TAR 372 – Ustekinumab for severe Crohn's disease.

This assessment provides an estimate of likely cost-effectiveness range of ustekinumab for Crohn's disease. Two indications are considered: as a second line biologic therapy (after infliximab) and as a third line biologic therapy (after infliximab and adalimumab).

A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical Ustekinumab (Stelara) 130ml / 26 mL single use vial for intravenous infusion 45mg / 0.5mL pre-filled syringe for subcutaneous injection 90mg / 1.0mL pre-filled syringe for subcutaneous injection
Supplier Janssen-Cilag Pty Ltd.
Proposed Indication Severe Crohn's disease in adults where conventional treatments and TNF-alpha treatment(s) have failed or were not tolerated.
Dosing Intravenous loading dose by weight (6mg/kg, up to a max of 520mg), then 90mg subcutaneous every 8 weeks.
Pharmaceutical Price Withheld net per unit (all strengths) Source of price: Supplier correspondence, November 2019 (A1354156).
PTAC PRIORITY Medium; February 2019.
PHARMCONNECT REFERENCE Ustekinumab proposals (2L and 3L)

Executive Summary

An application for the funding of ustekinumab for Crohn's disease was received from Janssen-Cilag Pty Ltd in May 2017. Crohn's disease is an autoimmune disease that can cause inflammation to occur anywhere along the length of the gastrointestinal tract, although most frequently involves the small bowel. The disease is lifelong. When the activity of the disease is high, symptoms can include disabling fatigue, frequent bowel movements, and abdominal pain. Current biologic treatment options include the tumour necrosis factor (TNF) inhibitors infliximab (an intravenous medicine) and adalimumab (a subcutaneous medicine). While these funded treatments work well as first- and second-line biologic treatments for Crohn's disease, a large proportion of patients will lose response over time. Surgery is frequently required to manage the disease process in the uncontrolled setting, though due to Crohn's disease affecting the length of the gastrointestinal tract, outcomes of surgery can have a highly variable effect on the quality of life of the patient.

The supplier provided a budgetary impact assessment but not a cost-utility analysis.

Summary of PHARMAC Cost-Utility Analysis

A cost-utility analysis (CUA) was undertaken by PHARMAC staff to estimate the cost-effectiveness of ustekinumab for patients with moderate to severe Crohn's disease who had lost response to currently funded biologic therapies. The economic model used data derived from the UNITI-1 and IM-UNITI clinical trials, which indicated that up to 37.8% of patients who have previously been exposed to biologic therapies are likely to demonstrate a clinical response to ustekinumab at 8 weeks post initiation. Of these patients who respond at 8 weeks, 59.4% have been reported to maintain a clinical response at 52 weeks post starting treatment. Beyond 52 weeks, the durability of the efficacy of ustekinumab is uncertain, requiring several assumptions to be made.

The incremental cost-effectiveness of ustekinumab for treating moderate to severe Crohn's disease patients who have lost response to currently funded biologic therapies is estimated to be in the range of Witheld QALYs per $million. In the absence of evidence to differentiate the efficacy of ustekinumab as a second- or third-line biologic treatment we did not differentiate the cost-effectiveness result.

Ustekinumab's cost effectiveness is driven by its high price. As is usual with high cost medicines, cost-effectiveness is relatively insensitive to large ranges in sensitivity analysis.

The CUA results are affected by the low primary response rate, a high secondary loss of response (unfortunately characteristic of biologic treatments in inflammatory bowel disease) and the relatively high cost of ustekinumab per dose. The likely range accounts for changes in the proportion of patients who may continue to receive alternative biologic therapy in the absence of ustekinumab, despite suboptimal response. The possible range accounts for changes in utility weights that best represent patients whilst in the non-response, clinical response and clinical remission health states.

Summary of PHARMAC Budgetary Impact Analysis

The 5-year net present value (NPV) to the Combined Pharmaceutical Schedule of funding ustekinumab is estimated to be Withheld million, with a cost for the first 12 months of Withheld million. The 5-year NPV to DHBs is estimated to be Withheld million, accounting only for net health system impacts resulting from net pharmaceutical distribution fees and infusion services.

1. Proposal Overview

1.1 Summary

An application for the funding of ustekinumab for the treatment of severe Crohn's disease was received from Janssen-Cilag Pty Ltd in May 2017. Two indications have been considered: as a second line biologic therapy (after infliximab) and as a third line biologic therapy (after infliximab and adalimumab).

Table 1 and Table 2 below provides a summary of the patient population; intervention; comparator treatment; and main outcomes of treatment.

Table 1. PICO for Ustekinumab as a second-line biologic therapy for Crohn's disease.

PICO	
POPULATION	Adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or are intolerant to infliximab (a TNFα antagonist).
INTERVENTION	Ustekinumab 390mg IV loading on day 1, then 90mg SC maintenance every 8 weeks thereafter.
COMPARISON	Adalimumab 160mg SC on day 1, then 80mg SC 2 weeks later, then 40mg every 2 weeks thereafter.
OUTCOME	Reduction in CDAI score, informing non-response, response, partial response and remission.

Table 2. PICO for Ustekinumab as a third-line biologic therapy for Crohn's disease.

PICO	
POPULATION	Adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or are intolerant to currently funded TNFα antagonists (infliximab and adalimumab).
INTERVENTION	Ustekinumab 390mg IV loading on day 1, then 90mg SC maintenance every 8 weeks thereafter.

COMPARISON	BSC with a proportion of patients remaining on infliximab despite suboptimal response.
OUTCOME	Reduction in CDAI score, informing non-response, response, partial response and remission.

Third-line treatment was considered in response to a request from the supplier in December 2019.

1.2 Patient Population

A detailed overview of Crohn's disease has previously been compiled by PHARMAC staff in January 2018 (A1109860). PTAC reviewed this record at the May 2018 meeting, and details from this record are included below.

Natural history of the disease

Crohn's disease (CD) is a severe inflammatory bowel disease (IBD) that affects the gastrointestinal tract. Inflammation can occur in any part of the gastrointestinal tract, but most often affects the distal ileum and colon. The natural history of CD is often characterised by a relapsing and remitting course, with episodes of acute symptomatic gut inflammation interspersed with periods of reduced disease activity or remission. In any one year, 50% of patients will experience symptoms. These will be severe in about one quarter of all patients. The cause of CD is not known but is believed to involve genetic, environmental, infectious and immunological factors.

CD occurs in all age groups, but most commonly presents in those aged 15 to 25 years. The prevalence of CD in New Zealand is 16.3 per 100,000, with prevalence at 145.3 per 100,000 [1]. With prevalence of 23.8 per 100,000, CD is generally rare among Māori, though the reasons for this are unclear.

The clinical manifestations of CD vary according to the anatomical location and severity of gut inflammation, the development of complications (e.g. abscesses, strictures or fistulae), the presence of specific extra-intestinal disease manifestations (including ocular, musculoskeletal, dermatological and hepatic problems) and the impact of previous surgery or drug treatments.

The spectrum of morbidity is very wide, ranging from a quiescent, symptom-free state to severe, life-threatening illness. Most patients have diarrhoea (70-90%), abdominal pain (45-66%), weight loss (65-75%) and anal lesions (50-80%). Fever (30-40%) and rectal bleeding (45%) are also common. People with Crohn's disease also have a 20-40% lifetime risk of developing a fistula [2], and may develop extra-intestinal manifestations including inflammation of the eyes, skin and joints.

HR-QoL studies have found that people with CD have significant decrements in quality of life compared to healthy controls, and that health-related quality of life in people with CD is directly correlated with disease activity [3]. Symptoms such as irregular sleeping and fatigue combined with unpredictable disease flare-ups lead to disruption in education, employment, personal relationships and social and family life. The frequent and urgent need to go to the toilet also affects self-esteem and social functioning [4]. There is evidence that anxiety and depression are more common in patients with IBD and that the symptoms of these conditions are more severe during periods of active disease; conservative estimates put the rate of depression to be at least twice the rate of those in the general community [5].

Crohn's disease activity index

Severity of CD is measured using the Crohn's disease activity index (CDAI) calculator. This calculator assesses the following 6 categories:

- Patient reported stool pattern
- Average abdominal pain rating over seven days
- General wellbeing each day over seven days
- Complications
- Finding of an abdominal mass
- Anaemia and weight change.

Points are attributed based on patient response. Moderate to severe Crohn's is assessed as having a CDAI score of 220-450. A CDAI score of <150 is considered to be asymptomatic remission. However, patients who achieve a score of <150 and still require steroids to remain asymptomatic are considered to be "steroid-dependent" and not in remission.

1.3 Current Treatment in New Zealand

Glucocorticoids, immunosuppressants and the biologic therapies including tumour necrosis factor (TNF) antagonists (anti-TNFα) and integrin inhibitors are the mainstay of treatment for Crohn's disease internationally [6]. Conventional therapies (oral steroids and immunomodulators) and two anti-TNFα therapies (adalimumab and infliximab) are currently listed in the Pharmaceutical Schedule for patients with mild-moderate, and severe and fistulising Crohn's disease, respectively.

1.4 Intervention

Clinical Pharmacology and Mechanism of Action

Ustekinumab is a human IgG1kappa monoclonal antibody directed against interleukin 12 and interleukin 23, naturally occurring proteins that regulate the immune system and immune-mediated inflammatory disorders. By binding to their shared p40 protein subunit, ustekinumab inhibits binding of p40 to the interleukin 12 receptor beta 1 subunit (IL-12Rβ1) receptor protein that is expressed on the surface of immune cells.

New Zealand Regulatory Approval

Ustekinumab is Medsafe-registered for the treatment of adult patients with moderately to severely active Crohn's disease. It is also registered for the treatment of some patients

with severe plaque psoriasis, patients with active psoriatic arthritis, and patients with moderately to severely active UC.

Recommended Dosage

Weight-based dosing is performed as follows for the initial intravenous (IV) dose:

- 260 mg for patients 55 kg and under (two 130 mg vials); or
- 390 mg for patients from 55 kg up to and including 85 kg (three 130 mg vials); or
- 520 mg for patients over 85 kg (four 130 mg vials).

Subsequent doses are administered subcutaneously, either:

- 90 mg at 8 weeks after the initial IV dose, then 8-weekly thereafter; or
- 90 mg at 8 weeks after the initial IV dose, then 12-weekly thereafter.

Proposed Treatment Paradigm

The supplier proposes that ustekinumab be funded for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, were intolerant to conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

PHARMAC staff have considered this proposal as addressing two separate indications involving adult patients with moderate to severe Crohn's disease:

1. Second line biologic therapy (after infliximab)
2. Third line biologic therapy (after infliximab and adalimumab).

Administration

The initial dose is administered by IV infusion. Ongoing 8-weekly maintenance doses are administered as subcutaneous injections. According to the Medsafe data sheet, ongoing maintenance dosing can be extended to 12 weeks in select patients according to clinician discretion.

Patients may continue treatment with regular non-biologic agents used to treat Crohn's disease, including corticosteroids, while receiving treatment with ustekinumab. In patients successfully treated with ustekinumab, treatment with corticosteroids may be reduced or discontinued at clinician discretion.

Proposed Special Authority Criteria

The following Special Authority criteria for ustekinumab for moderately to severely active ulcerative colitis have been proposed by the supplier.

INITIAL APPLICATION – Crohn's disease (adults) only from a gastroenterologist.
Approvals valid for 4 months
Re-assessment required after 4 months
Only from a gastroenterologist.
All of the following:

1. Patient has severe active Crohn's disease; and
2. Any of the following:
   2.1. Patient has a Crohn's Disease Activity Index (CDAI) score of greater than or equal to 300; or
   2.2. Patient has extensive small intestine disease affecting more than 50 cm of the small intestine; or
   2.3. Patient has evidence of short gut syndrome or would be at risk of short gut syndrome with further bowel resection; or
   2.4. Patient has an ileostomy or colostomy, and has intestinal inflammation; and
3. Patient has tried but had an inadequate response to, or has experienced intolerable side effects from, prior systemic therapy with immunomodulators at maximum tolerated doses (unless contraindicated) and corticosteroids; and
4. Surgery (or further surgery) is considered to be clinically inappropriate; AND
5. Patient must be re-assessed for continuation after 4 months of treatment

RENEWAL APPLICATION – Crohn's disease
Applications only from a gastroenterologist or practitioner on the recommendation of a gastroenterologist.
Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Either
   1.1. Applicant is a gastroenterologist; or
   1.2. Applicant is a Practitioner and confirms that a gastroenterologist has provided a letter, email or fax recommending that the patient continues with ustekinumab treatment and;
2. Either
   2.1. CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on ustekinumab; or
   2.2. CDAI score is 150 or less; or
3. Both:
   3.1. The patient has demonstrated an adequate response to treatment but CDAI score cannot be assessed (indicate reason); and
   3.2. Applicant to indicate the reason that CDAI score cannot be assessed and
4. Ustekinumab to be administered at doses no greater than 90 mg every 8 weeks.

Health Benefits

2.1 Clinical Evidence of benefit to the person, family and whānau

A detailed appraisal of the clinical evidence in support of Ustekinumab for treatment of severe Crohn's disease can be found in the supporting documentation provided by the Supplier (A1037625), as well as the PTAC clinical advice paper prepared by PHARMAC staff in advance of the May 2018 PTAC meeting (A1125933). A brief overview of the pivotal clinical evidence considered by PTAC and the Gastrointestinal Subcommittee is presented in Table 3 below.

2.2 Consequences for the health system

Funding of ustekinumab might conceivably result in a decrease in infliximab use. This would be a positive consequence for the health system. This is because ustekinumab is administered subcutaneously, whereas infliximab is administered via outpatient infusion services.

2.3 Suitability

The first loading dose of ustekinumab requires an intravenous infusion of at least one hour. Thereafter, maintenance doses are given by subcutaneous injection every 8 weeks. This compares to adalimumab, which requires fortnightly subcutaneous administration, and infliximab, which requires intravenous infusion up to every 8 weeks in a hospital setting.

Consequently, the 8-weekly administration of ustekinumab is advantageous compared to currently funded biologic therapies available for patients with Crohn's disease in New Zealand.

Table 3. Summary of pivotal ustekinumab clinical trials (adapted from supplier submission synopsis, A1037627).

Population	Trial; Citation	Type	Patient Number and Treatment[a]	Efficacy Results (PBO vs Ustekinumab)	Safety Results (PBO vs Ustekinumab)
Adult patients with moderate to severe CD (CDAI score ≥ 220 but ≤ 450) who had primary or secondary nonresponse to anti-TNFα therapy (IFX, ADA or certolizumab) or had unacceptable side effects.	UNITI-1 NCT01369342 Feagan et al (2016)	Phase 3 randomised double-blind, placebo controlled multicentre trial 8-week induction	N=741[a], randomised 1:1:1 to single infusion at W0: 1. Ustekinumab (IV) *130 mg (N=245)* 2. Ustekinumab (IV) Tiered weight-based dose (N=249) 3. PBO (N=247)	All primary and major secondary outcomes were achieved: PBO vs ustekinumab tiered weight-based dose. **Primary:** CR-100 at week 6: 21.5% vs 33.7%, p=0.003. **Key secondary:** 1. Remission at W8: 7.3% vs 20.9%, p<0.001. 2. CR-100 at W8:20.2% vs 37.8%, p<0.001. 3. CR-70 at W6:30.4% vs 43.8%, p=0.002. 4. CR-70 at W3: 27.1% vs 40.6%, p=0.001.	The number of patients reporting any AE were similar between trial arms, 64.9% vs 65.9%. The rate of SAEs reported was low and similar in both arms, 6.1% vs 7.2%. No deaths were reported. Most frequently reported AEs were infections (23.7% vs 25.7%) and GI related (32.2% vs 22.9%).

Population	Trial; Citation	Type	Patient Number and Treatment[a]	Efficacy Results (PBO vs Ustekinumab)	Safety Results (PBO vs Ustekinumab)
Adult patients with moderate to severe CD (CDAI score ≥ 220 but ≤ 450) who had failed conventional therapy or had unacceptable side effects but had not demonstrated inadequate response or intolerance to 1 or more anti-TNFα therapies.	UNITI-2 NCT01369329 Feagan et al (2016)		N=628[b], randomised 1:1:1 to single infusion at W0: 1. Ustekinumab *(IV) 130 mg (N=209)* 2. Ustekinumab (IV) Tiered weight-based dose (N=209) 3. PBO (N=210)	All primary and major secondary outcomes were achieved: PBO vs ustekinumab tiered weight-based dose **Primary:** CR-100 at week 6: 28.7% vs 55.5, p<0.001. **Key secondary:** 1. Remission at W8: 19.6% vs 40.2%, p<0.001. 2. CR-100 at W8: 32.1% vs 57.9%, p<0.001. 3. CR-70 at W6: 38.8% vs 64.6%, p<0.001. 4. CR-70 at W3: 31.6% vs 50.7%, p<0.001.	The number of patients reporting any AE were similar between trial arms, 54.3% vs 55.6%. The rate of SAEs reported was low and similar in both arms, 5.8% vs 2.9%. No deaths were reported. Most frequently reported AEs were infections (23.1% vs 21.7%) and GI related (20.2% vs 21.3%).
Patients from the UNITI-1 and UNITI-2 trials who were in clinical response (CR-100) at week 8 of ustekinumab induction therapy (this comprised the primary population). Those randomised to placebo induction or those not in response to ustekinumab	IM-UNITI NCT01369355 Feagan et al (2016)	Phase 3 randomised double-blind, placebo controlled multicentre trial 44-week maintenance	Primary population: N=397[c], randomised 1:1:1 to: *1. Ustekinumab (SC) 90 mg q12w (N=132)* 2. Ustekinumab (SC) 90 mg q8w (N=132) 3. Induction Only (Maintenance	All primary and most major secondary outcomes were achieved: Induction Only (PBO) vs ustekinumab q8w. **Primary:** Remission at W44 among CR-100 responders to ustekinumab induction: 35.9% vs 53.1%, p=0.005. **Secondary:** 1. CR-100 at W44:44.3% vs 59.4%, p=0.033	The number of patients reporting any AE were similar between trial arms, 83.5% vs 81.7%. The rate of SAEs reported was low and similar in both arms, 15% vs 9.9%. No deaths were reported. Most frequently reported AEs were infections, the rate

Population	Trial; Citation	Type	Patient Number and Treatment[a]	Efficacy Results (PBO vs Ustekinumab)	Safety Results (PBO vs Ustekinumab)
induction were also included in IM-UNITI, but not in the primary population			Placebo, PBO) (N=133) 4. for 44 weeks	2. Remission at W44 among ustekinumab induction remitters: 45.6% vs 66.7%, p=0.007. 3. Corticosteroid free remission at W44: 29.8% vs 46.9%, p=0.004 4. Remission at W44 in refractory patients: 26.2% vs 41.1%, p=0.102	was similar in both arms, 49.6% vs 48.1%.

ADA, adalimumab; AE, adverse event; CD, Crohn's disease; CDAI, Crohn's disease activity index; CR-70, defined as a reduction from baseline in the CDAI score of ≥70 points; CR-100, clinical response defined as a reduction from baseline in the CDAI score of ≥100 points; GI, gastrointestinal; IFX, infliximab; IV, intravenous; PBO: placebo, q8w, every 8 weeks; q12w, every 12 weeks, SAE, serious adverse event; SC, subcutaneous, TNF, tumour necrosis factor; W, week. Notes: osage regimes in italics in the included trials are not discussed in detail in this submission.

[a] A total of 769 patients were randomised, however due to a drug stability issue the study was temporarily suspended after 28 patients were randomised. All planned analyses were based on the 741 patients who were randomised after the study was restarted.

[b] A total of 640 patients were randomised, however due to a drug stability issue the study was temporarily suspended after 12 patients were randomised. All planned analyses were based on the 628 patients who were randomised after the study was restarted.

[c] Six patients were treated in the induction phase, but did not enter the randomised maintenance phase

1.5 Review of Clinical Evidence

Ustekinumab for the treatment of severe Crohn's disease has been considered at three separate clinical advice meetings to date, each providing a positive recommendation for funding. The link to the corresponding minutes is also provided linked to the date for each meeting.

Table 4. Clinical advice meetings where ustekinumab for severe Crohn's disease has been considered.

Meeting	Recommendation	Date
PTAC	Medium	February 2019
Gastrointestinal SC	High	October 2018
PTAC	Medium	May 2018

3 PHARMAC Cost-Utility Analysis

The IBD Core Model (2019; v.2.0) was utilised by PHARMAC staff to model the cost effectiveness of ustekinumab for moderate to severe Crohn's disease, non-responsive or intolerant to currently funded biologic therapies versus current standard of care.

The core model is a Markov model built with an annual cycle length and a 20-year time horizon. The model consists of nine health states, as shown below in

Figure 1.

3.1 Scope of Analysis

The analysis was undertaken from the perspective of the funder, with regards to PHARMAC's Factors for Consideration.

3.1.1 Target Population

The target population for this analysis was defined as Crohn's patients no longer maintaining clinical response, or intolerant to, currently funded TNF inhibitor therapies.

3.1.2 Comparator

The comparator used in the analysis was placebo. PHARMAC staff received clinical advice that there was a risk of slippage with current biologic treatments being prescribed to patients who may not strictly meet special authority criteria, in part due to the flexibility of the CDAI score, and due to patients remaining on biologic treatment in order to defer or delay surgery. PHARMAC also considered it likely that the funding of a new agent with a different mechanism of action would shorten the length of time patients spend on current treatments, particularly infliximab. Good quality data was not available to estimate this effect so a range of scenarios in which patients continued infliximab treatment with a muted response were also considered as part of the comparator. That is, the comparator also considered active treatment at full cost, but with a limited benefit.

3.2 Model Structure

PHARMAC's IBD core model was used to model the different treatment strategies.

3.2.1 Time Horizon

Consistent with a supplier cost-utility analysis submitted to PHARMAC for adalimumab for Ulcerative Colitis a time horizon of 20-years, rather than a life-time horizon, was chosen given the limited length of available clinical data, and the uncertain relapse and remitting natural history of the disease. All costs and benefits are discounted at 3.5%. The cycle length is annual.

3.2.2 Model Structure

A branch of the CUA model used in this analysis is presented in

Figure 1 below:

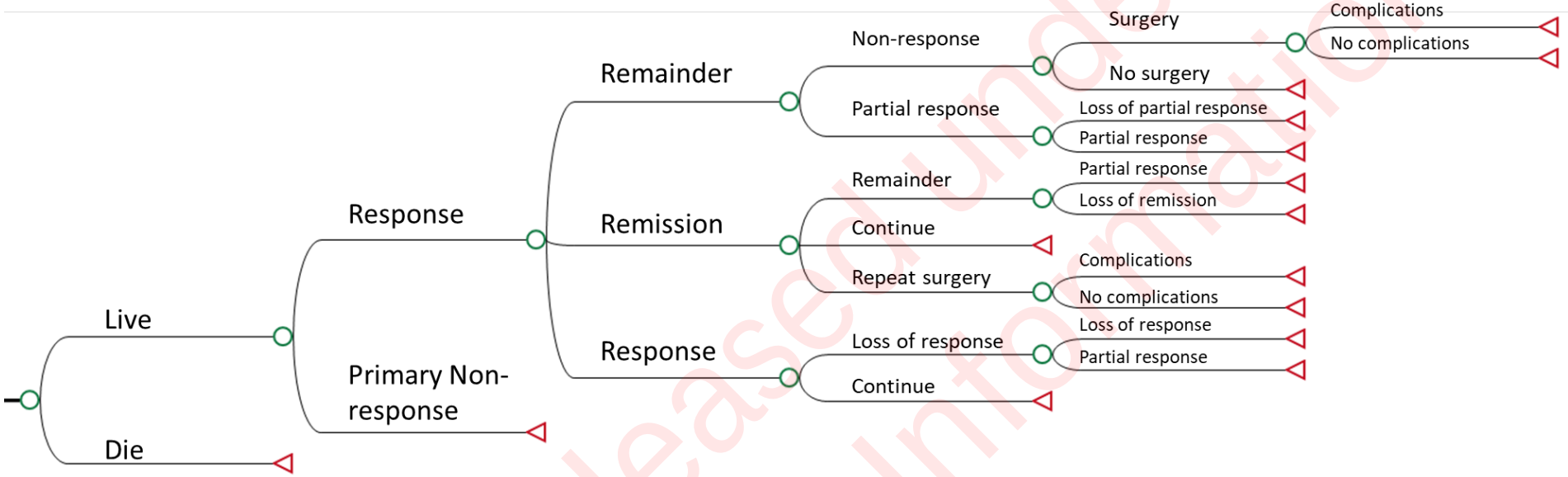

Figure 1. Transitions from each health state within CUA model (from the PHARMAC IBD core model)

The model included the following nine health states:

- Non-response
- Remission
- Response
- Surgery (with no long-term complications)
- Surgery (with long-term complications)
- Repeat surgery (with no long-term complications)
- Repeat surgery (with long-term complications)
- Partial response (slippage)
- Dead

All patients enter the model in the non-response health state and commence on induction therapy. As the model uses an annual cycle, induction is rolled into the first cycle, where patients have a chance of induction treatment failure (a primary non-response), a response or death. Patients achieving a response are further qualified as achieving 'remission' (best possible response), 'clinical response' (next level down), and 'partial response' (lowest possible response). At this point in the model, the patients transition out of the non-response health state to the respective health state best describing the level of response achieved after induction (remission, response, partial response).

Patients who experience primary loss of response or lose response over time (i.e. secondary loss of response), transition back to the non-response health state. Here, these patients face the prospect of surgery to manage their uncontrolled disease. Crohn's surgery is not without risk, and as such, the model accounts for the possibility that patients will suffer from long term complications arising from the surgery.

Further surgical intervention is a possibility. This possibility of relapse post-surgery and the need for further surgical intervention is faced with the prospect of long-term complications.

All patients face the risk of death at each stage of the model, in accordance with background mortality rates associated with the respective age of the patient.

3.3 Transformation and Extrapolation of Clinical Evidence

Two pivotal clinical trials (UNITI-1 and IM-UNITI), as outlined in the health benefits section above in Table 3, informed the clinical efficacy of ustekinumab in the target population considered in this CUA.

3.3.1 Clinical Parameter Estimates

The clinical parameters included in the analysis are outlined in Table 5 below.

Table 5. Clinical parameters as used in this CUA.

Variable	Value	Source
Probability of primary non-response following ustekinumab induction	62.2%	UNITI-1
Probability of primary non-response on placebo induction	79.8%	UNITI-1
Probability of maintaining remission on ustekinumab at 52 weeks	41%	IM-UNITI
Probability of remission on placebo at 52 weeks	26%	IM-UNITI
Probability of maintaining clinical response on ustekinumab at 52 weeks	5%	Estimate from IM-UNITI
Probability of maintaining clinical response on placebo at 52 weeks	6%	Estimate from IM-UNITI
Probability of maintaining partial response on ustekinumab at 52 weeks	40%	HE assumption
Probability of secondary loss of response on ustekinumab beyond 52 weeks	14% per annum	IM-UNITI long term extension
Probability of loss of response on comparator	14% per annum	Estimate, noting IM-UNITI extension study is single-arm
Probability of requiring surgery if patient does not achieve primary response, or loses response over time (per annum)	7.76%	NIHR (2016)
Probability of requiring repeat surgery for Crohn's patients (per annum)	2.1%	Overstraeten et al 2017
Probability of surgical complications	33.3%	HE assumption based on 23% complications rate for UC surgery

<u>Probability of primary non-response following ustekinumab induction.</u>

As per the findings of the UNITI-1 trial, 37.8% of Crohn's patients who had previously been treated with biologic therapies were reported to have achieved a clinical response to ustekinumab at week 8 of follow up. This implies that the inverse, or 62.2%, represents the patients who experienced a primary non-response to ustekinumab.

Probability of primary non-response on placebo.

As per the findings of the UNITI-1 trial, 20.2% of Crohn's patients who were randomised to placebo therapy were reported to have achieved a clinical response to placebo at week 8 of follow-up. This implies that the inverse, or 79.8%, represents the patients who experience a primary non-response to placebo.

Probability of maintaining remission at on ustekinumab at 52 weeks.

As per the findings of the IM-UNITI trial, 41% of patients with prior history of anti-TNF therapy who responded to ustekinumab by the end of the earlier 8-week long induction trial were found to have maintained remission at 44 weeks follow up (in effect, 52 weeks from starting ustekinumab).

Probability of remission on placebo at 52 weeks.

As per the findings of the IM-UNITI trial, 26% of patients with prior experience of anti-TNF therapy who responded to placebo by the end of the earlier 8-week long induction trial were found to have maintained remission at 44 weeks follow up (in effect, 52 weeks from starting placebo).

Probability of maintaining a clinical response (maintained ≥100-point reduction in CDAI compared to pre-treatment baseline) on ustekinumab and placebo at 52 weeks.

In the IM-UNITI trial, 59.4% of patients who responded to ustekinumab by the end of the earlier 8-week long induction trials were found to have maintained clinical response at 44 weeks follow up (in effect, 52 weeks from starting ustekinumab). Unlike remission, response results were not presented to PHARMAC, or identified in the literature, for subjects who were refractory or intolerant to TNF antagonist therapy. PHARMAC staff therefore estimated the response rate in this population and subjected this rate to sensitivity analysis. From this we estimated that approximately 5% of patients, intolerant or refractory to TNF antagonist therapy, would achieve a response at 12 months. Noting that the definitions of response and remission overlap as illustrated.

	IM-UTI all patients including refractory or intolerant to TNF antagonist therapy, 8 weekly treatment.	IM-UTI – patients refractory or intolerant to TNF antagonist therapy.
Remission	53.1%	41.1%

Response	59.4%	
Response only	6.3% (59.4%-53.1%)	*4.88% (41.1%*12%)*
Response only as % of remission	12% (6.3%/53.1%)	12%

Using the same method, the corresponding figure for placebo is 6%.

	IM-UTI all patients including refractory or intolerant to TNF antagonist therapy	IM-UTI – patients refractory or intolerant to TNF antagonist therapy.
Remission	35.9%	26.2%
Response	44.3%	
Response only	8.4% (44.3%-35.9%)	*6.13% (26.2%*23%)*
Response only as % of remission	23% (8.4%/35.9%)	23%

Probability of maintaining partial response on ustekinumab at 52 weeks.

PHARMAC staff understand that a proportion of patients that do not receive a clinical response to biologic therapy for CD (i.e. a ≥100 point decrease in CDAI score) may continue to receive biologics. Previous PHARMAC analysis of adalimumab for CD comparing actual prescribing of biologic therapy to what would be implied from trial data (A1327552) suggested this partial response (or slippage) rate may be as high as 40%. This number is, however, subject to significant uncertainty as the real-world setting invariably differs from the highly controlled environment of clinical studies. As such our estimate is subject to a large variation in sensitivity analysis.

As this is essentially a behavioural assumption, the same rate is applied to the comparator arm for infliximab.

Probability of secondary loss of response on either ustekinumab or placebo (beyond 52 weeks).

The model uses a secondary loss of response rate beyond the first year of therapy of 14%, based on the IM-UNITI long term extension study for ustekinumab [7]. Among patients with prior history of anti-TNFs, the proportion in remission at weeks 44 and 92 was 81.5% (22/27) and 70.4% (19/27) respectively, corresponding to a loss of remission of approximately 14.7% per annum. This is similar to the loss of remission rates observed for patients receiving adalimumab as a second-line biologic therapy for Crohn's disease (ADHERE), again from a small population (n=45)[8]. Given the small patient population and the uncertainty in how loss of response differs according to the mechanism of action of the biologic, this was subjected to a large variation in sensitivity analysis.

In the absence of data, we assumed the same loss of response rate for placebo. Noting all identified data beyond 12 months was single arm.

Probability of requiring surgery if patient does not achieve primary response, or develops secondary loss of response (annual).

We have assumed an annual probability of surgery of 7.76% based on a cost-utility analysis undertaken by the UK National Institute for Health Research (Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy)[9]. Noting we have assumed the same rate for CD as UC. Given the uncertainty implicit in this assumption we have subjected the estimate to a wide interval in sensitivity analysis.

A meta-analysis (2017) of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis reported similar pooled proportions of patients on placebo undergoing surgery for ulcerative colitis (7%) as for Crohn's disease (6%) [10]. Included trials were for moderate to severe patients. Rates were per patient year.

In a review of surgical rate in the biologic era (2017) [11, 12] the following surgical rates were noted in Crohn's disease:

- ACCENT I – 54 weeks - 2.8 versus 7.4%, p= 0.01 for infliximab vs placebo (median CDAI ~300 – moderate to severe disease).
- ACCENT II - major abdominal surgery rates (2.1 versus 12.6%, P < 0.05) for infliximab vs placebo. Follow-up time not specified.
- CHARM 56 weeks - (0.6 versus 3.8% p<0.001) adalimumab vs placebo. (moderate to severe patients)

Probability of requiring repeat surgery

We have assumed an annual probability of repeat surgery of 2.1%1 based on Van Overstraeten et al 2017 (n=538) recurrence requiring surgery of 19.1% at 10 years following primary ileocaecal resection for Crohn's disease [13].

Probability of surgical complication.

PHARMAC staff have previously used a rate of surgical complications for ulcerative colitis of 23% based on a suppliers cost utility analysis of adalimumab for ulcerative colitis (A1181660). Data on surgical complications for CD patients is generally scarce, though surgical outcomes are generally worse for patients with CD, with a greater number of

[1] This is the converted annual transition probability of a 19.1% probability over 10 years.

patients requiring repeat surgery. PHARMAC staff therefore adjusted the rate of surgical complications up by approximately 50%.

3.4 Health-Related Quality of Life

The utility values included in the analysis were informed by the default EQ-5D derived HRQOL weights incorporated in the IBD core model (2019; v.2.0). These weights are shown in Table 6 below, with more detailed explanation of how these values were derived outlined in Appendix I.

Table 6. Utility values as used in this CUA.

Variable	Base utility	High estimate	Low estimate
Utility of Crohn's disease in remission	0.80	0.9	0.75
Utility of Crohn's disease in response	0.743	0.8	0.65
Utility of Crohn's disease in non-response	0.542	0.75	0.45
Utility of Crohn's disease in post-surgical state without long term complications	0.77	0.85	0.70
Utility of Crohn's disease in post-surgical state with long term complications	0.71	0.79	0.64

PHARMAC staff note two quality of life studies highlighted by the supplier in the 2017 application (see section 3.2.3 A1037625). The first study by Wright el al (2015) investigated HRQOL in New Zealand and Australian patients before surgery, using both the SF-36 and the disease specific IBDQ instruments [14]. The corresponding weights are presented in Table 7 below, illustrating the poor quality of life experienced by patients with severe uncontrolled Crohn's disease prior to surgery.

Table 7. Pre and post-operative HRQOL data as provided as part of the supplier application.

Instrument	Preop	Post op (months)			Significance
		6	12	18	
N	165	148	121	108	(p-value)
SF-36 (PCS)	40	68	71	72	<0.001
SF-36 (MSC)	44	68	70	70	<0.001
IBDQ	125	171	175	175	<0.001

The second study by Gibson et al (2007) investigated the correlation between Crohn's disease activity, as measured by CDAI, and two quality of life instruments (IBDQ and AQoL) [15]. 143 patients with a broad range of disease severity were recruited from centres across Australia. As Figure 2 below illustrates, a negative correlation between disease severity and IBDQ was found ($p<0.0001$).

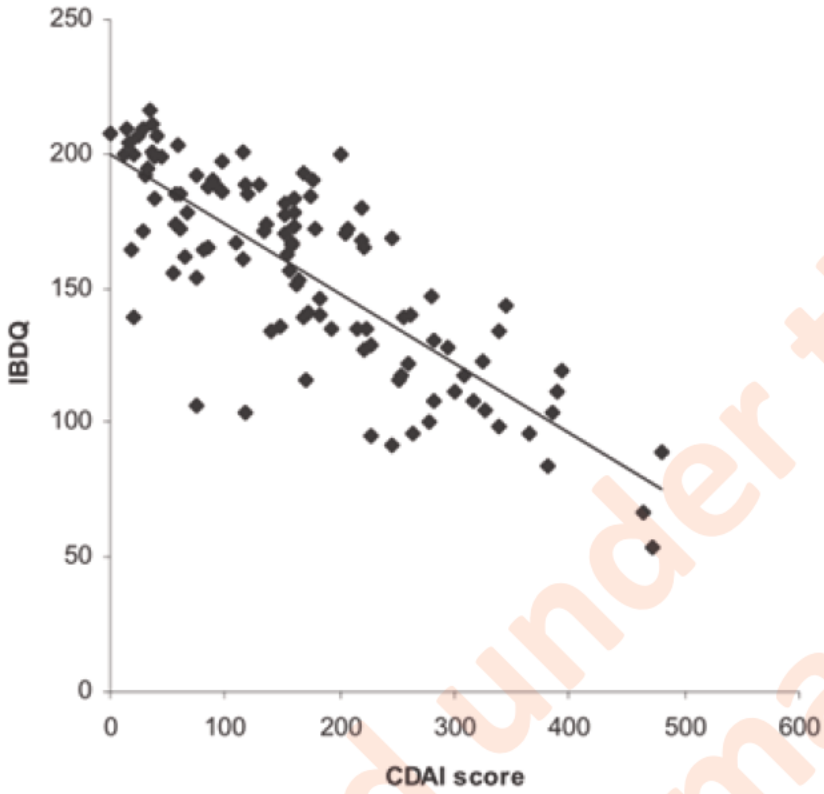

Figure 2. Disease specific quality of life (IBDQ) as a function of severity of Crohn's disease (CDAI) – adapted from Gibson et al, 2007 [15].

A similar relationship was found for AQoL and CDAI, as presented in Table 8 below:

Table 8. Mean estimated quality of life (AQoL) as a function of disease activity (CDAI).

Disease activity	**AQoL (mean)**
Remission	0.77
Mild disease (CDAI 150-219)	0.68
Moderate to severe (CDAI ≥220)	0.45

All values are lower than those included in our base case. Mild disease is what we have indicated as the response state. Of principle concern for cost-utility analysis is the difference between values especially the difference in utilities between remission and moderate to severe disease. In the supplier's submission this is a difference of 0.32 (0.77-0.45) whereas our base case is 0.258 (0.80 - 0.542). We test the utility values in sensitivity analysis.

3.5 Costs

3.5.1 Pharmaceutical Cost

The pharmaceutical costs are presented below in Table 9.

Table 9. Pharmaceutical costs included in this CUA.

Variable	Value
Cost of ustekinumab 130mg vial / 90mg prefilled syringe	Witheld
Cost of BSC	Witheld
Cost of infliximab 100mg vial	Witheld
Cost of adalimumab 40mg prefilled syringe	Witheld
Cost of ustekinumab	Witheld

Cost of ustekinumab

Ustekinumab has been offered by the supplier at a confidential net price of Witheld per 130mg vial (used only for loading regimen) and 90mg prefilled syringe (used only for maintenance dosing). As per the dosing required for a patient weighing up to 80kgs, 3 vials of ustekinumab have been costed to account for the loading regiment. Otherwise the model assumes each patient will consume one prefilled syringe every 8 weeks as part of a maintenance regimen. No allowance has been made to account for the possibility of dose titration by the attending physician to 12 weekly cycles.

Accounting for the increased number of doses requiring during loading (3x 130mg doses) the first-year cost of treatment is Witheld per patient. The annual cost reduces to Witheld from year two onwards, accounting for one 90mg dose being required every 8 weeks.

Cost of adalimumab

Adalimumab is subject to a confidential rebate. The net cost is Witheld per prefilled syringe (40mg). Accounting for the additional doses required during loading (4x 40mg doses) the first-year cost of treatment is Witheld. The annual cost reduces to Witheld from year two onwards, accounting for one 40mg dose being required every 2 weeks.

The cost of adalimumab was not included as part of the comparator for the CUA but has been modelled in the BIA. The CUA model, may be updated to include adalimumab as part of the comparator, but the impact is expected to be marginal.

Cost of infliximab

Infliximab is subject to a confidential rebate. The net price is Withel per vial (100mg). Dosing in the model is variable, allowing for both 5mg/kg and 10mg/kg dosing, in accordance with the special authority restrictions. Each patient receives infliximab on an 8-weekly cycle. Each patient is assumed to weigh less than 80kg. Wastage is also assumed. Therefore 4 vials of infliximab are consumed for each dose by each patient on 5mg/kg dosing, and 8 vials for patients on 10mg/kg dosing.

Cost of BSC

All patients, irrespective of biologic used, are assumed to use BSC in addition to biologic. The annual cost of BSC is based off the estimated weekly cost of BSC treatments (With per week per patient).

3.5.3 Health Sector Costs

The health sector costs as included in this CUA are presented below in Table 10.

Table 10. Health sector costs included in this CUA.

Variable	**Value**
Cost of non-response in Crohn's	$9,983
Cost of response in Crohn's	$1,013
Cost of ustekinumab infusion	$155
Cost of infliximab infusion	$259.12
Cost of surgery	$23,800

Cost of response and non-response in Crohn's

The health system cost for patients achieving a response in Crohn's disease is estimated by PHARMAC, using the 2018 Cost Resource Manual (CRM) to be $1,013. The estimated costs of Crohn's Disease non-response is $9,983.

These estimates are based on estimated annual utilisation of health system services previously used for adalimumab for ulcerative colitis (A1181660), which used information provided by the supplier from a small survey of clinicians. These costs were tested in the sensitivity analysis. The breakdown of costs and utilisation is shown in table 9 below.

Table 11: Health system costs (average annual utilisation by health state)

Item	Item cost source	Item cost	Remission	Response	Non-response	Post-surgery (no major complications)	Post-surgery (major complications)
Inpatient	WEISNZ13	$4,325.98	0	0	1	0	1
ED	Cost Manual	$680.00	0	0	1.5	0	1.25
Specialist	Cost Manual	$150.00	2	2.25	6.5	4	8
GP	Cost Manual	$80.00	1.625	1.625	5	2	6
Blood test	Cost Manual	$15.00	2.75	3.25	9.75	5	10.25
Imaging	Auckland X-Ray	$299.10	0	0.25	1.625	0.75	1.875
Endoscopy	Cost Manual	$843.36	0.125	0.5	2	0.5	0.625
Colonoscopy	NMPAC	$943.34	0	0	1	0	0
Average cost			$576.67	$1,012.71	$9,983.34	$1,481.01	$8,097.65

Cost of ustekinumab infusion

As per the supplier's application and the Medsafe registration for ustekinumab, the initial loading dose is recommended to be administered over a period over at least 1 hour in duration. In accordance with the 2018 CRM, one hour of infusion time has been costed for each patient requiring a loading dose of ustekinumab.

Cost of infliximab infusion

As per the Medsafe registration, infliximab is recommended to be administered over a period of two hours, followed by a further one hour of supervised observation. In accordance with the 2018 CRM, three hours of outpatient infusion service time has been costed.

Cost of surgery

We modelled the cost of surgery off the cost of surgery for ulcerative colitis provided in a prior supplier model and updated using 2018 DRG costs. Noting that for Crohn's disease the predominate surgery is partial small bowel resections[16], where colectomy are less frequent than for ulcerative colitis. Surgery is more frequent for Crohn's disease than ulcerative colitis, but the cost per event appears to be less. In a European study the cost of Crohn's disease surgery was estimated to be 35% less than for ulcerative colitis[17]. We have applied this multiplier to estimate the cost of surgery for Crohn's disease.

Average cost of IPAA surgery		**Average Cost**
Three stage procedure		
Stage 1	G02 A/B Major small and large bowel procedure	$18,214
Stage 2	G05 A/B/C Minor small and large bowel procedure	$9,814
Stage 3	G05 A/B/C Minor small and large bowel procedure	$9,814
Total		$37,842
Two stage procedure		
Stage 1	G01 A/B Rectal resection	$25,503
Stage 2	G05 A/B/C Minor small and large bowel procedure	$9,814
Total		$35,317
Weighted average surgical cost		
50%	Three stage procedure	$18,921
50%	Two stage procedure	$17,659

Average cost of IPAA surgery		Average Cost
Total	All procedures	$36,580
CD Cost Estimate (65%)		$23,777

3.6 Cost-Effectiveness Results

The incremental cost is estimated to be Witheld, with a QALY gain of 0.12. The estimated QALYs per $1million is therefore W (cost per QALY of Witheld). This is shown in the table below.

Table 2. Cost effectiveness results.

	Ustekinumab	Status quo	Incremental
QALYs	12.69	12.57	0.12
Cost	Witheld	Witheld	Witheld
QALYs per $1m	Wit		

The cost-offsets in the model are primarily due to a reduction in patients needing surgery due to a higher proportion of patients remaining in remission / clinical response with ustekinumab therapy. A further cost offset is achieved from less patients requiring ongoing infliximab infusions (despite known suboptimal response) and therefore incurring less health sector costs over time. There are also cost offsets arising from fewer patients with severe Crohn's disease requiring hospitalization.

3.7 Sensitivity Analysis

Multiple one-way (deterministic) sensitivity analyses were undertaken. An abridged overview of these analyses is presented in Table below.

Table 3. Sensitivity analyses.

Parameter	Base	High	Low	QALYs / $1m (ICER) (high)	QALYs / $1m (ICER) (low)
Ustekinumab price discount	Witheld under	75% discount	50% discount	With Witheld	Wit Witheld
Loss of response	14%	14%	5%	Wit Witheld	Wit Witheld
Utility from remission	0.80	0.9	0.75	Wit Witheld	Wit Witheld
Utility from response	0.743	0.8	0.6	Wit Witheld	Wit Witheld
Utility from non-response	0.542	0.7	0.3	Wit Witheld	Wit Witheld
Utility from partial response	0.64	0.70	0.54	Wit Witheld	Wit Witheld
Cost of non-response	$9,983	$14,975	$7,488	Wit Witheld	Wit Witheld
Patients on infliximab (placebo arm)	40%	80%	0%	Wit Witheld	Wit Witheld
Partial response	40%	80%	0%	Wit Witheld	Wit Witheld

Probability of LT complications after surgery	33.3%	33.3%	23%	Wit Witheld	Wit Witheld
Cost of surgery for Crohn's disease	$23,777	$23,777	$54,869	Wit Witheld	Wit Witheld

3.8 Summary of Overall Cost-Effectiveness

As outlined above, the base-case QALY per $1m estimate is W.

Ustekinumab's cost effectiveness is driven by its high price. As is usual with high cost medicines, cost-effectiveness is relatively insensitive to large ranges in sensitivity analysis.

Taking into account the results of the sensitivity analysis, the highly likely range is estimated to be Wit. The low end of the likely range reflects the uncertainty surrounding the proportion of patients who might reasonably experience a partial response to ustekinumab therapy, as well as the uncertainty surrounding the appropriate utility weight that best represents patients whilst in the clinical response and clinical remission health states. The high end of the likely range reflects the uncertainty of patients in the comparator arm who might reasonably be estimated to remain on infliximab therapy, despite suboptimal response.

The possible QALY per $1m range is Witheld. The lower end of the possible range is informed as for the low end of the likely range. The higher end of the possible range reflects the uncertainty surrounding the appropriate utility weight that best represents patients whilst in the non-response health state.

4 Budget Impact Analysis

Ustekinumab as 3rd line biologic therapy for patients with severe Crohn's disease.

The BIA compiled by PHARMAC staff for this indication can be reviewed directly via the following link (A1382949). This BIA has been built by undertaking several amendments to the comprehensive supplier BIA that was provided to PHARMAC in November 2019 (A1354156). The net result of these amendments was to significantly reduce the anticipated budgetary impact estimated by the Supplier to both the CPB and to DHBs overall.

These amendments are as follow:

1. The treatment survival curve (proportion of patients remaining on ustekinumab therapy over time) has been aligned with the treatment survival curve used to inform CUA modelling as described above. In short, the probability of remaining on treatment in the first 12 months is informed by clinical trial data obtained from IM-UNITI. Beyond 12-months, a 14% compounding rate has been applied.
2. The primary non-response rate has been applied at week 16 in the BIA model, as opposed to week 4 in the supplier BIA model. This allows for the real-world likelihood that patients in New Zealand would be likely to administer maintenance doses at week 8 and 16 that would be permitted under the proposed special authority criteria, during the initial 4-month trial period. PHARMAC staff note that the CR-100 in the UNITI-1 trial suggest response improves between week 6 and 8, providing an additional incentive for physicians to continue their patients on treatment during this initial trial period.
3. PHARMAC staff have amended the listing date from April 2020 to July 2021. This allows consideration of a full 12 months budgetary impact in the first year of listing (based on financial years), as opposed to the 8 months implied in the supplier model (which is based on calendar years).
4. PHARMAC staff have considered the population of warehoused (prevalent) Crohn's patients who would immediately trial ustekinumab on listing to be using funded biologics, despite suboptimal response (i.e. it is considered there are likely a number of patients in New Zealand who are using biologics despite experiencing only a partial response). Clinical advice has indicated that approximately 70% of these patients are likely to be using adalimumab, with the remainder on infliximab.
5. PHARMAC staff anticipate that the total biologic market for Crohn's disease is likely to expand on listing of a third biologic agent, beyond what is currently forecasted. Following internal consultation, 2% annual growth has been modelled in the first two financial years of listing, followed by 1% annual growth thereafter.

Summary of BIA results

The 5-year net present value (NPV) to the Combined Pharmaceutical Schedule of funding ustekinumab is estimated to be Witheld million, with a cost of the first 12 months of Withe million. This is outlined in Table below. The 5-year NPV to DHBs is estimated to be Witheld million. All costs are discounted at a rate of 8%.

Table 4. BIA Ustekinumab as 3rd line biologic therapy for Crohn's disease in New Zealand.

	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year NPV
Patient numbers (patient years on treatment)	151	133	209	290	369	-
Community Pharmaceutical Budget ($million)	Withheld	Withheld	Withheld	Withheld	Withheld	Withheld
Hospital Pharmaceutical Budget ($million)	Withheld	Withheld	Withheld	Withheld	Withheld	Withheld
Other DHB Costs ($million)	$0.08	$0.03	$0.17	$0.27	$0.38	$0.73
Total net budget impact to DHBs ($million)	Withheld	Withheld	Withheld	Withheld	Withheld	Withheld

Patient numbers.

An estimated ~130 patients are considered likely to be eligible to trial ustekinumab upon listing, representing the current prevalent pool of Crohn's patients who are thought to be in immediate need of a third line biologic agent. However, not all patients respond to therapy. It has been considered that only 35% of the prevalent pool of patients would be likely to demonstrate a primary response to ustekinumab following induction, and therefore meet the proposed eligibility criteria to continue treatment as per the proposed special authority criteria.

Incident patients are anticipated over the five years of the model as a result of Crohn's patients already on first (infliximab) and second line (adalimumab) biologic therapies losing response over time. Incidence of patients being commenced on ustekinumab induction is estimated to be ~40 patients in the first year, rising to ~170 patients by year five. Again, not all incident patients respond to therapy. In line with the findings of the IM-UNITI-1 trial, it is considered that only 37.8% of incident patients would be likely to demonstrate a primary response to ustekinumab following induction, and therefore meet the proposed eligibility criteria to continue on treatment as per the proposed special authority criteria.

All patients remain on treatment as long as they demonstrate a clinical response. Secondary loss of response over the first 12 months of the model has been informed by the findings of the IM-UNITI trial. Post 12 months, secondary loss of response is informed by the previously described 14% annual loss of response (compounding), as per the CUA model used in this analysis.

Community pharmaceutical budget impact.

Witheld under section 9(2)(b)(ii); 9(2)(ba)(i) and 9(2)(j) Over time, displacement of the current adalimumab market is anticipated to result in a net cost to the community pharmaceutical budget.

Witheld under section 9(2)(b)(ii); 9(2)(ba)(i) and 9(2)(j)

Witheld under section 9(2)(b)(ii); 9(2)(ba)(i) and 9(2)(j)

Hospital pharmaceutical budget (HPB) impact.

Ustekinumab requires an initial intravenous loading dose. The number of patients expected to require a one-off loading dose of ustekinumab per year are considerable, relative to the few patients in this category that are estimated to still be receiving ongoing 8-weekly infliximab despite suboptimal response. Consequently, a net cost to the HBP is expected following listing of ustekinumab.

Other DHB costs.

PHARMAC staff have quantified the result impact of ustekinumab on other DHB costs by accounting for resulting changes in net distribution fees paid to pharmacies (applies to gross pricing of ustekinumab 90mg PFS and adalimumab PFS only) and infusion costs associated with infliximab and loading doses of ustekinumab. PHARMAC staff have not quantified the impact, and potential cost offset, of a reduction of patients no longer requiring gastrointestinal surgery due to access to ustekinumab. While DHB cost may therefore be overstated, at least one recent systematic review has indicated that biologics have had a very limited impact on rates of surgery in IBD [12].

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6 Appendix I. Outline of HRQOL evidence used to inform the IBD Core Model (2019; v2.0)

Health States	Base Utility	EQ-5D weights	Best	Worst	Reference	Comments / Other Evidence
Disutility surgical complications	0.06		0.06	0.1	TAR 338	Supplier estimate for UC
CD non-response	0.542	1,1,(2-3),2,(1-2)	0.45	0.75	TAR 119	SF-6D (n=425) 0.587, for moderate and 0.505 for severe
CD remission	0.852	1,1, (1-2), (1-2),1	0.9	0.8	TAR 119	UK EQ-5D remission 0.89 (n=129) See TAR 119 SF-6D (n=425) 0.744
CD response	0.743	1,1,2, (1-2), 1	0.8	0.65	TAR 119	SF-6D (n=425) 0.638
CD partial response	0.64				HE	Mid-point of response and no response
Post-surgery without long-term complications	0.80		0.85	0.70	HE	Mid-point between remission and response – base case rewards biologics 0.05 utility vs surgery
Surgery with complications	0.74		0.79	0.64	HE	As above less disutility for on-going complications