC, indirect treatment comparison. **Bold** indicates statistically significant results.

<sup>a</sup>>1 favours RISA in ITC; <sup>b</sup>>0 favours RISA in ITC

**Table 7: Trial and indirect comparison results: risankizumab vs ustekinumab for maintenance**

Trial type or estimate	Trial ID	DMARD n/N (%)	PBO n/N (%)	OR [95% CI] <sup>a</sup>	RD [95% CI] <sup>b</sup>
<b>Clinical remission (CDAI &lt; 150)</b>					
RISA vs PBO	FORTIFY	74/141 (52.5)	67/164 (40.9)	<b>1.60 [1.02, 2.52]</b>	<b>0.12 [0.00, 0.23]</b>
USTE vs PBO	IM UNITI	68/128 (53.1)	47/131 (35.9)	<b>2.03 [1.23, 3.33]</b>	<b>0.17 [0.05, 0.29]</b>
ITC result	–	–	–	0.788 [0.402, 1.544] (p = 0.488)	-0.05 [-0.216, 0.116] (p = 0.5555)
<b>Clinical response (reduction of &gt;100 points in CDAI score from baseline)</b>					
RISA vs PBO	FORTIFY	87/141 (61.7)	79/164 (48.2)	<b>1.73 [1.10, 2.74]</b>	<b>0.14 [0.02, 0.25]</b>
USTE vs PBO	IM UNITI	76/128 (59.38)	58/131 (44.27)	<b>1.84 [1.12, 3.01]</b>	<b>0.15 [0.03, 0.27]</b>
ITC result	–	–	–	0.94 [0.48, 1.842] (p = 0.8575)	-0.01 [-0.176, 0.156] (p = 0.9061)

Source: Table 2.40, p119 of the submission

Abbreviations: –, not required; CI, confidence interval; n, number of participants with event; N, total number of participants in group; OR, odds ratio; RD, risk difference; RISA, risankizumab; PBO, placebo; UST, ustekinumab; ITC, indirect treatment comparison. **Bold** indicates statistically significant results.

<sup>a</sup>>1 favours RISA in ITC; <sup>b</sup>>0 favours RISA in ITC

- 6.25 A statistically significant greater proportion of patients treated with risankizumab compared to placebo achieved clinical remission (CDAI<150) at week 12 (induction phase) and at week 64 (maintenance phase). Similarly, a statistically significant greater proportion of patients treated with ustekinumab compared to placebo achieved clinical remission (CDAI<150) at week 8 (induction phase) and at week 52 (maintenance phase).
- 6.26 Three of the risankizumab trials (all except M15-993) showed a statistically significant greater proportion of patients achieved a clinical response when treated with risankizumab compared to placebo at week 12 (induction phase) and at week 64 (maintenance phase). The confidence interval of results from M15-993 (induction phase) crossed the null – OR 2.36 (95%CI: 0.90, 6.23) and RD 0.18 (95%CI: -0.02, 0.38). M15-993 had smaller patient numbers (N=80) and lower statistical power (82% power) compared to other three risankizumab trials. In all ustekinumab trials (UNITI-I, UNITI-II and IM-UNITI) a statistically significant greater proportion of patients treated with ustekinumab compared to placebo achieved clinical response at week 8 (induction phase) and at week 52 (maintenance phase).
- 6.27 Patients that were randomised in FORTIFY were patients from either ADVANCE and MOTIVATE trials who responded to treatment and these patients had different induction doses. Subgrouping by induction dose (either 1200 mg IV or 600 mg IV) was pre-specified and stratified at randomisation. Patients whose last induction dose was 600 mg IV (proposed PBS induction dose) did not show a statistically significant difference in clinical remission compared to placebo (51.9% vs 50.7%; response rate difference 1.2% (95%CI: -15.7, 26.9%)) (Table 9, p108 FORTIFY CSR). This contrasts with the statistically significant result presented in the submission when all patients were analysed together regardless of induction dose. The overall results were likely driven by the low placebo rates in the subgroup of patients who had the higher induction dose.
- 6.28 The PSCR argued that the full ITT population was the most appropriate basis upon which to evaluate the comparative effectiveness of risankizumab as the analyses by induction dosing subgroup would be underpowered to detect differences for the primary outcome (clinical remission). The ESC considered while it was appropriate undertake the indirect comparisons based on the ITT population of the FORTIFY trial, also noted there appeared to be differences in the placebo response rates between induction dosage arms in the pivotal trial (50.7% in cohort randomised to placebo after 600 mg induction dose, 32.6% in the cohort randomised to placebo after 1,200 mg induction dose (Table 9, pg. 108 of the FORTIFY CSR). The ESC considered apparent lower placebo response rate in the subgroup who initially received the 1,200 mg dose may have driven the observed differences in results based on induction dose. The Pre-PBAC response acknowledged and agreed with the ESC view that the full ITT trial

population was the most appropriate basis for the indirect comparisons and noted the FORTIFY trial demonstrated a statistically significant proportion of patients treated with risankizumab achieved clinical remission at week 64 (53% v 41%, risk difference [95% CI] 0.12 [0.00, 0.23]) when compared to placebo. The Sponsor acknowledged the differences in placebo rates as highlighted by ESC but noted the TGA did not request for additional clarification on outcomes by dosing subgroup.

- 6.29 In FORTIFY, the secondary endpoint results (Table 12, p116 of FORTIFY CSR) showed that among subjects with CDAI remission at start of maintenance phase (i.e., those who would have met PBS continuing criteria), the proportion of patients in the risankizumab arm (68.6%) who achieved clinical remission was higher compared to placebo (48.2%), although not statistically significant after adjusting for this randomisation stratification factor. It does not appear that there is a difference in the treatment effect between those who achieved CDAI remission at start of maintenance phase (14.3%; 95%CI: 0.5,28.1) and those using the less stringent criteria (14.6%; 95%CI: 4.3,25).
- 6.30 For both clinical outcomes, results from the meta-analyses for risankizumab versus placebo and ustekinumab versus placebo showed that both biologics performed statistically better than placebo in both clinical remission and clinical response outcomes ( $p < 0.00001$ ) at the end of the induction period. Heterogeneity across trials ranged between 0% and 48% and was not statistically significant.
- 6.31 There was no statistically significant difference in the efficacy results between risankizumab and ustekinumab based on the indirect comparison presented. A non-inferiority margin was not nominated by the submission to assist with interpretation of the evidence. The submission stated that no non-inferiority margin has previously been considered by the PBAC for severe Crohn's disease (vedolizumab PSD, March 2015; ustekinumab PSD, March 2017) or fistulising Crohn's disease (adalimumab PSD, November 2010). The submission also did not present a defined minimally clinically important difference (MCID) for any of the efficacy outcomes.
- 6.32 Some key considerations that may impact the transitivity assumption include:
- The differences in prior treatment eligibility between trials resulting in patients exposed to different treatments prior and may have been intolerant or refractory. For example, patients in the risankizumab trials that have been exposed to adalimumab, infliximab, vedolizumab and ustekinumab while no patients in the ustekinumab trials have been exposed to any of these prior therapies. This could impact on the treatment effect and transitivity. However, the direction of the impact is unclear.
  - The proportion of patients on concomitant therapies appears to be higher in the ustekinumab trials – corticosteroids (ranges from 35.7 to 48.5% ustekinumab vs 28% to 36.4% risankizumab), 5-ASA (ranges from 20.1% to 44.5% ustekinumab vs 15.4% to 33.7% risankizumab) and immunomodulator ranges from 31.3% to 35.3%

ustekinumab vs 18.8% to 46.2% risankizumab). This could impact on the treatment effect and transitivity. However, the direction of the impact is unclear.

- In the maintenance phase trials (FORTIFY and IM-UNITI), the entry response criteria were different. The criteria in FORTIFY was based on SF/APS clinical response that was less stringent than that in IM-UNITI (CDAI clinical response).
- There were differences in timing of assessments between the risankizumab and ustekinumab trials. For example, for induction, assessment was at Week 12 for risankizumab and Week 8 for ustekinumab and for maintenance, assessments were at Weeks 64 and 52 for risankizumab and ustekinumab respectively. This could impact the comparability between trials; however, the direction of impact is unclear.
- Across all maintenance trials, treatment switching, or rescue therapy was permitted if patients demonstrated inadequate response or had treatment flare. The timing of intervention varied between trials. This could impact the comparability between trials however, the direction of the impact is unclear.
- The event rates in the placebo arm for risankizumab trials were higher compared to placebo in the ustekinumab trials. For example, for the clinical remission outcome the pooled placebo response rate for risankizumab trials was 21.4% compared to 12.9% in ustekinumab trials. The difference in placebo response rate may also reflect differences in the populations recruited, concomitant medication use or response criteria. This may bias against risankizumab in the indirect comparison.

6.33 The submission also presented supplementary analyses comparing risankizumab to other PBS-listed biologics (adalimumab, infliximab and vedolizumab). The submission performed a series of secondary ITCs for the induction and maintenance phases comparing risankizumab with ustekinumab, adalimumab, infliximab and vedolizumab via placebo. Only results based on the clinical remission (CDAI<150) outcome were presented in the submission.

6.34 Results for the supplementary analyses in the induction phase indicated that overall, there were no statistically significant differences in the clinical remission outcomes when comparing risankizumab against adalimumab. The ITC result based on risk difference show a statistically significant difference (RD -0.23 (95%CI: -0.437, -0.023)) in favour of infliximab. The patient numbers were small (N=51) in the infliximab T16 trial. Conversely, when compared to vedolizumab, the ITC results based on risk difference show a statistically significant result (RD 0.14 (95%CI: 0.069, 0.211)) in favour of risankizumab.

6.35 There was no statistically significant difference in the overall results for the maintenance phase in the clinical remission outcomes when comparing risankizumab against infliximab and vedolizumab. The ITC result based on RR and RD show a

statistically significant result (RR 0.504 (95%CI: 0.306, 0.829); RD -0.14 (95%CI: -0.277, -0.003)) in favour of adalimumab.

- 6.36 These results need to be interpreted with caution given the number of exchangeability issues in the indirect comparison. Differences across trials include prior treatment and response to TNF $\alpha$  antagonists, timing of treatment assessments, date of the trials and response criteria for enrolment into the maintenance phase. These were noted in the ustekinumab PSD (paragraphs 7.1, 6.22 and 6.24, Ustekinumab PSD, March 2017 PBAC meeting) and are likely to also apply to the risankizumab comparisons.
- 6.37 The PSCR claimed that the longer biological half-life and durable effect of risankizumab may persist after treatment withdrawal, resulting in a higher response rate in the re-randomised withdrawal (i.e. placebo) arm in FORTIFY. The ESC agreed with the PSCR and considered these factors may have biased against risankizumab in the comparisons, however, was unsure as to the magnitude of the impact on the supplementary comparisons.

#### **FCD**

- 6.38 Table 6 below presents the subgroup analysis for the FCD population. The FCD population is represented as a subgroup of the total trial populations of the risankizumab severe CD evidence (ADVANCE, MOTIVATE and FORTIFY trials).

Table 8: Fistula response and remission outcomes in patients with draining fistulae at baseline<sup>a</sup>

Trial ID	Proposed medicine	Placebo	RR (95% CI)	Risk difference (95% CI)
<b>Outcome: Fistula remission<sup>d</sup></b>				
<b>INDUCTION</b>				
<b>Risankizumab (600 mg IV) at Week 12</b>				
ADVANCE	5/18 (27.8)	2/9 (22.2)	1.25 [0.30, 5.23]	0.06 [-0.29, 0.40]
MOTIVATE	1/14 (7.1)	2/15 (13.3)	0.54 [0.05, 5.27]	-0.06 [-0.28, 0.16]
Meta-analysis	6/32 (18.75)	4/24 (16.7)	0.98 [0.29, 3.31]	-0.03 [-0.21, 0.16]
<b>Adalimumab at Week 4</b>				
CLASSIC I	0/12 (0)	1/6 (17)	0.25 [0.00, 1.80]	-0.17 [-0.57, 0.12]
GAIN	1/20 (5)	2/25 (8)	0.63 [0.08, 4.46]	-0.03 [-0.21, 0.17]
<b>Infliximab at Week 18</b>				
T20	17/31 (55)	4/31 (13)	<b>4.25 [1.75, 11.15]</b>	<b>0.42 [0.19, 0.61]</b>
<b>MAINTENANCE</b>				
<b>Risankizumab (360 mg SC) at Week 64</b>				
FORTIFY	8/11 (72.7)	5/11 (45.5)	1.60 (0.76, 3.36)	0.27 (-0.12, 0.67)
<b>Adalimumab at Week 56</b>				
CHARM	11/30 (37)	6/47 (13)	<b>2.87 [1.23, 6.83]</b>	<b>0.24 [0.05, 0.44]</b>
<b>Infliximab at Week 54</b>				
ACCENT II	33/91 (36)	19/98 (19)	1.87 (1.16, 3.05)	0.17 (0.04, 0.29)
<b>Outcome: Fistula response (≥50% reduction in number of draining fistula<sup>c</sup>)</b>				
<b>INDUCTION</b>				
<b>Risankizumab (600 mg IV) at Week 12</b>				
ADVANCE	5/18 (27.8)	2/9 (22.2)	1.25 [0.30, 5.23]	0.06 [-0.29, 0.40]
MOTIVATE	3/14 (21.4)	2/15 (13.3)	1.61 [0.31, 8.23]	0.08 [-0.20, 0.36]
Meta-analysis	8/32 (25)	4/24 (16.7)	1.39 [0.47, 4.09]	0.07 [-0.14, 0.29]
<b>Adalimumab at Week 4</b>				
CLASSIC I	1/12 (8)	2/6 (33)	0.25 [0.04, 1.67]	-0.25 [-0.65, 0.13]
GAIN	3/20 (15)	5/25 (20)	0.75 [0.21, 2.51]	-0.05 [-0.28, 0.20]
<b>Infliximab at Week 18/14</b>				
T20	21/31 (68)	8/31 (26)	<b>2.63 [1.45, 5.13]</b>	<b>0.42 [0.17, 0.62]</b>
<b>MAINTENANCE</b>				
<b>Risankizumab (360 mg SC) at Week 64<sup>b</sup></b>				
FORTIFY	8/11 (72.7)	5/9 (55.6)	1.31 (0.66, 2.60)	0.17 (-0.25, 0.59)
<b>Infliximab at Week 54</b>				
ACCENT II	42/91 (46)	23/98 (23)	<b>1.97 [1.30, 3.01]</b>	<b>0.23 [0.09, 0.36]</b>

Source: Table 2.34, p112 of the submission and corrected during the evaluation based on results in Attachment 4.14 of the submission. Abbreviations: – = not required; CI = confidence interval; k = number of studies contributing to the pooled estimate of effect; n = number of participants with event; N = total participants in group;; RD = risk difference; RR = relative risk **Bold** indicates statistically significant results. Note: There were some discrepancies between the results presented in the submission compared to that provided in the Revman file- Attachment 4.14 of the submission. However, differences were small and unlikely to have a substantial impact.

a. Draining fistulae at baseline defined as a baseline SES-CD of ≥6 (or ≥4 for isolated ileal disease).

b. Draining fistulae at baseline defined as a baseline SES-CD of ≥6 (or ≥4 for isolated ileal disease) at the time a patient entered the induction trial.

c. Fistula response defined as: risankizumab: ≥50% reduction in fistulae; adalimumab: ≥50% reduction in fistulae at week 2 and 4; infliximab: ≥50% reduction in fistulae at 2 or more visits

d. Fistula remission defined as: risankizumab: no draining fistulae; all other trials: complete closure of fistulae

6.39 The submission used a naïve (unadjusted indirect) comparison approach between risankizumab and comparators, adalimumab and infliximab.

6.40 The ESC noted there was no statistically significant difference between risankizumab and placebo in demonstrating fistula remission or response in FCD patients for both

induction and maintenance phases. The results presented crossed the null and had wide confidence intervals. This contrasts with results from the adalimumab (for maintenance) and infliximab (for induction and maintenance) trials which showed significant improvements in fistula remission and fistula response.

- 6.41 The PSCR agreed that the confidence intervals for this subpopulation were wide due to the small sample size but argued the PBAC previously recommended adalimumab for the treatment of FCD based on subgroup analyses that did not demonstrate a statistical difference in treatment outcomes between the two arms of the CHARM trial for induction; however, the ESC noted the results did favour adalimumab for fistula remission in the maintenance phase (paragraph 6.37 refers). The PSCR also argued (similar to the severe CD comparison) that trial design and biological nature of risankizumab likely biased against risankizumab in the comparisons (paragraph 6.32 refers) and further noted that a more biologic-experienced and treatment refractory population was recruited to the FORTIFY trial compared to infliximab and adalimumab trials, also biasing against risankizumab. The PSCR argued the balance of evidence still favours treatment with risankizumab and noted the high unmet medical need and limited treatment options in the FCD population as noted by PBAC previously. The ESC considered that the trial data for risankizumab for the treatment of FCD was very limited, with only 11 patients in the FCD subgroup of the maintenance trial and was of the overall view that there was insufficient evidence available to demonstrate risankizumab is effective for the treatment of FCD.
- 6.42 The trials comparing adalimumab and placebo (CLASSIC I and GAIN) did not demonstrate a statistically difference in treatment outcomes between the two arms for induction. However, the fistula remission outcome favoured adalimumab in the maintenance study (CHARM) – 37% vs 13%, RR 2.87 (95%CI: 1.23, 6.82). No outcome relating to fistula response was presented for adalimumab.
- 6.43 The trials comparing infliximab and placebo (T20 and ACCENT II) demonstrated a statistically significant difference in the treatment outcomes in favour of infliximab. The results from T20 trial demonstrating fistula response was based on primary analysis performed according to ITT principle. Across all trials presented for the proposed FCD population, the infliximab trials were the only trials which specifically recruited and randomised FCD patients, therefore, the evidence presented for infliximab is considered most reliable.
- 6.44 The results from these trials were used to support the clinical claim using naïve comparison. In such comparisons, no attempts have been made to adjust for any discordance in comparators between and among trials. Naïve comparisons are akin to a descriptive comparison, therefore can be difficult to interpret as they are not able to determine if any differences noted between efficacy measures are solely attributable to the treatment. Additionally, differences in trial characteristics can affect the transitivity of trials in the comparison. Note the definitions of fistula remission and response differed slightly (e.g., demonstration of outcome at one time

point vs multiple time points) and there were differences in the timing of assessments between the risankizumab and comparator trials.

## Comparative harms

6.45 The tables (Table 7 and Table 8) below present a summary of the safety results (induction and maintenance phases).

**Table 9: Summary of key adverse events in the trials – safety outcomes for induction**

Trial type or estimate	Trial ID	DMARD n/N (%)	PBO n/N (%)	OR [95% CI] <sup>a</sup>	RD [95% CI] <sup>b</sup>
<b>Any AE</b>					
RISA vs PBO	M15-993	31/41 (75.6)	32/39 (82.1)	0.68 [0.23, 2.01]	-0.06 [-0.24, 0.11]
	ADVANCE	191/338 (56.5)	99/176 (56.3)	1.01 [0.70, 1.46]	0.00 [-0.09, 0.09]
	MOTIVATE	94/195 (48.2)	125/192 (65.1)	<b>0.50 [0.33, 0.75]</b>	<b>-0.17 [-0.27, -0.07]</b>
	Pooled	316/574 (55.1)	256/407 (62.9)	0.71 [0.41, 1.22]	-0.08 [-0.20, 0.04]
USTE vs PBO	UNITI I	164/249 (65.9)	159/245 (64.9)	1.04 [0.72, 1.51]	0.01 [-0.07, 0.09]
	UNITI II	115/207 (55.6)	113/208 (54.3)	1.05 [0.71, 1.55]	0.01 [-0.08, 0.11]
	Pooled	279/456 (61.2)	272/453 (60.0)	1.05 [0.80, 1.37]	0.01 [-0.05, 0.07]
ITC result	–	–	–	0.676 [0.368, 1.242] (p = 0.2072)	-0.09 [-0.224, 0.044] (p = 0.1886)
<b>Serious AEs</b>					
RISA vs PBO	M15-993	4/41 (9.8)	13/39 (33.3)	<b>0.22 [0.06, 0.74]</b>	<b>-0.24 [-0.41, -0.06]</b>
	ADVANCE	22/338 (6.5)	27/176 (15.3)	<b>0.38 [0.21, 0.70]</b>	<b>-0.09 [-0.15, -0.03]</b>
	MOTIVATE	10/195 (5.1)	23/192 (12.0)	<b>0.40 [0.18, 0.86]</b>	<b>-0.07 [-0.12, -0.01]</b>
	Pooled	36/574 (6.3)	63/407 (15.5)	<b>0.36 [0.23, 0.56]</b>	<b>-0.09 [-0.15, -0.04]</b>
USTE vs PBO	UNITI I	18/249 (7.2)	15/245 (6.1)	1.19 [0.59, 2.43]	0.01 [-0.03, 0.06]
	UNITI II	6/207 (2.9)	12/208 (5.8)	0.49 [0.18, 1.32]	-0.03 [-0.07, 0.01]
	Pooled	24/456 (5.3)	27/453 (6.0)	0.82 [0.34, 1.95]	-0.01 [-0.04, 0.02]
ITC result	–	–	–	0.439 [0.165, 1.170] (p=0.100)	<b>-0.08 [-0.143, -0.017]</b> (p = 0.0123)
<b>Serious infections</b>					
RISA vs PBO	M15-993	2/41 (4.9)	4/39 (10.3)	<b>0.45 [0.08, 2.60]</b>	-0.05 [-0.17, 0.06]
	ADVANCE	3/338 (0.9)	7/176 (4.0)	<b>0.22 [0.06, 0.85]</b>	<b>-0.03 [-0.06, -0.00]</b>
	MOTIVATE	1/195 (0.5)	5/192 (2.6)	<b>0.19 [0.02, 1.67]</b>	<b>-0.02 [-0.05, 0.00]</b>
	Pooled	6/574 (1.0)	16/407 (3.9)	<b>0.26 [0.10, 0.69]</b>	<b>-0.03 [-0.04, -0.01]</b>
USTE vs PBO	UNITI I	7/249 (2.8)	3/245 (1.2)	2.33 [0.60, 9.13]	0.02 [-0.01, 0.04]
	UNITI II	1/207 (0.5)	3/208 (1.4)	0.33 [0.03, 3.22]	-0.01 [-0.03, 0.01]
	Pooled	8/456 (1.8)	6/453 (1.3)	1.10 [0.17, 7.08]	0.00 [-0.02, 0.03]
ITC result	–	–	–	0.236 [0.029, 1.93] (p = 0.1782)	<b>-0.03 [-0.059, -0.001]</b> (p = 0.0437)

Source: Table 2.41, p 121-122 of the submission and corrected during the evaluation based on results in Attachment 4.14 of the submission. There were some discrepancies between the results presented in the submission compared to that provided in the Revman file- Attachment 4.14 of the submission. However, differences were small.

Abbreviations: –, not required; CI, confidence interval; n, number of participants with event; N, total number of participants in group; OR, odds ratio; RD, risk difference; RISA, risankizumab; PBO, placebo; UST, ustekinumab; ITC, indirect treatment comparison. **Bold** indicates statistically significant results.

<sup>a</sup><1 favours RISA in ITC; <sup>b</sup><0 favours RISA in ITC

**Table 10: Summary of key adverse events in the trials – safety outcomes for maintenance**

Trial type or estimate	Trial ID	biologic n/N (%)	PBO n/N (%)	Treatment effect (OR) <sup>a</sup>	Treatment effect (RD) <sup>b</sup>
<b>Any AE</b>					
RISA vs PBO	FORTIFY	114/159 (71.7)	120/166 (72.3)	0.97 [0.60, 1.58]	-0.01 [-0.10, 0.09]
USTE vs PBO	IM UNITI	107/131 (81.7)	111/133 (83.5)	0.88 [0.47, 1.67]	-0.02 [-0.11, 0.07]
ITC result	–	–	–	1.102 [0.496, 2.447] (p = 0.8109)	0.01 [-0.121, 0.141] (p = 0.8809)
<b>Serious AEs</b>					
RISA vs PBO	FORTIFY	19/159 (11.9)	20/166 (12.0)	0.99 [0.51, 1.93]	-0.00 [-0.07, 0.07]
USTE vs PBO	IM UNITI	13/131 (9.9)	20/133 (15.0)	0.62 [0.30, 1.31]	-0.05 [-0.13, 0.03]
ITC result	–	–	–	1.597 [0.592, 4.31] (p = 0.3556)	0.05 [-0.056, 0.156] (p = 0.3566)
<b>Serious infections</b>					
RISA vs PBO	FORTIFY	3/159 (1.9)	5/166 (3.0)	0.62 [0.15, 2.64]	-0.01 [-0.04, 0.02]
USTE vs PBO	IM UNITI	3/131 (2.3)	3/133 (2.3)	1.02 [0.20, 5.13]	0.00 [-0.04, 0.04]
ITC result	–	–	–	0.608 [0.07, 5.298] (p = 0.6522)	-0.01 [-0.06, 0.04] (p = 0.6951)

Source: Table 2.42, p 122 of the submission

Abbreviations: –, not required; CI, confidence interval; n, number of participants with event; N, total number of participants in group; OR, odds ratio; RD, risk difference; RISA, risankizumab; PBO, placebo; UST, ustekinumab; ITC, indirect treatment comparison. **Bold** indicates statistically significant results.

<sup>a</sup><1 favours RISA in ITC; <sup>b</sup><0 favours RISA in ITC

- 6.46 The safety outcomes observed at week 12 in clinical trials of risankizumab versus placebo showed a statistically significantly higher proportion of patients in the placebo arm experiencing higher serious AEs, serious infections, severe AE and having AEs leading to discontinuation compared to the risankizumab arm (p105-106 of the submission). The PBAC considered the higher rates of adverse events in the placebo treatment group may be attributable to the worsening of the underlying condition in placebo-treated subjects rather than due to the study drug exposure (p77, Risankizumab TGA Clinical Evaluation Report, March 2022).
- 6.47 Longer term safety data from the FORTIFY trial at week 64 did not show any statistically significant differences between the risankizumab and placebo arms.
- 6.48 None of the safety outcomes observed in the clinical trials of ustekinumab versus placebo at week 8 and week 52 were statistically significant.
- 6.49 The results from the indirect comparison of safety outcomes between risankizumab and ustekinumab showed patients treated with risankizumab had significantly lower rates of serious AEs and serious infections versus ustekinumab for induction (when tested using the RD statistic). In both cases these differences were driven by an increase in AEs in the placebo group rather than a decrease in AEs within the risankizumab group. The reason for the higher AE rate in the placebo group may be due to disease worsening. These results should be interpreted with caution due to transitivity issues.
- 6.50 The proportion of patients who discontinued was consistent across all risankizumab and ustekinumab trials.

- 6.51 The submission provided an extended assessment of harms which included data from long-term open-label extension (OLE) sub-studies from the main risankizumab trials. Across these studies, a total of 1,574 patients received at least 1 dose of risankizumab, representing a total of 2,059.2 patient-years (PY) of risankizumab exposure.
- 6.52 In the integrated analysis of subjects receiving any SC risankizumab, the rate of AEs was 272.0 events per 100 PY (E/100 PY), the rate of serious AEs was 18.1 E/100 PY, and the rate of AEs leading to discontinuation of study drug was 3.7 E/100 PY, which were similar to the corresponding rates observed in the placebo-controlled 52-week maintenance period safety analysis set. The submission referenced the Summary of Clinical Safety, Section 2.7.4.1.2, p. 46 as the data source for information to demonstrate the long-term safety of risankizumab. This document could not be located during the evaluation and the data provided could not be verified.
- 6.53 The submission did not present safety data on the sub-population of FCD. The submission claimed that for FCD, the low patient numbers as a result of deriving evidence from a subset of patients with fistulae at baseline from risankizumab, adalimumab and infliximab trials would make FCD-specific safety analysis uninformative (p98 of the submission). The submission also stated that PBAC has previously found that ustekinumab is non-inferior to adalimumab in terms of safety (ustekinumab PSD, March 2017) and that adalimumab is non-inferior to infliximab in terms of safety (adalimumab PSD, November 2010), therefore, a comparison with ustekinumab on an ITT basis is a reasonable proxy for determining safety versus other biologics in fistulising Crohn’s disease. The ESC considered this approach was inappropriate and agreed safety data specific to FCD should be presented, however noted that given the size of the FCD subgroups in the risankizumab trials the data would be very limited.

### **Clinical claim**

#### **Severe CD**

- 6.54 The submission described risankizumab in severe CD as non-inferior in terms of effectiveness and safety compared to ustekinumab. The ESC considered that the claim was overall adequately supported because:
- Risankizumab demonstrated statistically significant superiority over placebo in efficacy outcomes in the respective trials (for both induction and maintenance phases).
  - There was no statistically significant difference in the efficacy results between risankizumab and ustekinumab based on the indirect comparison presented.
  - There was no statistically significant difference in the safety outcomes between risankizumab and ustekinumab based on the indirect comparison presented.
- 6.55 With regards to the supplementary indirect comparisons versus adalimumab, infliximab and vedolizumab, the ESC noted the submission did not make an explicit

clinical claim versus these therapies and also considered there were uncertainties with the results of the supplementary indirect comparisons with adalimumab, infliximab and vedolizumab, which are discussed in paragraphs 6.29 to 6.32.

- 6.56 The PBAC considered the claims of non-inferior comparative effectiveness and safety were reasonable.

#### **FCD**

- 6.57 The submission described risankizumab in FCD as non-inferior in terms of effectiveness compared to adalimumab and infliximab.

- 6.58 The ESC considered, based on the limited evidence presented in FCD, that risankizumab had not adequately demonstrated superior comparative effectiveness over placebo (paragraph 6.35 to 6.39) and therefore the claim of non-inferior comparative effectiveness to adalimumab was not adequately supported.

- 6.59 The ESC noted the PBAC had previously considered that ustekinumab was not significantly more effective in inducing fistula response ( $\geq 50\%$  reduction in fistulas) compared with placebo in either induction (UNITI-1 and UNITI-2) or maintenance trials (IM-UNITI) and the PBAC therefore concluded that non-inferiority of ustekinumab compared with adalimumab or infliximab was not supported in the submission (paragraph 7.10, ustekinumab PSD, March 2017 PBAC meeting). The ESC considered the outcomes of the comparison of ustekinumab appeared to be similar to the results of the risankizumab comparisons in the current submission.

- 6.60 The submission described risankizumab as non-inferior in terms of safety compared to adalimumab and infliximab for FCD. The ESC considered that this claim was not adequately supported. The submission contended that a comparison with ustekinumab served as a reasonable proxy for determining safety versus other biologics, therefore, did not present any safety data for the FCD population to support their safety claims. The ESC considered this was inappropriate and the comparative safety of risankizumab to other biologics cannot implicitly be inferred from the safety comparison in severe CD (especially in the context of ustekinumab not being a relevant alternative in FCD).

- 6.61 As noted in paragraph 6.1 above, the sponsor withdrew the request for the FCD population in the Pre-PBAC Response.

#### ***Economic analysis***

- 6.62 The submission presented separate CMA for severe CD and FCD. For severe CD, risankizumab is compared to ustekinumab. For FCD, risankizumab is compared to adalimumab. The claim of non-inferior efficacy and safety for severe CD appears adequately supported by the evidence presented in the submission. The ESC considered that the claim of non-inferior efficacy and safety for FCD was not supported by the evidence presented the submission and therefore the use of a cost minimisation approach for FCD was not appropriate.

- 6.63 Cost minimisation analyses were performed based on published prices for ustekinumab and adalimumab. Ustekinumab has an SPA, and the effective price is not available to the sponsor.
- 6.64 The equi-effective doses for severe CD were estimated as risankizumab 600 mg IV at week 0, 4 and 8 followed by 360 mg SC every 8 weeks over two years and ustekinumab 425 mg IV at week 0 followed by 90 mg SC every 8 weeks over two years. The equi-effective doses for FCD were estimated as risankizumab 600 mg IV at week 0, 4 and 8, followed by 360 mg SC every 8 weeks over two years and adalimumab 160 mg SC at week 0, 80 mg SC at week 2 and 40 mg every 2 weeks over two years. The equi-effective doses are in line with the proposed doses in the draft TGA product information (PI) for risankizumab, and the recommended doses in the approved TGA PI for ustekinumab and adalimumab. The submission estimated the average weight-based loading dose (3.27 vials of 130 mg vial, 425mg) of ustekinumab based on the PBS utilisation data. The estimation was not made based on average body weight of severe CD patients; however, the estimated initial dose is similar to the average loading doses in the ustekinumab trials (417 mg and 431 mg in UNITI-I and UNITI-II, respectively).
- 6.65 The submission included the MBS administration fees for IV dosing as additional costs in the CMA. Other healthcare resource utilisation such as periodic face-to-face consultation visits and associated monitoring are assumed to occur equally across treatments.
- 6.66 The submission requested flat pricing of the 600 mg vial and the 360 mg pre-filled cartridge of risankizumab. On the basis of equivalence of cost over two years, the requested AEMP for risankizumab was calculated at \$7,151.98 for severe CD and \$ for FCD in the submission (Table 9, Table 10). The proposed AEMP for severe CD does not correspond to the requested price (\$) presented in the submission. These results were based on the published price of the comparators.

**Table 11: Results of the cost-minimisation analysis – severe Crohn’s disease**

Component	Risankizumab	Ustekinumab
Cost per vial (AEMP)	\$7,151.98 <sup>a</sup>	\$3,809.08 <sup>b</sup>
Treatment duration	two years	two years
Vials over two years	14.5 <sup>c</sup>	27.27 <sup>d</sup>
Administration cost per dose		
- IV	\$79.75 <sup>e</sup>	\$79.75 <sup>e</sup>
- SC	\$0	\$0
Doses over two years	3 IV + 11.5 SC <sup>c</sup>	1 IV + 12 SC
Total medicine cost over two years	\$103,943.03	\$103,943.03
Difference in cost	\$0	-

Source: Table 3-7, p143 of the submission.

Abbreviations: AEMP, approved ex-manufacturer price; IV, intravenous; SC, subcutaneous.

<sup>a</sup> flat priced for IV and SC vials or devices.

<sup>b</sup> published AEMP.

<sup>c</sup> adjusted for last dose covering 4 weeks beyond Year 2.

<sup>d</sup> including average vials of the initial doses derived from PBS utilisation

<sup>e</sup> MBS item 116

**Table 12: Results of the cost-minimisation analysis – fistulising Crohn’s disease**

Component	Risankizumab	Adalimumab
Cost per vial (AEMP)	\$ <sup>a</sup>	\$409.27 <sup>b</sup>
Treatment duration	two years	two years
Vials over two years	14.5 <sup>c</sup>	56
Administration cost per dose		
- IV	\$79.75 <sup>d</sup>	\$0
- SC	\$0	
Doses over two years	3 IV + 11.5 SC <sup>c</sup>	56 SC
Total medicine cost over two years	\$	\$ 22,919.12
Difference in cost	\$	-

Source: Table 3-9, p144 of the submission.

Abbreviations: AEMP, approved ex-manufacturer price; IV, intravenous; SC, subcutaneous.

<sup>a</sup> flat priced for IV and SC vials or devices.

<sup>b</sup> published AEMP.

<sup>c</sup> adjusted for last dose covering 4 weeks beyond Year 2.

<sup>d</sup> MBS item 116

6.67 The ESC advised the cost minimisation approach was reliable for decision-making for the severe CD population only, as the claim of non-inferiority to alternative therapies in FCD was not supported by the available evidence.

### **Drug cost/patient/year**

6.68 The submission presented the cost per patient per year for severe CD and FCD based on the published price of ustekinumab and adalimumab (Table 13).

**Table 13: Annual cost per patient with risankizumab**

Therapy	IV Vials	SC Vials	IV Admin	IV Admin Cost	Drug Cost AEMP	Total Cost AEMP + IV Admin
<b>Severe Crohn’s disease</b>						
Year 1	3	5	3	\$	\$ <sup>b</sup>	\$ <sup>b</sup>
Year 2	0	7 <sup>a</sup>	0	\$	\$ <sup>b</sup>	\$ <sup>b</sup>
<b>Fistulising Crohn’s disease</b>						
Year 1	3	5	3	\$	\$ <sup>b</sup>	\$ <sup>b</sup>
Year 2	0	7 <sup>a</sup>	0	\$	\$ <sup>b</sup>	\$ <sup>b</sup>

Source: Table 3-8 and Table 3-10, p143-p144 of the submission. And corrected during the evaluation.

Abbreviations: IV, intravenous; SC, subcutaneous; AEMP, approved ex-manufacturer price; Admin, administration.

<sup>a</sup> note that with 8 weekly dosing, 6.5 SC injections are required per year of maintenance therapy

<sup>b</sup> calculation corrected using proposed AEMP for both Year 1 and Year 2 during the evaluation. Note Year 1 drug cost was calculated using the proposed AEMP and Year 2 drug cost was calculated using proposed DPMQ for risankizumab in the submission.

### **Estimated PBS usage & financial implications**

6.69 This submission was not considered by DUSC. The submission used a market share approach to estimate the use of risankizumab and financial implications using PBS utilisation data.

**Table 14: Key inputs for financial estimates – severe CD**

Parameter	Value applied and source	Comment
Market growth without the listing of risankizumab	Functional form: Linear Source: Assumed a linear trend of growth in Year 1 to 6 following listing reflecting the 2017-2021 PBS usage and each modelled list item was projected individually.	It may be reasonable to assume linear growth of infliximab, ustekinumab and vedolizumab. The usage of adalimumab initiation therapy fluctuates, and it is uncertain if it follows a linear trend. It is unclear whether the increased uptake rate of ustekinumab is expected to plateau. Likely overestimated the usage.
Substitution rates of risankizumab	Yr 1: 5%; Yr 2: 7%; Yr 3: 9%; Yr 4: 11%; Yr 5: 13%; Yr 6: 15% Source: Assumptions.	The substitution rates assumed appear reasonable. The assumption of equal substitution rate across all comparators is uncertain.
% of initiation scripts of ustekinumab	Yr 1: 42.04%; Yr 2: 24.65%; Yr 3: 18.04%; Yr 4: 17.41%; Yr 5: 17.36%; Yr 6: 17.31% Source: Historical ustekinumab usage data since its listing in 2017.	It is uncertain if the % of initiation scripts of risankizumab following listing will be similar to the trend for ustekinumab. It appears reasonable to fit a power function to predict the proportion of initiation scripts, although there was an error in the function. Slightly overestimated the financial implications.
Ustekinumab vials	3.27 vials per initial IV script Source: PBS utilisation data for PBS item 11182M for 2021	This is appropriate.
Infliximab vials (Initiating/first continuing)	4.34 vials per script Source: PBS utilisation data for PBS item 5754W for 2021	This is appropriate.
Infliximab vials (continuing, no Max Qty)	4.54 vials per script Source: PBS utilisation data for PBS item 11389K for 2021	This is appropriate.
Risankizumab 600 mg/ 10.0 mL IV – Initiating	\$7,151.98 Source: Proposed DPMQ for s100 Public/Private in Section 3 of the submission	This is appropriate. However, it is different from the requested price in the Requested listing section.
Risankizumab 360 mg/2.4 mL SC – Initiating & Continuing	\$█ Source: Proposed DPMQ for s85	The submission used \$█ in the financial impact estimation. The error in the DPMQ (i.e., Tier One AHI Fee of \$4.3 not included) underestimated the financial implications.
IV administration for risankizumab / ustekinumab / vedolizumab	\$79.75 Source: MBS item 116	
IV administration for infliximab	\$101.90 Source: MBS item 14245	This is appropriate. However, it is noted that a subcutaneous injection form of IFX is currently listed for CD and was recommended for listing for FCD at the March 2022 PBAC meeting.

Source: Table 4-1 – Table 4-32, p146-171 and Attachment 4.6 of the submission. And corrected during the evaluation.

Abbreviations: CD, Crohn's Disease; PBS, Pharmaceutical Benefits Scheme; MBS, Medicare Benefits Scheme; SC, sub-cutaneous; Max Qty, maximum quantity; DPMQ, dispensed price for maximum quantity; s85, Section 85; s100, Section 100; AHI, Administration, Handling and Infrastructure.

**Table 15: Key inputs for financial estimates – FCD**

Parameter	Value applied and source	Comment
Market growth without the listing of risankizumab	Functional form: Linear Source: Assumed a linear trend of growth in Year 1 to 6 following listing reflecting the 2017-2021 PBS usage and each modelled list item was projected individually.	It may be reasonable to assume linear growth of infliximab. The market growth of adalimumab is uncertain.
Substitution rates of risankizumab	Yr 1: 10%; Yr 2: 14%; Yr 3: 18% Yr 4: 22%; Yr 5: 26%; Yr 6: 30% Source: Assumptions.	Given the lack of evidence demonstrating the clinical efficacy of risankizumab compared to placebo, the uptake rate of risankizumab is unclear.
% of initiation scripts of ustekinumab	Yr 1: 42.04%; Yr 2: 24.65%; Yr 3: 18.04%; Yr 4: 14.46%; Yr 5: 14.31%; Yr 6: 14.27% Source: Historical ustekinumab usage data since its listing in 2017.	It is uncertain if the % of initiation scripts of risankizumab following listing will be similar to the trend for ustekinumab. It appears reasonable to fit a power function to predict the proportion of initiation scripts, although there was an error in the function. Slightly overestimated the financial implications.
Infliximab vials (Initiating/first continuing)	4.23 vials per script Source: PBS utilisation data for PBS item 9654D for 2021	This is appropriate.
Infliximab vials (continuing, no Max Qty)	4.53 vials per script Source: PBS utilisation data for PBS item 11424G for 2021	This is appropriate.
Risankizumab 600 mg/ 10.0 mL IV – Initiating	\$1,564.13 Source: Proposed DPMQ for s100 Public/Private in Section 3 of the submission	This is appropriate.
Risankizumab 360 mg/2.4 mL SC – Initiating & Continuing	\$█ Source: Proposed DPMQ for s85	This is appropriate.
IV administration for risankizumab	\$79.75 Source: MBS item 116	This is appropriate.
IV administration for infliximab	\$101.90 Source: MBS item 14245	This is appropriate. However, it is noted that a subcutaneous injection form of IFX is currently listed for CD and was recommended for listing for FCD at the March 2022 PBAC meeting.

Source: Table 4-1 – Table 4-32, p146-171 and Attachment 4.7 of the submission. And corrected during the evaluation revisions: FCD, Fistulising Crohn's Disease; PBS, Pharmaceutical Benefits Scheme; MBS, Medicare Benefits Scheme; SC, sub-cutaneous; Max Qty, maximum quantity; DPMQ, dispensed price for maximum quantity; s85, Section 85; s100, Section 100.

6.70 The estimated use and financial implications of risankizumab for severe CD and FCD are presented in Table 16 and Table 17.

**Table 16: Estimated use and financial implications – severe CD (using published prices)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	1	1	2	2	2	3
<b>Estimated financial implications of risankizumab</b>						
Cost to PBS/RPBS less copayments	\$4	\$5	\$6	\$7	\$7	\$7
<b>Estimated financial implications for ustekinumab, adalimumab, infliximab and vedolizumab</b>						
Cost to PBS/RPBS less copayments	-\$8	-\$9	-\$10	-\$5	-\$11	-\$12
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$9	\$4	\$10	\$5	\$13	\$6
Net cost to MBS	-\$14	-\$14	-\$14	-\$14	-\$14	-\$14

Source: Table 4-23, p166 and Attachment 4.6 of the submission. And corrected during the evaluation.

Abbreviations: CD, Crohn's Disease; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriations Pharmaceutical Benefits Scheme; MBS, Medicare Benefits Scheme.

<sup>a</sup> Assuming + scripts per year ( scripts in the first year of treatment) as estimated by the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> 5,000 to < 10,000

<sup>2</sup> 10,000 to < 20,000

<sup>3</sup> 20,000 to < 30,000

<sup>4</sup> \$30 million to < \$40 million

<sup>5</sup> \$50 million to < \$60 million

<sup>6</sup> \$80 million to < \$90 million

<sup>7</sup> \$100 million to < \$200 million

<sup>8</sup> \$10 million to < \$20 million

<sup>9</sup> \$20 million to < \$30 million

<sup>10</sup> \$40 million to < \$50 million

<sup>11</sup> \$70 million to < \$80 million

<sup>12</sup> \$90 million to < \$100 million

<sup>13</sup> \$60 million to < \$70 million

<sup>14</sup> \$0 to < \$10 million

**Table 17: Estimated use and financial implications – FCD (using published price)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	1	1	2	2	2	3
<b>Estimated financial implications of risankizumab</b>						
Cost to PBS/RPBS less copayments	\$4	\$4	\$4	\$5	\$5	\$5
<b>Estimated financial implications for adalimumab and infliximab</b>						
Cost to PBS/RPBS less copayments	-\$4	-\$4	-\$4	-\$5	-\$5	-\$5
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$4	\$4	\$4	\$4	\$4	\$4
Net cost to MBS	-\$4	-\$4	-\$4	-\$4	-\$4	-\$4

Source: Table 4-29, p169 and Attachment 4.6 of the submission. And corrected during the evaluation

Abbreviations: FCD, Fistulising Crohn's Disease; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriations Pharmaceutical Benefits Scheme; MBS, Medicare Benefits Scheme.

<sup>a</sup> Assuming scripts per year ( scripts in the first year of treatment) as estimated by the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> 10,000 to < 20,000

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$10 million to < \$20 million

- 6.71 As the Sponsor withdrew the request for listing for the FCD population in its Pre-PBAC Response, the total cost to the PBS/RPBS of listing risankizumab for severe CD, was estimated to be \$80 million to < \$90 million in year 6 and a total of \$200 million to < \$300 million in the first 6 years of listing. The costs may differ between the Section 100 listings (risankizumab IV) and General Schedule (risankizumab SC) listings.
- 6.72 Some calculation errors were noted during the evaluation, including the inconsistent use of DPMQ of risankizumab SC formulation and an error in extrapolating script numbers for estimating initiation/continuation risankizumab scripts. These resulted in slightly overestimated financial impact estimates for severe CD. Similar issues with incorrect power function were noted for FCD.
- 6.73 If recommended on a cost minimisation basis with the least costly alternative, the listing of risankizumab for severe CD and/or FCD would be expected to be cost neutral (or modestly cost saving if it replaced more expensive alternatives).
- 6.74 The submission did not clarify if the grandfathered patients were accounted in the projected usage or financial impact estimates.

### **Quality Use of Medicines**

- 6.75 The sponsor has a risk management plan submitted to the TGA. A patient support program was proposed.

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

## **7 PBAC Outcome**

- 7.1 The PBAC deferred making a recommendation to list risankizumab (RIS) for the treatment of severe Crohn's disease (CD) in adult patients as the TGA Delegate's Overview was not available at time of PBAC consideration. However, the PBAC was of a mind to recommend the Authority Required (in writing), Section 100 (Highly Specialised Drugs Program) listing (for IV induction therapy) and General Schedule, listing of RIS for initial and continuing therapy on the basis of cost-minimisation to the lowest cost biologic disease modifying anti-rheumatic drug (bDMARD) for this indication.
- 7.2 The PBAC noted that the sponsor withdrew their request for listing of fistulising Crohn's disease (FCD) in its pre-PBAC response (paragraph 6.1 refers) and did not consider that request further.
- 7.3 The PBAC considered the nominated main comparator of ustekinumab (UST) was reasonable and the nominated supplementary comparators of adalimumab (ADA), vedolizumab (VDZ) and infliximab (IFX) were appropriate for the treatment of severe CD in adult patients and agreed the supplementary comparators were alternative therapies. The PBAC considered the equi-effective doses for RIS of 600 mg IV at week

0, 4 and 8 followed by 360 mg SC every 8 weeks over two years and UST of 425 mg IV at week 0 followed by 90 mg SC every 8 weeks over two years were reasonable, and the equi-effective doses with the alternative therapies could be derived with reference to the therapeutic relativity sheets and product information documents.

- 7.4 The PBAC considered that the restriction for RIS should be consistent with other bDMARDs for the treatment of severe CD and noted a grandfather restriction may be required for the listing. The Committee was not supportive of the request to lower the authority level to an electronic/telephone authority for continuing treatment as it was inconsistent with existing listings and the PBAC noted it had recently not recommended such a change as part of its recent review of authority required listings (Review of Authority Required (Written) PBAC listings Tranche 3, July 2021 PBAC outcomes).
- 7.5 The PBAC noted no direct trials comparing RIS to UST or the supplementary comparators were available, and the submission relied on indirect treatment comparisons with placebo as the common comparator. The PBAC also noted patients included in the RIS trials had moderate to severe CD (CDAI score of  $\geq 220$  and  $\leq 450$ ), however the proposed PBS listing was for severe CD (CDAI score  $\geq 300$ ) only. The PBAC noted it has previously considered trials that included patients with moderate to severe CD to support the clinical and safety claims for severe CD in the UST and VDZ considerations. The PBAC also noted there were a number of transitivity issues across the trials, including differences in prior exposure to biologics, concomitant use of other therapies (e.g. corticosteroids, 5-ASA and immunomodulators), differences in placebo response rate and differences in primary outcome measures for RIS and UST and considered that whilst these added a degree of additional uncertainty to the indirect comparisons, the analyses were generally reliable for informing a comparison of RIS and UST.
- 7.6 For induction treatment, the PBAC noted the results of the indirect comparisons showed no statistically significant differences between RIS and UST for the outcomes of clinical response or clinical remission and considered the available evidence supported a conclusion that RIS is likely of non-inferior comparative effectiveness to UST.
- 7.7 For maintenance therapy, the PBAC agreed with the ESC that the full ITT population were the most appropriate basis to consider the effectiveness of RIS. The PBAC noted there was no statistically significant differences between RIS and UST for the outcomes of clinical response or clinical remission in the maintenance phase and considered the available evidence supported a conclusion that RIS is also likely of non-inferior comparative effectiveness to UST in maintenance therapy for severe CD.
- 7.8 The PBAC noted the submission described RIS as being of non-inferior comparative safety to UST and the supplementary comparators and considered this claim was reasonable.
- 7.9 The PBAC considered that a listing based on a cost minimisation approach with costs

over two years, consistent with the approach previously used for bDMARDs, was appropriate to determine the cost minimised price of RIS. The PBAC considered the cost of RIS should be no greater than the least costly of the alternative therapies.

- 7.10 The PBAC considered the uptake of RIS may be overestimated as RIS requires 3 IV infusions in the induction phase, whilst UST requires only 1 IV infusion at commencement of treatment. This issue notwithstanding, the PBAC considered that, if listed on a cost minimisation basis with the least costly alternative of UST, ADA, VDZ and IFX, that the listing of RIS would likely be cost neutral to the PBS or result in a modest net save as it will replace therapies that are either of equivalent cost or more expensive.

**Outcome:**

Deferred

## **8 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.

## **9 Sponsor's Comment**

The sponsor had no comment.

**Addendum to the July 2022 Public Summary Document:**

**4.02 RISANKIZUMAB,**

**Solution concentrate for I.V. infusion 600 mg in  
10 mL,  
Injection 360 mg in 2.4 mL in pre-filled cartridge,  
Skyrizi<sup>®</sup>,  
AbbVie Pty Ltd.**

**10 Background**

- 10.1 At its July 2022 meeting, the PBAC deferred making a recommendation for the listing of risankizumab (RIS) for the treatment of severe Crohn's disease (CD) in adult patients as the TGA Delegate's Overview was not available at the time of PBAC consideration. The PBAC was of a mind to recommend the Authority Required (in writing), Section 100 (Highly Specialised Drugs Program) listing (for IV induction therapy) and General Schedule, listing of RIS for initial and continuing therapy on the basis of cost-minimisation to the lowest cost biologic disease modifying anti-rheumatic drug (bDMARD) for this indication pending receipt of a positive TGA Delegate's Overview.
- 10.2 The TGA Delegate's Overview was provided prior to the November 2022 PBAC meeting. The Delegate proposed to approve the registration of RIS as follows:
- 'Skyrizi is indicated for the treatment of moderate to severe Crohn's disease in adult patients, who have an inadequate response, a lost response, an intolerance or a contra-indication to either conventional or biologic therapy.'*

**11 PBAC Outcome**

- 11.1 The PBAC recommended the listing of risankizumab (RIS) for the treatment of severe Crohn's disease (CD) in adult patients. The PBAC recommended the Authority Required (in writing), Section 100 (Highly Specialised Drugs Program) listing (for IV induction therapy) and General Schedule, listing of RIS for initial and continuing therapy on the basis of cost-minimisation to the lowest cost biologic or targeted synthetic disease modifying anti-rheumatic drug (bDMARD/tsDMARD) for this indication.
- 11.2 The PBAC reiterated its view that the Committee was not supportive of the request to lower the authority level to an electronic/telephone authority for continuing treatment as it was inconsistent with existing listings (paragraph 7.4).
- 11.3 The PBAC reiterated that the cost of RIS should be no greater than the least costly of the alternative therapies, which include adalimumab (ADA), vedolizumab (VDZ) and infliximab (IFX) (paragraph 7.9). The PBAC also reiterated the equi-effective doses for

RIS of 600 mg IV at week 0, 4 and 8 followed by 360 mg SC every 8 weeks over two years and UST of 425 mg IV at week 0 followed by 90 mg SC every 8 weeks over two years were reasonable, and the equi-effective doses with the alternative therapies could be derived with reference to the therapeutic relativity sheets and product information documents.

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

**Outcome:**

Recommended

## 12 Recommended listing

12.1 Add new item(s):

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RISANKIZUMAB					
Risankizumab 600 mg/ 10 mL injection, 10 mL vial	NEW	1	1	2	Skyrizi
<b>Restriction Summary 9772 / Treatment of Concept: 9710</b>					
Concept ID (for internal Dept. use)	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Writing				

	<p><b>Administrative Advice:</b></p> <p>TREATMENT OF ADULT PATIENTS WITH SEVERE CROHN DISEASE,</p> <p>The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological medicines for adult patients with severe Crohn disease. Where the term 'biological medicine' appears in the following notes and restrictions, it refers to the tumour necrosis factor (TNF) alfa-antagonists (adalimumab and infliximab), the alpha-4 beta-7 integrin inhibitor (vedolizumab) and the human IgG1kappa monoclonal antibody (ustekinumab <i>and risankizumab</i>)., Patients are eligible for PBS-subsidised treatment with only 1 of the above PBS-subsidised biological medicines at any one time., From 1 September 2017, under the PBS, all patients will be able to commence a treatment cycle where they may trial PBS-subsidised a biological medicine without having to experience a disease flare when swapping to the alternate agent. Under these arrangements, within a single treatment cycle, a patient may continue to receive long-term treatment with a biological medicine while they continue to show a response to therapy., A patient who received PBS-subsidised treatment with a biological medicine prior to 1 September 2017 is considered to have started their treatment cycle as of 1 September 2017., Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised biological medicine more than once., Once a patient has either failed or ceased to respond to treatment for this condition 3 times, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 5-year break in PBS-subsidised biological medicine therapy for this condition before they are eligible to commence the next cycle. The 5-year break is measured from the date of the last approval for PBS-subsidised 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., A patient who has failed fewer than 3 trials of biological medicine therapy in a treatment cycle and who has a break in therapy of less than 5 years, may commence a further course of treatment within the same treatment cycle., A patient who has failed fewer than 3 trials of biological medicine therapy in a treatment cycle and who has a break in therapy of more than 5 years, may commence a new treatment cycle., There is no limit to the number of treatment cycles a patient may undertake in their lifetime., (1) How to prescribe PBS-subsidised adalimumab, infliximab, vedolizumab, <i>risankizumab</i> or ustekinumab therapy after 1 September 2017., (a) Initial treatment., Applications for initial treatment should be made where:, (i) a patient has received no prior PBS-subsidised biological medicine treatment in this treatment cycle and wishes to commence such therapy Initial 1 (new patient); or, (ii) a patient has received prior PBS-subsidised (initial or continuing) biological medicine and wishes to trial an alternate agent - Initial 2 (change or recommencement of treatment after a break in therapy of less than 5 years) [further details are under 'Swapping therapy' below]; or, (iii) a patient wishes to recommence treatment with a specific biological medicine following a break in PBS-subsidised therapy with that agent - Initial 2 (change or recommencement of treatment after a break in therapy of less than 5 years); or, (iv) a patient wishes to recommence treatment with a biological medicine following a break in PBS-subsidised therapy of more than 5 years - Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)., From 1 September 2017, a patient must be assessed for response to any course of initial PBS-subsidised treatment following a minimum of 12 weeks of therapy and no later than 4 weeks from the date that course was ceased for adalimumab, <i>risankizumab</i> or infliximab subcutaneous form or ustekinumab or vedolizumab subcutaneous form, and up to 12 weeks after the first dose (6 weeks following the third dose) for infliximab intravenous form or vedolizumab intravenous form., Where a response assessment is not conducted within these timeframes, the patient will be deemed to have failed to respond to treatment with that biological medicine unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment., Infliximab subcutaneous form only:, Initial treatment to subcutaneous form of infliximab should be permitted after administration of at least 2 initial intravenous infusions of infliximab. A maximum quantity and number of repeats to provide for weeks 6, 8, 10, 12, 14 and 16 will be authorised., Ustekinumab only: Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a weight-based loading dose, containing a quantity of up to 4 vials of 130 mg and no repeats. The second prescription should be written under S85 (General) for the subsequent first dose, containing a quantity of 2 vials of 45 mg and no repeats., Vedolizumab subcutaneous form only: initial treatment to subcutaneous form of vedolizumab should be permitted after administration of at least 2 of the 3 initial intravenous infusions of vedolizumab. Where two initial doses of vedolizumab (at weeks 0 and 2) is administered via intravenous infusion, initial</p>
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	<p>treatment with subcutaneous form will commence at week 6. A maximum quantity and number of repeats to provide for weeks 6, 8, 10, 12, 14 and 16 will be authorised. Where three initial doses of vedolizumab (at weeks 0, 2 and 6) is administered via intravenous infusion, initial treatment with subcutaneous form will commence at week 14 (8 weeks after the third dose). A maximum quantity to provide for weeks 14 and 16 will be authorised., (b) Continuing treatment., Following the completion of an initial treatment course with a biological medicine, a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response., It is recommended that a patient be reviewed in the 4 weeks prior to completing their current course of treatment to ensure uninterrupted supply of treatment., A patient must be assessed for response to a course of continuing therapy, and the assessment must be conducted within 4 weeks of the last dose. Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with that biological medicine, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment., Infliximab patients:, A patient may swap between the intravenous and subcutaneous forms of infliximab at any time under the continuing treatment restrictions provided the patient has demonstrated adequate response to treatment with infliximab., Vedolizumab patients:, A patient may swap between intravenous and subcutaneous forms of vedolizumab at any time under the continuing treatment restrictions provided the patient has demonstrated adequate response to treatment with vedolizumab., Adalimumab and infliximab intravenous form only:, Following the completion of an initial treatment course with a specific biological medicine, a patient remains eligible to receive up to 24 weeks per course of continuing treatment under the First continuing treatment and Subsequent continuing treatment restrictions with that drug providing they continue to sustain the response., It is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment., (2) Swapping therapy., Once initial treatment with the first PBS-subsidised biological medicine therapy is approved, a patient may swap if eligible to the alternate biological medicine within the same treatment cycle without having to requalify with respect to the indices of disease severity (i.e. Crohn Disease Activity Index (CDAI) Score, confirmation of Crohn disease), or the prior conventional therapies of corticosteroid therapy and immunosuppressive therapy., A patient may trial an alternate biological medicine at any time, regardless of whether they are receiving therapy (initial or continuing) with a biological medicine at the time of the application. However, they cannot swap to a particular biological medicine if they have failed to respond to prior treatment with that drug once within the same treatment cycle., To ensure a patient receives the maximum treatment opportunities allowed under these arrangements, it is important that they are assessed for response to every course of treatment, within the timeframes specified in the relevant restriction., A patient who is not able to complete an initial treatment course for a biological medicine will be deemed to have failed treatment with that, biological medicine unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment., (3) Baseline measurements to determine response., A response to treatment is to be determined by comparison of current disease activity measurements relative to the baseline measurements of the CDAI or evidence of intestinal inflammation submitted with the first authority application for a biological medicine., However, prescribers may provide new baseline measurements any time that an initial treatment authority application is submitted within a treatment cycle and the eligibility for continuing treatment must be assessed according to these revised baseline measurements., To ensure consistency in determining response, the same indices of disease severity used to establish baseline must be used to assess response to all subsequent treatments., (4) Recommencement of treatment after a 5-year break in PBS-subsidised therapy., A patient who wishes to recommence treatment following a break in PBS-subsidised biological medicine therapy of at least 5 years, must requalify for initial treatment with respect to the indices of disease severity under the Initial 3 restriction. A re-trial of systemic therapy is not required.</p>
	<p><b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.</p>
	<p><b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.</p>

	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Indication:</b> Severe Crohn disease
	<b>Treatment Phase:</b> Initial treatment - Initial 1 (new patient, <del>or re-commencement of treatment after a break in biological medicine of more than 5 years</del> )
	<b>Clinical criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	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.
	<b>AND</b>
	<b>Clinical criteria:</b>
	<del>The treatment must not exceed a total of 2 doses to be administered at weeks 0 and 8 under this restriction.</del> <i>The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction.</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	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.
	<b>Treatment criteria:</b>
	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)]
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescriber Instructions:</b> The authority application must be made in writing and must include: (1) two completed authority prescription forms; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

	<p><b>Prescriber Instructions:</b> 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.</p>
	<p><i>Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a quantity of 3 vials of 600 mg (1 Supply and two repeats). The second prescription should be written under S85 (General) for a quantity of 1 subcutaneous injection of 300 mg and no repeats.</i></p>
	<p><del>A maximum quantity of a weight based loading dose is up to 4 vials with no repeats and the subsequent first dose of 90 mg (2 vials of 45 mg) with no repeats provide for an initial 16 week course of this drug will be authorised.</del>  A maximum quantity and number of repeats to provide for an initial 812 week intravenous course of this drug will be authorised under this item code. A further 8 week subsequent subcutaneous dose course of treatment for injection at week 12 can be accessed will be authorised under the balance of supply criteria.</p>
	<p><del>Where fewer than 6 vials in total are requested at the time of the application, authority approvals for a sufficient number of vials based on the patient's weight to complete dosing at weeks 0 and 8 may be requested by telephone through the balance of supply restriction.</del></p>
	<p>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.</p>
	<p>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.</p>
	<p>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.</p>
	<p>Details of the accepted toxicities including severity can be found on the Services Australia website.</p>
	<p>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.</p>
	<p><del>An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of between weeks 12 weeks and 20 of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted to the Department of Human Services Australia no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</del>  An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</p>
	<p>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.</p>
	<p>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.</p>

	<p><b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></p> <p>Or mailed to:</p> <p>Services Australia</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
<b>Restriction Summary 9746 / Treatment of Concept: 9655</b>	
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> S100 – Section 100 (Highly Specialised Drugs)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – In Writing
	<b>Indication:</b> Severe Crohn disease
	<b>Treatment Phase:</b> Initial treatment – Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
	<b>Clinical criteria:</b>
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle,
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>The treatment must not exceed a total of 3 doses to be administered at weeks 0,4 and 8 under this restriction.</i>
	<b>Treatment criteria:</b>
	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)]
	<b>Population criteria</b>
	Patient must be aged 18 years or older
	<b>Prescriber Instructions:</b> The authority application must be made in writing and must include: (1) two completed authority prescription forms; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

	<i>Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a quantity of 3 vials of 600 mg (1 supply and two repeats). The second prescription should be written under S85 (General) for a quantity of 1 subcutaneous injection of 300 mg and no repeats.</i>
	<i>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.</i>
	<i>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.</i>
	<i>Details of the accepted toxicities including severity can be found on the Services Australia website.</i>
	To demonstrate a response to treatment the application must be accompanied by the results of the most recent course of biological medicine therapy within the timeframes specified in the relevant restriction.
	Where the most recent course of PBS-subsidised biological medicine treatment was approved under either Initial 1, Initial 2, Initial 3 or continuing treatment restrictions, an assessment of a patient's response must have been conducted following a minimum of 12 weeks of therapy for adalimumab, risankizumab or ustekinumab and up to 12 weeks after the first dose (6 weeks following the third dose) for infliximab and vedolizumab and submitted to the Services Australia no later than 4 weeks from the date of completion of treatment.
	<i>A maximum quantity and number of repeats to provide for an initial 8 week intravenous course of this drug will be authorised under this item code. A subsequent subcutaneous dose of treatment for injection will be authorised.</i>
	<del>An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of between weeks 12 weeks and 20 of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted to the Department of Human Services Australia no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</del> An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Where a response assessment is not conducted within the required timeframe, the patient will be deemed to have failed to respond to treatment with this drug, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.
	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.

	<p><b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></p> <p>Or mailed to:</p> <p>Services Australia</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
<b>Restriction Summary 9709 / Treatment of Concept: 9656</b>	
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> S100 – Section 100 (Highly Specialised Drugs)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – non-immediate assessment by Services Australia
	<b>Indication:</b> Severe Crohn disease
	<b>Treatment Phase:</b> Initial treatment – Initial 3 – <del>transitioning from non-PBS to PBS-subsidised supply – Grandfather arrangements (recommencement of treatment after a break in biological medicine of more than 5 years)</del>
	<b>Clinical criteria:</b>
	<i>Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>Patient must have a break in treatment of 5 years or more from the most recently approved PBS-subsided biological medicine for this condition</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	<del>The treatment must not exceed a total of 2 doses to be administered at weeks 0 and 8 under this restriction.</del> <i>The treatment must not exceed a total of 3 doses to be administered at weeks 0, 4 and 8 under this restriction.</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>Patient must have evidence of intestinal inflammation; or</i>
	<i>Patient must be assessed clinically as being in a high faecal output state; or</i>
	<i>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</i>
	<b>Treatment criteria:</b>
	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)]
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescriber Instructions:</b> The authority application must be made in writing and must include: (1) two completed authority prescription forms; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	<b>Prescriber Instructions:</b> 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.
	Two completed authority prescriptions should be submitted with every initial application for this drug. One prescription should be written under S100 (Highly Specialised Drugs) for a quantity of up to 3 vials of 600 mg and two repeats. The second prescription should be written under S85 (General) for a quantity of 1 subcutaneous injection of 300 mg and no repeats.
	<i>A maximum quantity and number of repeats to provide for an initial 8 week intravenous course of this drug will be authorised under this item code. A subsequent subcutaneous dose of treatment for injection at week 12 will be authorised.</i>
	<i>Details of the accepted toxicities including severity can be found on the Services Australia website.</i>
	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.

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	<p><del>An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of <i>between weeks 12 weeks and 20</i> of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted to the Department of Human Services <i>Australia</i> no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</del></p> <p>An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</p>
	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.
	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.
	<i>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.</i>
	<p><b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></p> <p>Or mailed to:</p> <p>Services Australia</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
RISANKIZUMAB					
Risankizumab 360 mg/ 2.4 mL injection, 2.4 mL cartridge	NEW	1	1	0	Skyrizi
<b>Restriction Summary [new] 9797 / Treatment of Concept: [new] 9711</b>					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – In writing				
	Add and edit note 27712 as above				
	Administrative Advice:				

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	No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Indication:</b> <i>Severe Crohn disease</i>
	<b>Treatment Phase:</b> <i>Initial treatment with subcutaneous form</i>
	<b>Clinical criteria:</b>
	<i>Patient must have received 3 initial intravenous infusions with this drug for this condition at weeks 0, 4 and 8 under Initial 1 (new patient); or</i>
	<i>Patient must have received 3 initial intravenous infusions with this drug for this condition at weeks 0, 4 and 8 under Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years); OR</i>
	<i>Patient must have received 3 initial intravenous infusions with this drug for this condition at weeks 0, 4 and 8 under Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years); OR</i>
	<i>Patient must have a concurrent authority application for the intravenous infusion for this condition under either 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).</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>The treatment must not exceed a total of 1 dose to be administered at week 12.</i>
	<b>Treatment criteria:</b>
	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)]
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescriber Instructions</b>
	The maximum listed quantity and number of repeats to provide for an 8 week subcutaneous course of treatment can be accessed under this restriction to allow for injection at week 12. This follows an 8 week intravenous course of treatment accessed under the Initial 1, Initial 2, or Initial 3 criteria.
	<del>The assessment of the patient's response to this initial course of treatment, including the week 12 subcutaneous dose must be made following a minimum of between weeks 12 and 20 of therapy so that there is adequate time for a response to be demonstrated.</del> An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	<del>It is recommended that an application for continuing treatment is submitted posted to the Services Australia at the time of the assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</del>
	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.
	<i>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.</i>

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<p><b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></p> <p>Or mailed to:</p> <p>Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
RISANKIZUMAB					
Risankizumab 360 mg/ 2.4 mL injection, 2.4 mL cartridge	NEW	1	1	2	Skyrizi

**Restriction Summary [new] 9747 / Treatment of Concept: [new] 9657**

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
(for internal Dept. use)	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – <del>Telephone</del> <i>In writing</i>
	Add and edit note 27712 as above
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Indication:</b> Severe Crohn disease
	<b>Treatment Phase:</b> Continuing treatment
	<b>Clinical criteria:</b>
	Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition
	<b>AND</b>
	<b>Clinical Criteria</b>
	Patient must have an adequate response to this drug define 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)

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	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not receive more than 24 weeks of treatment under this restriction
	<b>Population criteria</b>
	Patient must be aged 18 years or older
	<b>Treatment criteria:</b>
	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)]
	<b>Prescriber Instructions</b>
	Applications for authorisation must be made in writing and must include: (a) a completed authority prescription form; and, (b) a completed Crohn Disease PBS Authority Application - Supporting Information Form which includes the following: (i) the completed Crohn Disease Activity Index (CDAI) Score calculation sheet including the date of the assessment of the patient's condition, if relevant; or, (ii) the reports and dates of the pathology test or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; and, (iii) the date of clinical assessment.
	All assessments, pathology tests, and diagnostic imaging studies must be made within 1 month of the date of application.
	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.
	The assessment of the patient's response to a continuing course of therapy must be made within the 4 weeks prior to completion of that course and posted to the Department of Human Services Australia no less than 2 weeks prior to the date the next dose is scheduled, in order to ensure continuity of treatment for those patients who meet the continuation criterion.
	Where an assessment is not submitted 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.
	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.
	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.
	Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.
	<b>Administrative Advice</b>
	<b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).  Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>  Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a>  Or mailed to:

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Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RISANKIZUMAB					
Risankizumab 360 mg/2.4 mL injection, 2.4 mL cartridge	NEW	1	1	2	Skyrizi

**Restriction Summary [new] 12251 / Treatment of Concept: [new] 12077**

<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
(for internal Dept. use)	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
	Add and edit note 27712 as above
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.
	<b>Indication:</b> Severe Crohn disease
	<b>Treatment Phase:</b> <del>Initial treatment</del> – Grandfather treatment
	<b>Clinical criteria:</b>
	Patient must have a documented history of severe Crohn disease
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [LISTING DATE]
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have previously received induction treatment consisting of at least 3 doses with this drug for this condition in the intravenous form
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must be receiving treatment with this drug for this condition at the time of application
	<b>AND</b>
	<b>Clinical criteria:</b>
	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

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	or CDAI score of greater than or equal to 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
	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.
	<b>Treatment criteria:</b>
	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)]
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>Prescriber Instructions:</b>
	The authority application must be made in writing and must include: (a) a completed authority prescription form(s); 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).
	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.
	<del>An application for the continuing treatment must be accompanied with the assessment of response between weeks 12 and 20 of therapy with this drug and submitted 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.</del> An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	<del>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.</del>
	<del>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.</del>
	Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to sustain a response.
	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.

	<p>Evidence of failure to achieve an adequate response to prior therapy must include at least one of the following:</p> <ul style="list-style-type: none"> <li>(a) patient must have evidence of intestinal inflammation;</li> <li>(b) patient must be assessed clinically as being in a high faecal output state;</li> <li>(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.</li> </ul> <p>Evidence of intestinal inflammation includes:</p> <ul style="list-style-type: none"> <li>(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</li> <li>(ii) faeces: higher than normal lactoferrin or calprotectin level; or</li> <li>(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.</li> </ul>
	<p>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.</p>
	<p>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.</p>
	<p>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.</p>
	<p>Details of the accepted toxicities including severity can be found on the Services Australia website.</p>
	<p>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.</p>
	<p>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.</p>
	<p>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.</p>
	<p><b>Administrative Advice:</b></p>
	<p>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria</p>
	<p><b>Administrative Advice:</b> Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a></p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at <a href="http://www.servicesaustralia.gov.au/hpos">www.servicesaustralia.gov.au/hpos</a></p> <p>Or mailed to:</p> <p>Services Australia</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
	<p><b>Indication:</b> Severe Crohn disease</p>

	<b>Treatment Phase:</b> Balance of Supply
	<b>Treatment criteria:</b>
	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)].
	<b>AND</b>
	<b>Clinical criteria:</b>
	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 under the Continuing treatment restriction to complete 24 weeks of treatment
	<b>AND</b>
	<b>Clinical criteria</b>
	The treatment must provide no more than the balance of up to 12 weeks therapy available under Initial 1, 2 or 3 treatment
	The treatment must provide no more than the balance of up to 24 weeks treatment available under Continuing treatment
	<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

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

## 13 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.

## **14 Sponsor's Comment**

The sponsor had no comment.