PHARMAC
TE PĀTAKA WHAIORANGA

TAR 465 – Risankizumab for Chronic Plaque Psoriasis

Date	14 January 2022
Level of Analysis	Standard

This assessment provides an estimate of likely cost-effectiveness range of Risankizumab for the first- and second-line treatment of moderate to severe Chronic Plaque Psoriasis (CPP).

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

PROPOSAL OVERVIEW
Pharmaceutical Risankizumab (Skyrizi) 75mg pre-filled syringe
Supplier AbbVie New Zealand Limited
Proposed Indication Moderate to severe plaque psoriasis
Dosing 150 mg (2 injections) subcutaneously administered at week 0, week 4, and every 12 weeks thereafter
Pharmaceutical Price s9(2)(b)(ii)); ber 2 x 75mg syringes (equal to one 150mg dose)
PTAC PRIORITY First line: high priority (Dermatology Subcommittee, November 2020); medium priority (PTAC, May 2021) Second line: high priority (Dermatology Subcommittee, November 2020; PTAC, May 2021)
PHARMCONNECT REFERENCE First-line: P-001180 Second-line: P-001656

Executive Summary

An application for the funding of risankizumab for the first- and second-line treatment of moderate-to-severe chronic plaque psoriasis was received from AbbVie NZ in August 2018.

Chronic plaque psoriasis is a skin disease that presents as large, well-demarcated, thick, silvery-white patches of skin. The impact on patients is mostly quality-of-life related however patients with severe psoriasis do experience an average reduction in life expectancy of three to four years. Psoriasis has an adverse impact on many aspects of daily life, including clothing choice, bathing frequency, washing clothes, sports activities, and the ability to from social and romantic connections due to feelings of self-consciousness and embarrassment. In addition, the prevalence of depression in patients with psoriasis is estimated to be up to 30%.

Under current Special Authority restrictions, patients with moderate to severe chronic plaque psoriasis must have tried, but had an inadequate response to, or experienced intolerable side effects from, at least three of phototherapy, methotrexate, ciclosporin, or acitretin treatment, prior to biologic treatment. The currently funded biologics for CPP are adalimumab, etanercept, infliximab and secukinumab.

Review of Cost-Utility Analyses

The application to PHARMAC for the listing of risankizumab included a Cost Utility Analysis (CUA), which reported a QALYs per $1 million invested of s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(j)). PHARMAC staff have reviewed the CUA and note that while the analysis was generally sound, a few model components were deemed inappropriate in this context:

- The utility values used in sensitivity analysis likely overstated the gain in quality of life for some health states, resulting in the upper bound of the CUA range being very high
- Inpatient days for psoriasis patients on Best Supportive Care (BSC) appear much higher than NZ ICD discharge data would suggest
- The comparator in the New Zealand context is likely to involve a combination of currently available biologics and BSC, rather than just adalimumab (first-line comparison in supplier model) and BSC (second-line comparison in supplier model).

To estimate a CUA range more applicable to the NZ context, Pharmac has undertaken its own CUA.

Summary of PHARMAC Cost-Utility Analysis

The Pharmac CUA used data derived from a number of phase III trials (IMMvent, UltIMMa 1/2, , IMMerge, IMMhance) which all indicated that risankizumab was more effective at reducing the patients Psoriasis Area and Severity Index (PASI) score than all comparators, including all those funded in NZ.

The incremental QALYs gained per $million invested in risankizumab compared to current treatments for treating CPP is estimated to be in the range of s9(2)(b) for first-line treatment, and s9(2)(b) for second-line. The results of the CUA were relatively insensitive to most input parameters, with the exception of the number of inpatient days for patients on biologics and BSC and to a lesser extent, the utility values and discontinuation rates. The relative insensitivity of the model indicates that Pharmac has a high degree of confidence in the likely CUA range at the current price of risankizumab.

Summary of Budget Impact Analysis

For first-line treatment, patient numbers were estimated to be 261 in year 1, increasing to 1,433 in year 5. For second-line, they were expected to increase from 208 in year 1 to 838 in year 5.

The net cost to the CPB of listing risankizumab first-line is expected to be s9(2)(b) in year 1 with a 5-year net present value (NPV) of s9(2)(b). Second-line listing is expected to cost s9(2)(b) in year 1 with a 5-year NPV of s9(2)(b).

Listing risankizumab is expected to generate a small amount of savings to the wider health system. The savings generated by first-line listing are expected to be approximately $60,000 in year 1 with a 5-year NPV of $490,000. Second-line listing is expected to generate savings of approximately $60,000 in year 1 with a 5-year NPV of $615,000. The saving to the wider health system is driven by the displacement of infliximab, which, unlike risankizumab, requires an infusion.

1. Proposal Overview

1.1 Summary

An application for the funding of Risankizumab for the first- and second-line treatment of moderate to severe Chronic Plaque Psoriasis (CPP) was received from AbbVie in August 2018.

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

Table 1. PICO

PICO	
POPULATION	**First-line**: Patients with moderate-to-severe chronic plaque psoriasis intolerant, contraindicated or with inadequate benefit from prior systemic therapy and/or biologic therapy **Second-line**: As per first-line, except patients must have previously trialled at least one prior biologic.
INTERVENTION	150 mg (two 75 mg injections) of Risankizumab administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. In case of risankizumab failure, patients proceed through other biologics (adalimumab, secukinumab and etanercept) then finally to best supportive care
COMPARISON	Other listed biologic treatments: • Adalimumab 80mg at week 0, then 40mg every other week • Secukinumab 300mg each week for the first 4 weeks, 300mg once per month thereafter • Etanercept 50mg twice per week for 12 weeks, then once per week thereafter If all biologic treatments fail, patients move to BSC
OUTCOME	Greater rates of PASI 75 / 90 / 100 response resulting in improved quality of life

1.2 Patient Population

Disease Description

Chronic plaque psoriasis is a skin disease that presents as large, well-demarcated, thick, silvery-white patches of skin. It is caused by an immune system problem causing the skin to regenerate at faster than normal rates, often triggered by an environmental factor such as an infection or stress.

Chronic plaque psoriasis is considered severe if it results in 'whole body' psoriasis with a Psoriasis Area and Severity Index (PASI) score of greater than 10 or involving the face, or palm of a hand or sole of a foot, where lesions have been present for at least 6 months from the time of initial diagnosis.

Risk factors for CPP include intrinsic factors such as metabolic syndrome and mental stress as well as extrinsic factors such as infection and smoking/alcohol.

Epidemiology

Chronic plaque psoriasis is the most common type of psoriasis (approximately 80-90%). The Dermatology Subcommittee noted that approximately 2% of the New Zealand population are affected, but that the majority of patients have clinically mild psoriasis which is not extensive enough to warrant treatment with biologics.

The supplier has estimated the prevalence of severe CPP in adults in New Zealand using the assumptions detailed in Table 2. They estimated a prevalence of 12,678 in 2018.

Table 2: Supplier epidemiology assumptions[1]

Parameter	Central estimate	Source	Source justification
Adult (≥18 years)			
NZ adult population 2018	3,740,720	www.stats.govt.nz[a]	NZ population data
Psoriasis prevalence	3.3%	ABS NHS 2014-15[b]	Most recent data, low risk bias, comparable population (Australian)
Proportion CPP	79%	Icen 2009	Low risk bias, results consistent over time, large study
Proportion PASI >10	13%	Eden 2016	Low risk bias
Estimated NZ prevalence CPP with PASI >10	**12,678**	**Calculated**	**NA**

If the subcommittee's psoriasis prevalence estimate (2%) is used instead, the prevalence of severe CPP falls to 7,683.

The Subcommittee noted that there is no evidence that the prevalence of psoriasis in Māori and Pacific peoples is significantly different to the rest of the population. However, comorbidities associated with psoriasis are more prevalent among Māori and Pacific peoples, suggesting they may have a greater health need.

The health need of the person

Psoriasis has been described by the World Health Organization (WHO) as a chronic, painful, disfiguring, and disabling disease for which there is no cure and with significant impairment in quality of life. In 2014, the WHO recognised psoriasis as a serious noncommunicable disease, highlighting that many people in the world suffer needlessly from psoriasis due to delayed diagnosis, inadequate treatment options, insufficient access to care, and because of social stigmatisation (WHO, 2016).

The burden of psoriasis on patients touches most aspects of life. Patients with severe psoriasis have an all-cause mortality rate that is twice as high as the general population, with an average reduction in life expectancy of three to four years, comparable to the impact of severe hypertension (Friedewald et al. Am J Cardiol. 2008;102:1631-43, Salahadeen et al. J Eur Acad Dermatol Venereol. 2015; 29(5):1002-5). Psoriasis is also strongly associated with other immune-mediated inflammatory diseases including psoriatic arthritis and inflammatory

[1] Main body of AbbVie Risankizumab submission, August 2018 (A1174632)

bowel disease, as well as psychiatric disorders and obesity (Mrowietz et al. Arch Dermatol Res. 2010;298:309-19).

A large European study found that 48% of psoriasis patients reported an impact on activities of daily living, with adverse impacts on daily activities such as clothing choice, bathing frequency, washing clothes, sports activities, and work and school activities (Dubertret et al. Br J Dermatol. 2006;155:729-36, World Health Organisation, 2016). The prevalence of depression in patients with psoriasis is estimated to be up to 30% (Moon et al. Dermatol Ther (Heidelb). 2013;3:117-30).

In addition, the skin disfigurement caused by psoriasis can limit the patient's ability to form social and romantic relationships due to feelings of self-consciousness, embarrassment, frustration, and stigmatisation.

1.3 Current Treatment in New Zealand

Under current Special Authority restrictions, patients with moderate to severe chronic plaque psoriasis (PASI >10) must have tried, but had an inadequate response to, or experienced intolerable side effects from, at least three of phototherapy, methotrexate, ciclosporin, or acitretin treatment, prior to biologic treatment. Both methotrexate and ciclosporin are currently funded without restriction, while acitretin has safety restrictions in place.

Adalimumab, etanercept, infliximab and secukinumab are the currently funded biologics of severe chronic plaque psoriasis, subjects to restrictions.

Analysis of the current biologic market in NZ found that the market was dominated by adalimumab and, increasingly, secukinumab. The market share for the year ending 31 October 2021 is displayed in Table 3. This market share data was used to inform cost-utility and budget impact modelling assumptions, as detailed in sections 4 and 5.

Table 3: Current biologic market share, year ending October 2021[2]

Pharmaceutical	Average number of patients on treatment each month	Market share
Adalimumab	547	43%
Secukinumab	587	46%
Etanercept	94	7%
Infliximab	49	4%
Total	**1,277**	**100%**

[2] Special Authority database

1.4 Intervention

Clinical Pharmacology and Mechanism of Action

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor complex. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. IL-23 supports the development, maintenance and activation of Th17 cells, which produces IL-17A, IL-17F, and IL-22, as well as other pro-inflammatory cytokines, and plays a key role in driving inflammatory autoimmune diseases, such as psoriasis. IL-23 is up-regulated in lesional skin in comparison to non-lesional skin of patients with plaque psoriasis. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of pro-inflammatory cytokines.

New Zealand Regulatory Approval

AbbVie's brand of risankizumab, Skyrizi is Medsafe approved for the treatment of moderate to severe plaque psoriasis in adults.

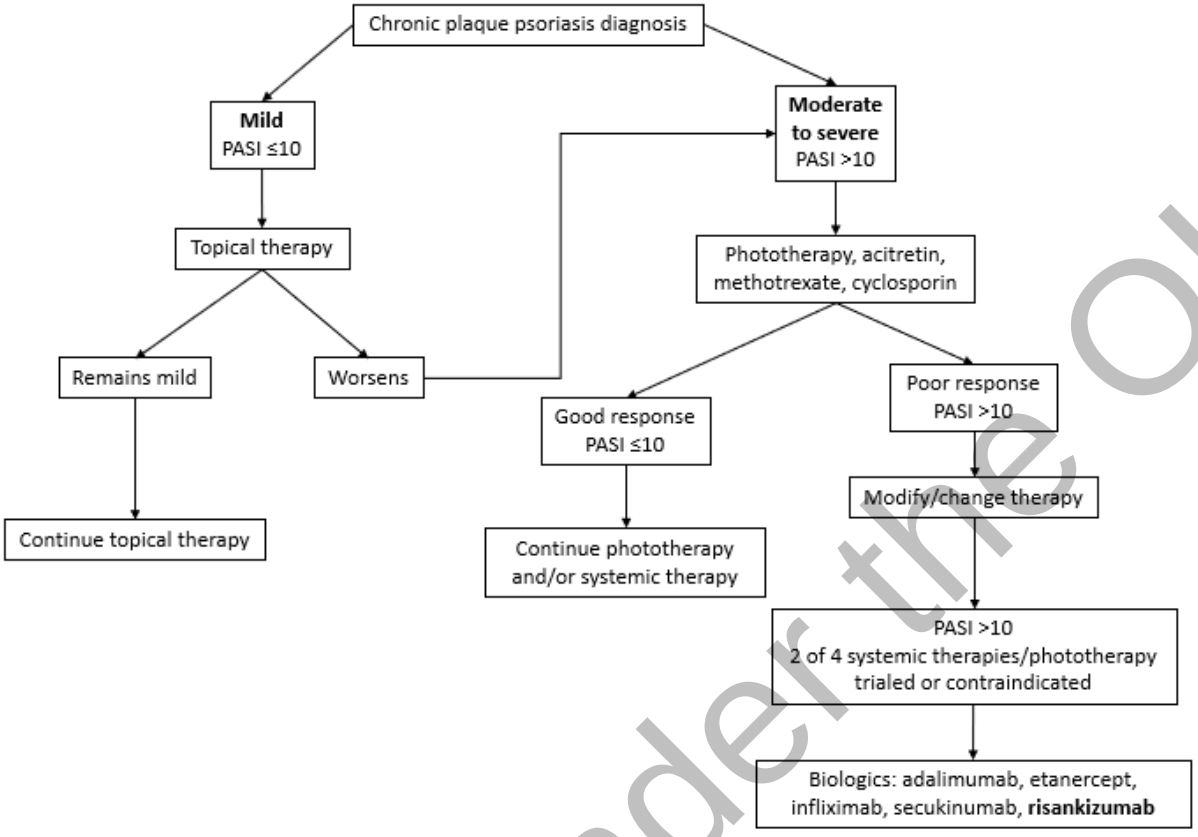
Recommended Dosage

The recommended dosage of risankizumab is 150 mg (two 75 mg injections) administered subcutaneously at Week 0, Week 4, and every 12 weeks thereafter.

Proposed Treatment Paradigm

The supplier has proposed the following treatment algorithm depicted in Figure 1, which would place risankizumab in the same line as other first-line current biologics:

Figure 1: Proposed treatment paradigm (first-line therapy)



In the case of risankizumab being used as a second-line therapy, the treatment paradigm would be the same as above, but with an additional branch: Risankizumab would be used following a poor response (PASI > 10) to the first-line biologic.

Proposed Special Authority Criteria

PTAC recommended that risankizumab for the **first line treatment** of chronic plaque psoriasis be listed with a medium priority subject to the following Special Authority criteria:

Initial application – (severe chronic plaque psoriasis, first line biologic) only from a dermatologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
Either:
1 Both:
1.1 The patient has had an initial Special Authority approval for adalimumab, etanercept or secukinumab, or has trialled infliximab in accordance with the General Rules of the Pharmaceutical Schedule, for severe chronic plaque psoriasis; and
1.2 Either:
1.2.1 Patient has experienced intolerable side effects from adalimumab, etanercept, infliximab or secukinumab; or
1.2.2 Patient has received insufficient benefit from adalimumab, etanercept, infliximab or secukinumab; or
2 All of the following:
2.1: Either:
2.1.1 Patient has "whole body" severe chronic plaque psoriasis with a Psoriasis Area and Severity Index (PASI) score of greater than 10, where lesions have been present for at least 6 months from the time of initial diagnosis; or

2.1.2 Patient has severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot, where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis; and

2.2 Patient has tried, but had an inadequate response* to, or has experienced intolerable side effects from, at least three of the following (at maximum tolerated doses unless contraindicated): phototherapy, methotrexate, ciclosporin, or acitretin; and

2.3 A PASI assessment or Dermatology Life Quality Index (DLQI) assessment has been completed for at least the most recent prior treatment course, preferably while still on treatment but no longer than 1 month following cessation of each prior treatment course; and

2.4 The most recent PASI or DLQI assessment is no more than 1 month old at the time of application.

*A treatment course is defined as a minimum of 12 weeks of treatment. “Inadequate response” is defined as: for whole body severe chronic plaque psoriasis, a PASI score of greater than 10, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment; for severe chronic plaque psoriasis of the face, hand or foot, at least 2 of the 3 PASI symptom sub scores for erythema, thickness and scaling are rated as severe or very severe, and the skin area affected is 30% or more of the face, palm of a hand or sole of a foot, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment.

Renewal – (severe chronic plaque psoriasis) only from a dermatologist or practitioner on the recommendation of a dermatologist. Approvals valid for 6 months for applications meeting the following criteria:

Both:

1. Either:

1.1 Patient’s PASI score has reduced by 75% of more (PASI 75) as compared to baseline PASI prior to commencing risankizumab; or

1.2 Patient has a Dermatology Life Quality Index (DLQI) improvement of 5 or more, as compared to baseline DLQI prior to commencing risankizumab; and

2. Risankizumab is to be administered at a maximum dose of 150 mg every 12 weeks, following induction doses at 0 and 4 weeks

PTAC recommended that risankizumab for the **second line treatment** of chronic plaque psoriasis be listed with a high priority subject to the following Special Authority criteria

Initial application – (severe chronic plaque psoriasis, second line biologic) only from a dermatologist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

1 The patient has had an initial Special Authority approval for adalimumab, etanercept or secukinumab, or has trialled infliximab in accordance with the General Rules of the Pharmaceutical Schedule, for severe chronic plaque psoriasis; and

2 Either:

2.1 Patient has experienced intolerable side effects from adalimumab, etanercept, infliximab or secukinumab; or

2.2 Patient has received insufficient benefit from adalimumab, etanercept, infliximab or secukinumab; and

3 A PASI assessment or Dermatology Life Quality Index (DLQI) assessment has been completed for at least the most recent prior treatment course, preferably while still on treatment but no longer than 1 month following cessation of each prior treatment course; and

4 The most recent PASI or DLQI assessment is no more than 1 month old at the time of application.

*A treatment course is defined as a minimum of 12 weeks of treatment. “Inadequate response” in defined as: for whole body severe chronic plaque psoriasis, a PASI score of greater than 10, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment; for severe chronic plaque psoriasis of the face, hand or foot, at least 2 of the 3 PASI symptom sub scores for erythema, thickness and scaling are rated as severe or very severe, and the skin area affected is 30% or more of the face, palm of a hand or sole of a foot, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment.

Renewal – (severe chronic plaque psoriasis) only from a dermatologist or practitioner on the recommendation of a dermatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Either:
1.1 Patient's PASI score has reduced by 75% of more (PASI 75) as compared to baseline PASI prior to commencing risankizumab; or
1.2 Patient has a Dermatology Life Quality Index (DLQI) improvement of 5 or more, as compared to baseline DLQI prior to commencing risankizumab; and
2. Risankizumab is to be administered at a maximum dose of 150 mg every 12 weeks, following induction doses at 0 and 4 weeks

2. Health Benefits

2.1 Clinical Evidence

The supplier identified four trials that provide the primary evidence for the health benefits of risankizumab for the treatment of chronic severe plaque psoriasis. A summary of these trials is provided in Table 4 below. The trials summarised below include patients who have had previous treatment with biologics, as well as patients who are treatment naïve. There has, however, been limited analysis of these subgroups to assess risankizumab in a second- or later-line setting for these patients.

Table 4: Summary of evidence for risankizumab for the treatment of severe chronic plaque psoriasis[3]

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
IMMvent	Randomised, double-blind, active-comparator-controlled phase 3 trial	Adults aged ≥18 years, with stable (≥6 months) moderate-to-severe CPP, with body surface area involvement 10% or greater, PASI ≥12, and sPGA score ≥3. Patients were candidates for systemic therapy or phototherapy and eligible adalimumab. 70% male, 25.5-26.5% mean body surface area involvement. Mean PASI: 20.0 RIS, 19.7 ADA.	n=605 RIS, n=301 ADA, n=304	150 mg RIS SC at weeks 0 and 4 or 80 mg ADA SC at week 0 and then 40 mg every other week from week 1 up to the end of week 15. In part B, patients continuing ADA were given study drug every other week from week 17 up to the end of week 41; patients switching to RIS were given study drug at weeks 16, 20, and 32; and patients remaining on RIS were given study drug at weeks 16 and 28.	44 weeks	Previous biologic treatment: 39% of RIS group vs 37% of ADA group • Previous TNF inhibitor (excl. ADA): 15% RIS vs 15% ADA • Previous non-TNF inhibitor: 32% RIS vs 27% ADA • IL-12 and IL-13 inhibitor treatment: 12% RIS vs 7% ADA • IL-17 inhibitor treatment: 20% RIS vs 21% ADA PASI 90 at Week 16, adjusted absolute differences: • 24.9% (95% CI: 17.5-32.4, p<0.0001) PASI 90 at week 44, adjusted absolute differences: • 45.0% (95% CI: 28.9-61.1, p<0.0001) sPGA clear or almost clear at week 16, adjusted absolute differences: • 23.3% (95% CI: 16.6-30.1, p<0.0001) sPGA clear or almost clear at week 44, adjusted absolute differences: • 38.9% (95% CI: 22.0-55.8, p<0.0001)	SAEs: 3% both groups Most frequently reported AEs: viral upper respiratory tract infection, upper respiratory tract infection, and headache. Infection occurred in 29% RIS and 24% ADA, serious infection <1% in both groups. N=1 death RIS group, n=2 deaths ADA group, all considered unrelated to study drug.	Reich et al. Lancet. 2019;394:576-86

[3] Note: CSRs for IMMvent, UltIMMa 1 and 2, and IMMhance are available upon request.

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
UltIMMa-1 and UltIMMa-2	Phase 3, randomised, double-blind, placebo-controlled and active comparator-controlled trials (3:1:1)	Adults aged ≥18 years, with stable (≥6 months) moderate-to-severe CPP, with body surface area involvement 10% or greater, PASI ≥12, and sPGA score ≥3. Patients were candidates for systemic therapy or phototherapy and eligible UST. Mean PASI: 20. Mean body surface area involvement: 26%. Previous systemic therapy reported in 67-70% of patients.	*UltIMMa-1:* n=506 RIS, n=304 UST, n=100 PCB, n=102 *UltIMMa-2:* n=491 RIS, n=294 UST, n=99 PCB, n=98	• RIS 150 mg SC at week 0, week 4, and q12w thereafter • UST 45 mg SC or 90 mg SC based on screening weight at weeks 0 and 4, then q12w thereafter • PBO SC at Weeks 0 and 4, then RIS 150 mg SC at weeks 16, 28, and 40.	52 weeks. 16-week randomised treatment.	Previous biologic therapy: • *UltIMMa-1:* 34% RIS, 30% UST, 39% PCB • *UltIMMa-2:* 40% RIS, 43% UST, 43% PCB Prior treatment exposure to ustekinumab or other IL-23 inhibitors was not permitted PASI 90 at Week 16: *UltIMMa-1:* • RIS difference from UST: 33.5% (95% CI: 22.7-44.3, p<0.0001) • RIS difference from PCB: 70.3% (95% CI: 64.0-76.7, p<0.0001) *UltIMMa-2:* • RIS difference from UST: 27.6% (95% CI, 16.7-38.5, p<0.0001) • RIS difference from PCB: 72.5-78.2, p<0.0001) sPGA of clear or almost clear (0 or 1) at Week 16: *UltIMMa-1:* • RIS difference from UST: 25.1% (95% CI: 15.2-35.0, p<0.0001) • RIS difference from PCB: 79.9% (95% CI: 73.5-86.3, p<0.0001) *UltIMMa-2:* • RIS difference from UST: 22.3% (95% CI: 12.0-32.5, p<0.0001) • RIS difference from PCB: 78.5% (95%CI: 72.4-84.5, p<0.0001)	Most frequently reported AEs were viral upper respiratory tract infection, upper respiratory tract infection, psoriasis, and diarrhoea. *UltIMMa-1* AEs occurred in 151 (49·7%) RIS, 52 (51·0%) PCB, and 50 (50·0%) on UST, and AEs in *UltIMMa-2* in 134 (45·6%) RIS, 45 (45·9%) PCB, and 53 (53·5%) UST. *UltIMMa-1* infection occurred in 75 (24·7%) RIS, 20 (20·0%) UST, and 17 (16·7%) PCB. And infections in *UltIMMa-2* in 56 (19·0%) RIS, 20 (20·2%) UST, and 9 (9·2%) PCB.	Gordon et al. Lancet. 2018;392:650-61

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
IMMhance	Phase III, randomised, double-blind, placebo-controlled, multi-centre	Adults with stable moderate to severe plaque psoriasis (BSA involvement ≥10%; PASI ≥12; sPGA ≥3) of ≥6 months duration; with or without PsA; who are candidates for systemic therapy or phototherapy	n=407 RIS n=100 PCB	*Part A1* •Risankizumab 150 mg SC at Weeks 0 and 4 (Arm 1) •Placebo SC at Weeks 0 and 4 (Arm 2) *Part A2* All patients received risankizumab 150 mg SC at Week 16 *Part B* For patients in Arm 1: sPGA clear or almost clear: re-randomised in a 1:2 ratio to DB risankizumab SC q12w or placebo SC q12w Did not meet sPGA response criteria: OL risankizumab 150 mg q12w For patients in Arm2: sPGA clear or almost clear: DB	Part A1: 16 weeks. Part A2: 12 weeks. Part B: 60 weeks	Any prior biologic therapy: • Part A1: 56.5% RIS vs 51.0% PCB • Part B: 51.4% RIS vs 55.6% PCB Prior TNF inhibitor: • Part A: 36.9% RIS vs 35.0% PCB • Part B: 33.3% RIS vs 33.3% PCB Prior IL-17 inhibitor exposure: • Part A: 26.0% RIS vs 26.0% PCB • Part B: 27.0 % RIS vs 24.9% PCB Prior IL-12/IL-23 inhibitor exposure: • Part A: 21.6% RIS vs 20.0% PCB • Part B: 16.2% RIS vs 21.3% PCB. *Co-primary endpoints* PASI 90 at Week 16 (Part A): • 298 patients (73.2%) RIS vs 2 patients (2.0%) PCB (adjusted risk difference: 70.8%; 95% CI 65.7%-76.0%; P <0.001). sPGA of clear or almost clear (0 or 1) at Week 16 (Part A): • 340 patients (83.5%) RIS vs 7 patients (7.0%) PCB (adjusted risk difference: 76.5%; 95% CI 70.4%-82.5%; P < 0.001) *Key secondary endpoints* sPGA score of clear or almost clear (0 or 1) at Week 52 (Part B): • 97 (87.4%) RIS/RIS vs 138 (61.3%) RIS/PCB (adjusted risk difference 25.9%; 95% CI 17.3% to 34.6%).	*Part A:* Any AE: 186 (45.7%) RIS vs 49 (49%) PCB Serious AEs: 8 (2.0%) RIS vs 8 (8.0%) PCB Severe AEs: 7 (1.7%) RIS vs 4 (4.0%) PCB AEs leading to drug discontinuation: 2 (0.5%) RIS vs 4 (4%) PCB *Part B:* Any AE: 91 (82.0%) RIS/RIS vs 155 (68.9%) RIS/PCB Serious AEs: 13 (11.7) RIS/RIS vs 17 (7.6%) RIS/PCB Severe AEs: 9 (8.1%) RIS/RIS vs 16 (7.1%) RIS-PCB AEs leading to drug discontinuation: 4 (3.6%) RIS/RIS vs 4 (1.8%) RIS/PCB	Blauvelt et al. JAMA Dermatol. 2020;156:649-658

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
				risankizumab 150 mg q12w Did not meet sPGA response criteria: OL risankizumab 150 mg q12w Patients who received blinded study drug in Part B and then had an sPGA ≥3 (relapse) from Week 32 onwards were switched to OL risankizumab		sPGA score of clear or almost clear (0 or 1) at Week 104 (Part B): • 90 (81.1%) RIS/RIS vs 16 (7.1%) RIS/PCB (adjusted risk difference: 73.9%; 95% CI 66.0% to 81.9%) PASI 75 at week 52 (Part B): • 103 (92.8%) RIS/RIS vs 161 (71.6%) RIS/PCB (adjusted risk difference: 21.2%; 95% CI 24.0% to 42.2%). PASI 90 at week 52 (Part B): • 95 (85.6%) RIS/RIS vs 118 (52.4%) RIS/PCB (adjusted risk difference: 33.1%; 95% CI 24.0% to 42.2%). PASI 100 at week 52 (Part B): • 71 (64.0%) RIS/RIS vs 68 (30.2%) RIS/PCB (adjusted risk difference: 33.7%; 95% CI 23.2% to 44.2%)		
IMMerge	Phase III, international, multicentre, randomized, open-label, efficacy-assessor-blinded, active-comparator study	Adults with stable moderate to severe plaque psoriasis (BSA involvement ≥10%; PASI ≥12; sPGA ≥3) of ≥6 months duration; with or without PsA; who are candidates for systemic therapy or phototherapy	RIS n=164 SEC n=163	RIS administered as two SC injections of 75 mg (150 mg total) at weeks 0 and 4, and every 12 weeks thereafter until the last dose at week 40. SEC administered as two SC injections of 150 mg (300 mg total) at weeks 0, 1, 2, 3 and 4, and every 4 weeks thereafter until the last dose at week 48.	48-week treatment, final efficacy assessment at week 52.	Any prior biologic therapy: 37.8% RIS vs 35.6% SEC • Previous IL-17 inhibitor: 7.9% RIS vs 7.4% SEC • Previous IL-23 inhibitor: 1.8% RIS vs 1.2% SEC • Previous TNF inhibitor: 23.2% RIS vs 23.3% SEC • IL-12/IL-23 inhibitor: 9.1% RIS vs 13.5% SEC *Primary endpoints* PASI 90 at week 16:	Any TEAEs: 71.3% RIS vs 71.2% SEC. Severe TEAE: 6.7% RIS vs 4.3% SEC TEAE leading to drug discontinuation: 1.2% RIS vs 4.9% SEC Malignant tumours (nonmelanoma skin cancer): 0.6% RIS vs 1.8% SEC	Warren et al. Br J Dermatol. 2020 (online ahead of print).

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
						• 121 (73.8%) RIS vs 107 (65.6%) SEC (adjusted between-group difference: 8.2%; 96.25% CI -2.2% to 16.8%). The endpoint of noninferiority of risankizumab to secukinumab at week 16 was met. PASI 90 at 52 weeks: • 142 (86.6%) RIS vs 93 (57.1%) SEC (adjusted difference: 29.8%; 95% CI 20.8% to 38.8%, P<0.001). The primary endpoint of superiority of risankizumab to secukinumab at week 52 was met. *Secondary endpoints* PASI 100 at 52 weeks: • 65.9% RIS vs 39.9% SEC (adjusted difference: 26.2%; 95% CI 15.9% to 36.5%, P<0.001. sPGA score of 0 or 1 at 52 weeks: • 87.8% RIS vs 58.3% SEC (adjusted difference 29.8%; 95% CI 20.9% to 38.8%, P<0.001). PASI 75 at 52 weeks: • 89.6% RIS vs 69.9% SEC (adjusted difference 20.0%; 95% CI 11.7% to 28.3%, P<0.001).		

ADA, adalimumab; AE, adverse event; BSA, body surface area; CPP, chronic plaque psoriasis; OL, open label; PASI, Psoriasis Area Severity Index; PCB, placebo; q12w, every 12 weeks; RIS, risankizumab; SEC, secukinumab; SC, sub-cutaneous; sPGA, static Physician's Global Assessment; TEAEs, treatment emergent adverse events; TNF, treatment necrosis factor; UST, ustekinumab

Literature Search

PHARMAC staff conducted a PubMed search (search terms: risankizumab AND plaque psoriasis) and identified one additional publication that was not identified by the supplier.

Strober et al. J Eur Acad Dermatol Venereol. 2020; online ahead of print: an integrated analysis of the phase III UltIMMa-1 and UltIMMa-2 studies investigating the efficacy of risankizumab in patients with moderate-to-severe plaque psoriasis by baseline demographics, disease characteristics and prior biologic therapy. Risankizumab demonstrated superior efficacy compared with ustekinumab regardless of patient subgroup (baseline demographics, disease characteristics or prior biologic exposure). Across all patient subgroups analysed, a significantly greater proportion of patients receiving risankizumab achieved PASI 90 responses at week 16 (70.3 to 82.2%) and week 52 (77.6 to 85.9%) compared with those receiving ustekinumab (34.6 to 55.6% and 30.8 to 56.3%, respectively, all $P < 0.01$).

2.2 Review of Clinical Evidence

Dermatology Subcommittee

The application and clinical evidence were first reviewed by the Dermatology subcommittee in November 2020[4]. The subcommittee gave a high priority recommendation for funding of risankizumab for both first- and second-line treatment.

The Subcommittee made these recommendations based on the high health need of these patients (particularly after failure of a previous biologic), the increased benefit and efficacy of risankizumab compared to currently funded treatments, and an appropriate suitability profile (less frequent dosing schedule) with the option for community use.

PTAC

PTAC subsequently reviewed the application in May 2021[5] and provided a medium-priority recommendation for first-line treatment and a high-priority recommendation for second-line treatment.

In making these recommendations, the Committee noted the high health need of patients with chronic plaque psoriasis and their whanau, the superior efficacy of Risankizumab compared to currently funded treatments, and also took into account the lack of long-term follow-up data meaning there is little or no information pertaining to development of antibodies to risankizumab, the durability of clinical effect, the lack of long-term safety data, and the lack of an appropriate treatment algorithm upon drug failure.

The Committee considered that the evidence for risankizumab for the treatment of moderate to severe chronic plaque psoriasis to be of high strength and quality. The Committee also considered that the evidence suggests that risankizumab has similar or higher efficacy to other biologic treatments, is substantially better at achieving a PASI90 score than

[4] Dermatology Subcommittee record November 2020 (A244228)
[5] PTAC meeting record May 2021

adalimumab and is incrementally superior to secukinumab in achieving a PASI90, especially when compared directly in the several head-to-head RCTs noted earlier.

The Committee noted that there are limited data on the long-term effectiveness of risankizumab, and that it is unclear if prior treatment with risankizumab would influence the efficacy of biologics in a later line of treatment if risankizumab should fail. The Committee considered that if risankizumab were to be funded, it may be more beneficial as a second line treatment as there is proven efficacy of risankizumab following other biologics, but limited evidence for the inverse scenario. The Committee considered that it would be clinically useful to have a biologic with a different mechanism of action to the currently funded treatment options, so that clinicians have a broader range of treatment options.

3. Supplier and International Cost-Utility Analyses

3.1 Cost-Utility Analysis in Application

The supplier application included a cost-utility analysis, the key results of which are:

- An incremental treatment cost of s9(2)(b) and an incremental Quality-Adjusted Life Year (QALY) gain of 0.52, resulting in an Incremental Cost Effectiveness Ratio (ICER) of s9(2)(b) per QALY gained
- In terms of QALYs gained per $m spent; the supplier estimates the listing of risankizumab would result in s9(2)(b)(ii); s9(2) QALYs per additional $1 million health care expenditure. However, this value is not consistent with the reported ICER of s9(2)(b) (which would be consistent with s9(QALYs per $m spent).

The supplier's univariate sensitivity analysis showed that the model was most sensitive to the costs of best supportive care and the utility values attributed to PASI response categories:

- Changing the costs of care by ± 50% resulted in an ICER range of s9(2)(b)(ii)); s9(2)(ba)(i));
- Using an alternative set of utility values from analyses from the National Institute for Care Excellence (NICE) and the University of York resulted in an ICER range of s9(2)(b) (York values) to s9(2)(b)(ii)); (NICE values).
- These results would imply a very wide range of QALYs per $m estimates, from s9(2) (Costs of care - 50%) to s9(2) (York utility values).

Pharmac staff have reviewed the CUA and provided a summary of the model in Table 5 below.

Table 5: Review of Supplier CUA Model

Model Input/ Assumption	Details	Pharmac Comment
Type of analysis	Cost-utility analysis using Markov model structure	A cost-utility analysis using a Markov structure was considered by PHARMAC staff to be appropriate.
Target population	The model considered adults (age 18 years or older) with moderate-to-severe plaque psoriasis who are candidates for systemic therapy i.e. patients for whom conventional	The target population considered appears to be a reasonable representation of the population who would be eligible to receive the

Model Input/ Assumption	Details	Pharmac Comment
	systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.	proposed treatment in New Zealand.
Treatment regimen (including dose)	The model consists of four distinct treatment states: Primary response period, subsequent maintenance period, best supportive care and death. Each primary response period is modelled as up to four 4-week tunnel states. If a PASI 75 response is observed, the patient moves to the maintenance period and continue to receive the same treatment. Those who do not achieve the minimum level of response transition to BSC. Patients stay in the maintenance state until discontinuation. Upon discontinuation, they are assumed to revert to their baseline PASI score and transition to BSC. The absorbing state in the model is death with patients transitioning to death from any of the other states, based on all-cause mortality risk, derived from the NZ life-tables 2016. The dosage of risankizumab was 150mg at weeks 0 and 4 then every 12 weeks in the maintenance period, while Adalimumab was 80mg at week 0, then 40mg EOW starting week 1	The treatment regimen and dosage appears appropriate.
Comparator	The model used adalimumab as the comparator for first-line treatment and best supportive care as the comparator in second-line treatment. Etanercept and infliximab were included as alternative first-line comparators in sensitivity analysis. Secukinumab is not included as a sensitivity since pricing information was not available at the time the application was submitted.	Adalimumab is an appropriate comparator. However, ~57% of the biologic market in NZ is made up of biologics other than adalimumab, so a combination of these treatments would be a more accurate comparator.
Efficacy	The evidence for relative clinical effect is based on the direct head-to-head trial, IMMvent as well as a network meta-analysis of the four phase 3 clinical trials of risankizumab (IMMvent, UltIMMa-1. UltIMMa-2 and IMMhance). Results are reported for both sets of efficacy values.	The efficacy values used seem appropriate. PTAC considered that the evidence for risankizumab for the treatment of moderate to severe CPP to be of high strength and quality. The four phase 3 trials (and IMMerge) formed the core of this evidence base.
Time horizon and cycle length	The model has a lifetime time horizon and a 4-week cycle length, with no half-cycle correction. The lifetime horizon was used to capture all relevant costs and benefits associated with	The lifetime time horizon is appropriate given the long-term nature of the condition The cycle length of 4-weeks also seems appropriate given the short response times, however a half-

Model Input/ Assumption	Details	Pharmac Comment
	treatment with risankizumab, adalimumab and BSC. A 4-week cycle length was deemed sufficiently short to capture varying response periods for different treatments. No half-cycle correction was applied as it was considered unlikely to have a large impact on results.	cycle correction would have been beneficial
Health states and model structure	The model uses a Markov structure, following patients across mutually-exclusive treatment states (response period, maintenance period, BSC and death). The health states included in the model are based on PASI response scores (PASI <50, PASI 50-74, PASI 75-89, PASI 90-99, PASI 100).	The Markov structure is appropriate and the health states based on PASI response rates are the standard efficacy measure for psoriasis response assessment in clinical practice
Key parameters and assumptions	All costs and benefits were discounted at 3.5%, with sensitivities of 0% and 5% included. The starting age of the cohort was 47.5, based on the pooled intention-to-treat population from the phase 3 trials of risankizumab No half-cycle correction was applied as it was considered unlikely to have a large impact on results	The discount rate of 3.5% applied to both costs and benefits is appropriate. Use of 0% and 5% discount rates as sensitivities is consistent with the PFPA. The starting age of the population seems sensible, and is similar to the average age of patients in the Australian Psoriasis Registry (51.6). A half-cycle correction should have been included, although with such a short cycle length this would have had no material impact on results.
Transformation and extrapolations	Efficacy data was transformed into QALYs based on utility values derived from the UltIMMa-1 and UltIMMa-2 trials: • Patients in the trials responded to EQ-5D-5L questionnaires at various stages throughout the trial • These values were then mapped onto the EQ-5D-3L dataset using the crosswalk developed by van Hout et al. (2012) • A regression model was then built to approximate the change in utility from baseline associated with each PASI response category • For a PASI response below 75, the change in utility was set to zero to reflect the discontinuation of treatment for these patients. Two other sets of utilities were included in sensitivity analysis. The supplier notes that the UK EQ-5D-3L utility values are considered appropriate for NZ based on the high and significant correlation between the UK and NZ value sets	This methodology seems appropriate given the available data and high correlation between UK and NZ utility value sets

Model Input/ Assumption	Details	Pharmac Comment
Health-Related Quality of life	Quality of life was measured by utility values associated with PASI response rates. As noted previously, these values were derived from the UltIMMa-1 and UltIMMa-2 trials via mapping of EQ-5D-5L values onto EQ-5D-3L values and regression analysis. The utility values used for each PASI response category represented the change in utility from baseline associated with that PASI response, rather than an absolute utility value. UK utility values were used to approximate NZ values	The estimation methodology seems appropriate, however the alternate values used in sensitivity analysis are significantly different to the base case values, which has a very large impact on model results. UK utility values are appropriate given the high correlation between UK and NZ utility value sets
Pharmaceutical cost	Pharmaceutical costs are calculated based on price per unit, units per dose, doses in each cycle and cycle length. The supplier notes that prices may need to be updated. The model does not include an assumption about a generic becoming available since the patent for risankizumab exceeds 10 years, and the supplier expects less than 5% of patients will still be receiving treatment once a generic does become available. The dosage used in cost calculations was based on the dosage from the key clinical trials and varies based on whether the patient is in a primary response or maintenance period. No wastage was accounted for in the model	Pharmaceutical costs were appropriately calculated. The exclusion of a generic after 25 years is unlikely to have a material impact on model results. The dose used in cost calculations is consistent with PTAC and Dermatology Subcommittee recommendations. The assumption of an average patient weight of 90kg seems reasonable given the association between psoriasis and obesity. As the treatment is an injection, it may have been appropriate to assume some amount of wastage.
Pharmacy costs	No pharmacy costs such as pharmacy handling, patient co-payments and pack fees were included	
Other relevant costs	Risankizumab and adalimumab are self-administered sub-cutaneous injections, while infliximab is an intravenous infusion delivered in an outpatient setting. The model assumes zero cost for self-administered injections and estimates $143 per outpatient intravenous injection based on the 2015 Cost resource manual. Best supportive care costs are the same for the treatment and comparator. BSC costs were derived from Fonia et al (2010), a retrospective cohort study in the UK that examined the impact of biologic treatment initiation on resource use among 76 patients with moderate-to-severe psoriasis, and then applied to the NZ context using the Pharmac cost resource manual 2015. The annual cost was then converted to a cost per 4-week cycle and applied to the period of time that patients remained in the BSC state. The annual cost per patient on BSC was $12,119. The costs of adverse events were also estimated. The probability of an adverse	Administration cost assumptions seem reasonable. Health system costs seem high due to the high number of inpatient admissions assumed for both patients on BSC and on biologic treatment, and it was unclear how the source of health system costs was identified. Adverse event assumptions seem reasonable.

Model Input/ Assumption	Details	Pharmac Comment
	event (events per patient year) for risankizumab was estimated using the average probability across the UltIMMa-1/2, IMMvent and IMMhance trials, while the rates for comparators were based on other studies and prescribing data. The costs of treatment for adverse events were based on WiesNZ unit costs 2018/19.	
Results	The key results reported were costs per QALY (ICERs) and QALYs per $m. The ICER is estimated to be s9(2)(b), and the additional QALYs per $m Is estimated to be s9(2. This appears to be an error, since an ICER of s9(2)(b) would imply s9(2 QALYs per $m.	The conversion of the ICER (s9(2)(b)) to a QALYs per $m figure is incorrect, resulting in Risankizumab appearing roughly half-as effective as the correct result would imply (s9(2 QALYs per $m instead of s9(2 QALYs per $m). Overall, the analysis appears replicable and generally sound.
Sensitivity analysis	Univariate sensitivity analysis has been conducted for the following model parameters: • Efficacy • Discontinuation rates • Utility values • Discounting • Monitoring costs • Best supportive care costs The sensitivity analysis shows that the model is highly sensitive to the BSC costs, and the set of utility values used. The ICER ranged from a minimum value of s9(2)(b) (using York model utility values) to a maximum of s9(2)(b) (50% lower BSC costs). Therefore, the QALYs per $m could be as high as s9(2) and as low as s9(2	The variables selected for sensitivity analysis appear reasonable. Results have been interpreted accurately and conclusions reached from the analysis are appropriate. The model is highly sensitive to several model parameters, resulting in a wide range of QALYs per $m estimates.
Analysis	The supplier notes that there is limited evidence on the long-term effectiveness of risankizumab. The supplier has therefore assumed an annual discontinuation rate to capture those who end treatment as the effectiveness wears off.	It is reasonable to vary the discontinuation rate to capture the uncertainty around the long-term effectiveness of the treatment. It would have been helpful to provide sensitivity analysis on this variable given that it is somewhat speculative.

Pharmac have built a separate CUA model to validate these results, test the robustness of supplier assumptions and to evaluate the cost-effectiveness of Risankizumab with the most accurate and up-to-date data in the NZ context.

4. PHARMAC Cost-Utility Analysis

A cost-utility analysis (CUA) was undertaken to estimate the cost-effectiveness of both first-line and second-line use of risankizumab for moderate-to-severe chronic plaque psoriasis.

4.1 Scope of Analysis

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

4.1.1 Target Population

The target population for this analysis was defined separately for first-line and second-line use:

- **First-line**: Patients with moderate-to-severe chronic plaque psoriasis intolerant, contraindicated or with inadequate benefit from prior systemic therapy
- **Second-line**: Patients with moderate-to-severe chronic plaque psoriasis intolerant, contraindicated or with inadequate benefit from prior systemic therapy and at least one other biologic therapy

The starting age of the cohort in the model was 47.5, based on the pooled intention-to-treat population from the phase 3 trials of Risankizumab. As noted previously, this age is close to the average age of patients in the Australian Psoriasis Registry (51.6).

4.1.2 Comparator & treatment sequence

The comparator treatments used in this analysis were other biologics listed for psoriasis in New Zealand: Adalimumab, secukinumab and etanercept. Infliximab was not included in the analysis due to the very small market share (4% in the year ending October 2021) it represents.

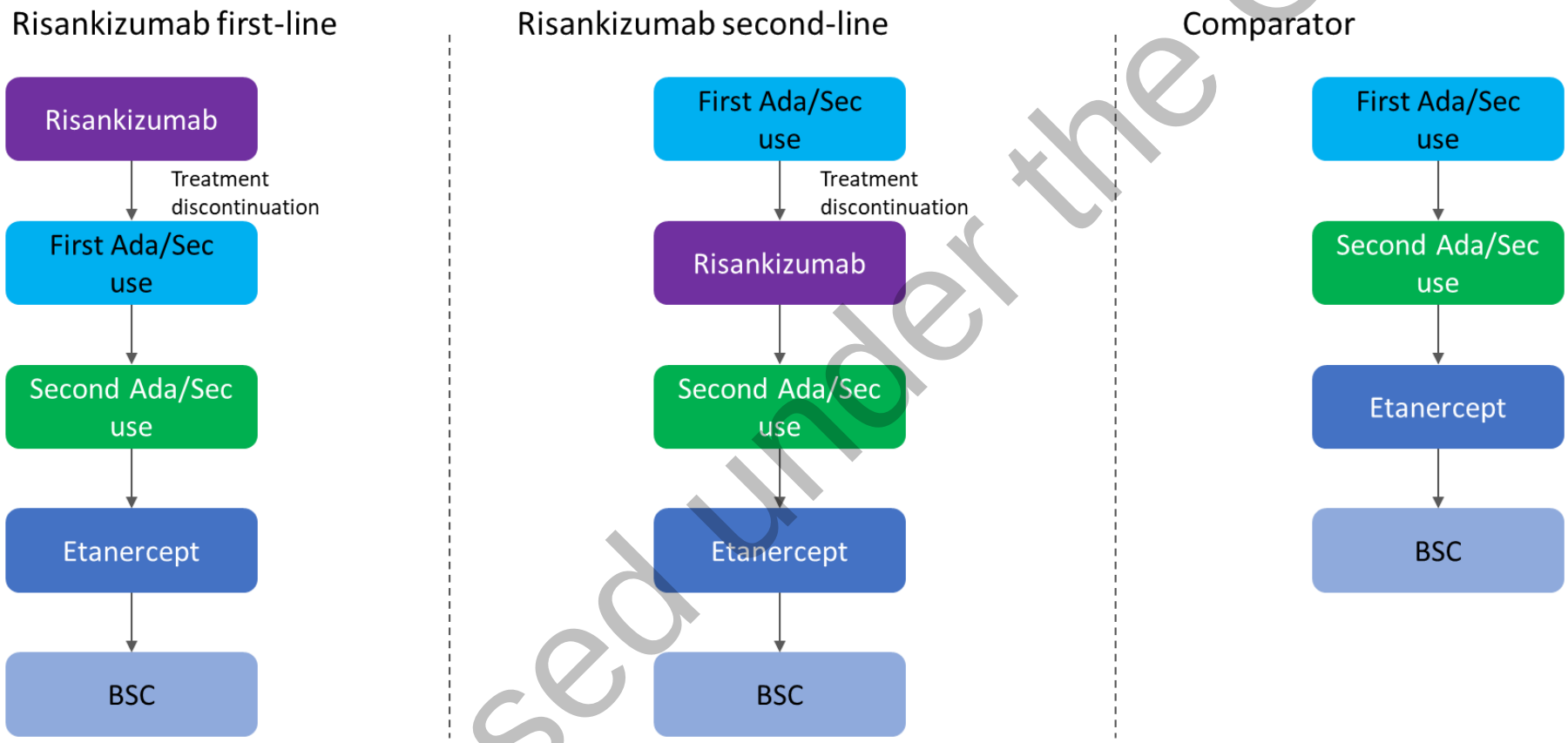
Due to the similar number of patients currently receiving adalimumab (43% of market share) and secukinumab (46%) treatment, it was deemed likely that the first-line treatment in the comparator arm (and in the Risankizumab second-line intervention) would be adalimumab for approximately half of patients, and secukinumab for the other half. To account for this in the model, an average of the two (using a 50:50 weighting of costs, treatment efficacies and discontinuation rates) was estimated and applied in the model as the first two treatments patients receive other than Risankizumab.

Patients receive the 'average treatment' (referred to as 'first adalimumab/secukinumab use' and 'second adalimumab/secukinumab use') twice to reflect half of the patients receiving adalimumab first then, upon treatment failure, secukinumab – while the other half receive secukinumab first then adalimumab. The treatment sequence for the comparator and for both first- and second-line interventions is illustrated in Figure 2 below.

In both the intervention and comparator arms of the analysis, patients proceed to best supportive care upon treatment failure. It is assumed that only 50% of patients try etanercept before proceeding to BSC, while the other 50% proceed directly to BSC after the failure of

both adalimumab and secukinumab. This assumption was informed by the low market share etanercept represents (7%) and discussion at the hot topic presentation that indicated some patients preferred not to take etanercept after other biologic treatments had failed.

Figure 2: Treatment paradigm*



* It is assumed that only 50% of patients take etanercept since it is unlikely to be effective following the failure of at least two previous biologic treatments – the rest proceed directly to BSC. This proportion is varied in sensitivity analysis (see section 4.7), and the model proved insensitive to this proportion. .

4.2 Model Structure

A Markov model structure was deemed the appropriate type of model for the CUA to reflect patients moving through treatment cycles at regular intervals.

4.2.1 Time Horizon

The CUA used a lifetime time-horizon to reflect the long-term nature of psoriasis and the potentially long treatment duration. Each Markov cycle was six months, which is long enough to capture treatment effect but short enough to reflect discontinuation of patients for whom treatment loses effect. A half-cycle correction was applied.

All costs and benefits were discounted at 3.5%.

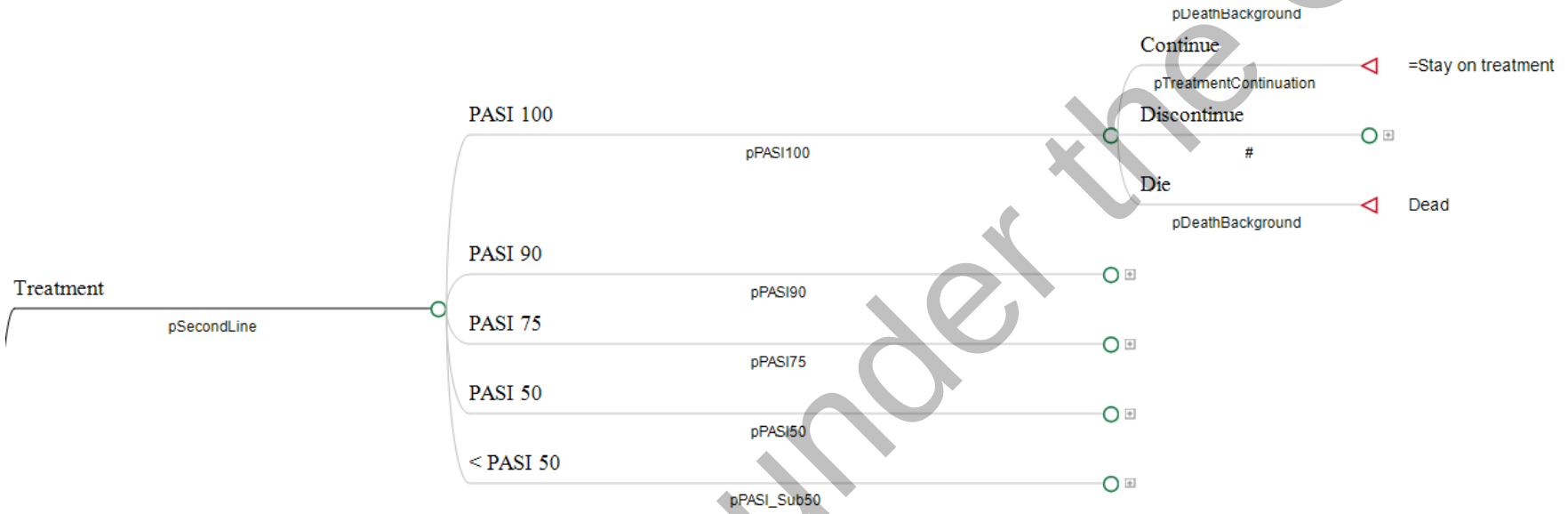
4.2.2 Model Structure

The model includes the following mutually exclusive health states:

- PASI 100: The patient achieves a 100% decrease in their initial PASI score i.e., complete remission of psoriasis
- PASI 90: Patient achieve a 90-99% reduction in their initial PASI score
- PASI 75: Patient achieves a 75-89% reduction in their initial PASI score
- PASI 50: Patient achieves a 50-74% reduction in their initial PASI score
- PASI < 50: Patients does not achieve a 50% reduction in their initial PASI score
- Dead: Patient has died from background mortality

Patients move to each of these health states based on transition probabilities (which differ by treatment type) detailed in the following section. A branch of the Markov model is presented in Figure 3 on the following page.

Figure 3: Cost-utility model structure



4.3 Transformation and Extrapolation of Clinical Evidence

The economic model uses data derived from phase 3 clinical trials as well as the network meta-analysis (NMA) provided by the supplier and research undertaken by Pharmac staff. Table 6 below summarises the source for each of the key clinical assumptions made in the model.

Table 6: Sources of clinical evidence

Model component	Source (s)
Treatment efficacy	• Phase 3 trials described in Table 4 (weighted average across trials used) • Supplier NMA
Adverse events	• Supplier assumptions (based on pooled data from phase 3 trials and other clinical studies
Background mortality	• Statistics New Zealand period life tables (2017-19) • Background mortality for the population with psoriasis estimated by multiplying the period life table values with the hazard ratio of all-cause mortality for patients with psoriasis (compared to the general population).
Long-term discontinuation	• Adalimumab for plaque psoriasis long-term dispensing data • Swedish cohort study on biologic persistence for psoriasis patients: Schmitt-Egenolf et al., 2021

4.3.1 Treatment Efficacy

In each model cycle, patients proceed to any of the health states other than death (e.g. PASI 100) based on treatment efficacy probabilities largely determined by the phase 3 clinical trials. In other words, the treatment efficacy probabilities are interpreted as transition probabilities. These probabilities are determined by which treatment the patient receives only – background mortality and long-term discontinuation are handled elsewhere in the model. Table 7 below displays the transition probabilities used in the model.

Table 7: Initial transition probabilities

PASI response	Risankizumab	First Ada/Sec use	Second Ada/Sec use	Etanercept	BSC
< 50	3.0%	11.65%	11.65%	s 9(2)(B)ii) and s 9(2)	85.4%
50	5.0%	17.50%	17.50%	s 9(2)(B)ii) and s 9(2)	9.3%
75	8.5%	18.60%	18.60%	s 9(2)(B)ii) and s 9(2)	4.1%
90	22.4%	20.80%	20.80%	s 9(2)(B)ii)	1.1%
100	61.1%	31.45%	31.45%	s 9(2)(B)ii)	0.1%

These probabilities are derived predominantly from the phase 3 trials, using a weighted average from patient response rates at week 52. In cases where there were data gaps, the supplier NMA was used e.g. for etanercept. However, the supplier NMA was not preferred since it reflected treatment efficacy at 12 weeks.

Patients who achieved a PASI 75 response or greater continued on the same treatment, based on the special authority renewal criteria. For example, in the case of Risankizumab,

92% (8.5% + 22.4% + 61.1%) of patients remained on treatment after the first cycle. Patients who do not achieve this response (i.e., PASI 50 or < 50) move to the next treatment line (see Figure 2 for the sequence of treatments).

The patients who do achieve a PASI 75 response and remain on the same treatment are then assumed to stay on this treatment until discontinuation (detailed in the following subsection). In other words, after the first cycle on each treatment, the long-term discontinuation rate determines the proportion of patients who move to the next treatment. Therefore, patients who have a PASI 75 response or greater continue biologic treatment and maintain their initial level of PASI response in subsequent cycles, until treatment discontinuation

4.3.2 Long-term discontinuation & background mortality

The efficacy of biologic treatments for psoriasis tends to wane over time. To reflect this, a long-term discontinuation rate has been included in the model. After patients move to the health states based on the transition probabilities described in section 4.3.1, there are three different possibilities as to where they start the next treatment cycle:

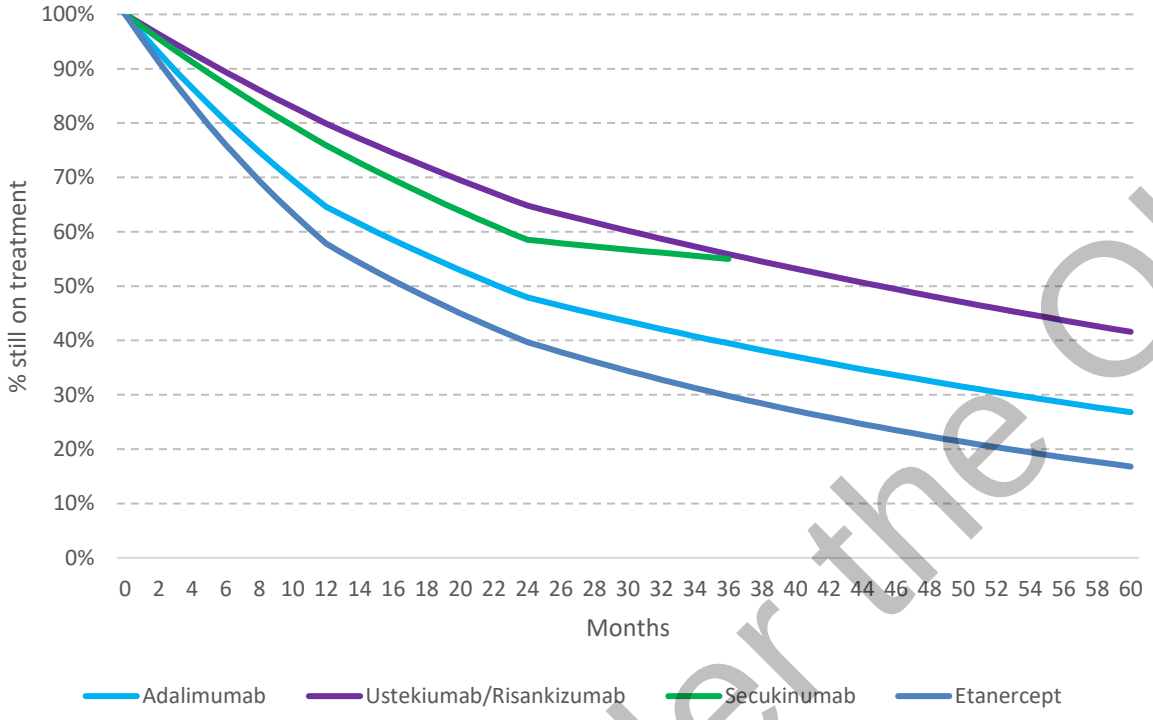
- Patients continue treatment – based on long-term discontinuation data (detailed below)
- Patients discontinue treatment - based on long-term discontinuation data (detailed below) and proceed to the next treatment-line
- Patients die from background mortality and move into the 'Dead' health state

Discontinuation rates

Discontinuation rates were sourced from two places. First, long-term adalimumab dispensing data for plaque psoriasis (i.e., not for any other indications) in New Zealand was used to construct a survival curve for adalimumab. Second, a cohort study on biologic persistence for psoriasis patients in Sweden (Schmitt-Egenolf et al., 2021) was used to assess the relative persistence of other biologics compared to adalimumab. This study provided discontinuation data for adalimumab, secukinumab, etanercept, ustekinumab and ixekizumab.

There is no long-term discontinuation data for Risankizumab since it is a new agent. To approximate Risankizumab discontinuation, ustekinumab was used based on it having a similar mechanism of action to Risankizumab. The survival curves of each biologic (based on Schmitt-Egenolf et al. only) are presented in Figure 4 below. Note that these are not directly used in the CUA, and are presented to give a sense of the relativities between discontinuation rates of different biologics only.

Figure 4: Biologic survival curves



The adalimumab dispensing data was considered to be the most applicable data source since it is directly relevant to the NZ context. Therefore, the adalimumab dispensing data was used to inform the discontinuation rate for adalimumab, while for the other three biologics, the adalimumab dispensing data was used as a baseline and was then adjusted based on the survival curves (and relative risk of discontinuation vs adalimumab) from Schmitt-Egenolf et al.

These adjusted survival curves were then used to estimate the probability of a patient still being on treatment between years 1 and 2 and years 2-5. The probability of discontinuation from years 2-5 was then converted into an annual probability. The rates used at different cycles on each treatment are presented in Table 8 below. The discontinuation rate for the first two cycles is zero for all treatments since the transition probabilities for the first 12 months on treatment are reflected in the treatment efficacy calculations.

Table 8: Annual discontinuation rates by treatment

Cycles on treatment	Risankizumab	First Ada/Sec use	Second Ada/Sec use	Etanercept
First 2 cycles	0%	0%	0%	0%
Cycles 3-4	9.5%	12.3%	12.3%	20.5%
Cycles 5+	6.3%	8.1%*	8.1%*	12.1%

*There was no discontinuation data for secukinumab past year 3, so the pure adalimumab rate was used

Finally, these probabilities presented above were converted into six-monthly probabilities to align with the model cycle length via the probtoprob function in TreeAge.

Background mortality

Patients with moderate to severe plaque psoriasis have an increased risk of mortality compared to the general population. Background mortality at each age was estimated using the Statistics New Zealand period life tables (2017-19), which estimate the probability of death for an individual in each year of life, provided they have already lived to that age. These probabilities were then adjusted for the population with psoriasis by multiplying the period life table values with the hazard ratio of all-cause mortality for patients with psoriasis (compared to the general population).

A hazard ratio of 1.36 was used, representing an average of four hazard ratio values found across three separate studies. The hazard ratio values used, and their sources are detailed in Table 9 below.

Table 9: Hazard ratios used to estimate background mortality for psoriasis patients

Study	Description	Value
Dhana et al., 2019	All cause mortality for psoriasis	1.21
Dhana et al., 2019	All cause mortality for severe psoriasis	1.52
Gelfand et al., 2007	Severe psoriasis	1.5
Springate et al., 2016	All cause mortality for psoriasis	1.21
-	**Average value**	**1.36**

4.4 Health-Related Quality of Life

Utility values representing the quality of life for the patient were assigned to each health state in the model. A utility value of 1 would represent full health for the patient, while 0 would represent no quality-of-life at all, a value most often used in cost-utility analysis to represent patients in the 'Dead' health state. The utilities used for each health state in the model are presented in Table 10 below.

Table 10. Utility Values

Health State	Utility	Source
Dead	0.0	N/A
PASI < 50	0.7510	Hendrix et al., 2018 (CUA that used trial data and regression mapping to estimate utilities)
PASI 50	0.8350	Hendrix et al., 2018
PASI 75	[redacted]	Hendrix et al., 2018 value for PASI < 50 plus the incremental utility of a PASI 75 response from supplier model. This estimate was derived from the UltIMMa 1/2 trials via mapping of EQ-5D-5L values onto EQ-5D-3L values and regression analysis.
PASI 90	[redacted]	Hendrix et al., 2018 value for PASI < 50 plus the incremental utility of a PASI 90 response from supplier model.
PASI 100	[redacted]	Hendrix et al., 2018 value for PASI < 50 plus the incremental utility of a PASI 100 response from supplier model.

Note that it was not possible to use NZ-specific utility values derived from the EQ-5D New Zealand Tariff 2, since the average sets of responses to EQ-5D questionnaire were not reported in the trials. The use of overseas health-related quality of life values is not expected to produce utility values inappropriate for the NZ context due to the high degree of overlap between the NZ EQ-5D tariff and international EQ-5D values.

The incremental utilities from the supplier analysis were deemed preferable to use as they were derived from clinical trial data. These values aligned closely with the rest of the utility values (PASI 75-100) in Hendrix et al., 2018, as well as additional analyses/studies sourced by Pharmac staff: Igarashi et al., 2018, Johansson et al., 2018 and Woolacott et al., 2016 (NICE). An alternate utility value for a PASI 100 response is included in the sensitivity analysis (see section 4.7) because it seemed plausible that the very small difference in utility between PASI 90 and PASI 100 was due to the supplier's linear regression model not being well fitted to values at the high end of the spectrum.

The utility values used in the supplier sensitivity analysis were not tested, since they were deemed inappropriate in this context:

- The values used in the Brodalumab NICE appraisal were for a more severe patient group (DLQI >10, which corresponds to a "very large to extremely large effect on patient's life"), so they are likely to overestimate utility gains for this patient group i.e. those with moderate-to-severe psoriasis. If these incremental utilities were added to the baseline, values for some PASI responses would be above 1.
- The values from Woolacott et al., 2016 (NICE) used in the supplier sensitivity analysis were for those patients with the most severe baseline quality of life (highest quartile in terms of DLQI score). Therefore, the incremental utilities used also likely to be overestimates and would also result in utilities above 1 for some PASI responses.

In each cycle of the model, utility is accrued based on the proportion of patients in each health state and the utility value assigned to that health state. Since cycles are six-monthly, and utilities are designed to produce quality-adjusted life years, this utility value needs to be divided by two to represent the utility accrued in a cycle. For instance, if 50% of patients in the model achieved a PASI 100 response, the utility accrued in that health state and cycle would be 0.2292 ([50% * 0.9170] / 2).

4.5 Costs

4.5.1 Pharmaceutical Cost

Pharmaceutical costs per cycle for each biologic treatment in the model are based on confidential net prices (the list price minus the confidential rebate paid by the pharmaceutical company to Pharmac) and standard dosage. Costs of treatment on BSC are not included in this section, they are detailed in section 4.5.3.

Table 11 below outlines the dose regimen for each biologic as per their respective Medsafe datasheets (which were consistent with the phase 3 clinical trials).

Table 11: Pharmaceutical dose

Biologic (dose)	Dose frequency	Number of doses: first six-monthly cycle	Number of doses: subsequent six-monthly cycles
Risankizumab (150mg)	150mg at weeks 0, 4 and every 12 weeks thereafter	3.83	2.17
Adalimumab (40mg)	80mg at week 0, 40mg every other week thereafter	14.0	13.0
Secukinumab (300mg)	300mg at weeks 0, 1, 2, 3 & 4, then once per month thereafter	10.0	6.0
Etanercept (50mg)	50mg twice per week for first 12 weeks, then oncer per week thereafter	38.0	26.0

The dosing information in the above table has been used to estimate the pharmaceutical cost of treatment on each biologic. Costs have been estimated for the first cycle (when the dose is more frequent) and subsequent cycles by multiplying the net price per dose with the number of doses in each cycle.

The net price of each biologic is assumed to remain the same over time – there is no assumption around the uptake of generics and the corresponding price reductions. It is noted that the PFPA guidance recommends including the uptake of a generic in sensitivity analysis. However, given uncertainties around the development of biosimilars, as well as timing, no generic uptake is included in the model.

As in other parts of the model, the first- and second-use of adalimumab/secukinumab is estimated by applying a 50:50 weighting to the pharmaceutical cost of adalimumab and secukinumab, respectively. The net prices and costs per cycle for pharmaceuticals are displayed in Table 12 below.

Table 12: Pharmaceutical costs

Biologic	Net price per dose	Pharmaceutical cost: first cycle	Pharmaceutical cost: subsequent cycles
Risankizumab	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
Adalimumab	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
Secukinumab	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
Etanercept	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
First use of adalimumab/ secukinumab	-	s9(2)(b)(ii); s9(2)(ba)(i);	s9(2)(b)(ii); s9(2)(ba)(i);
Second use of adalimumab/ secukinumab	-	s9(2)(b)(ii); s9(2)(ba)(i);	s9(2)(b)(ii); s9(2)(ba)(i);

4.5.2 Pharmacy margin

The costs to pharmacies of procurement and stockholding each biologic were assumed to be 4% of pharmaceutical cost estimated above, with the one difference being the list price being used rather than the net price. The pharmacy margin costs and the list price used to estimate them are shown in Table 13 below.

Table 13: Pharmacy margin costs

Biologic	List price per dose	Pharmacy margin: first cycle	Pharmacy margin: subsequent cycles
Risankizumab	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
Adalimumab	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
Secukinumab	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
Etanercept	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
First use of adalimumab/ secukinumab	-	s9(2)(b)(ii); s9(2)(ba)(i);	s9(2)(b)(ii); s9(2)(ba)(i);
Second use of adalimumab/ secukinumab	-	s9(2)(b)(ii); s9(2)(ba)(i);	s9(2)(b)(ii); s9(2)

4.5.3 Health Sector Costs

Additional costs to the health sector are made up of two components:

- System costs (admissions etc.)
- Other pharmaceutical costs associated with treatment.

These costs were based on the supplier analysis. Significant changes were made to the utilisation of inpatient services and the cost of other (non-biologic) pharmaceuticals; changes were also made to the costs of these items. The annual health sector utilisation and costs for patients on BSC and biologic treatment used in the Pharmac model are summarised in Table 14 below; note that the resulting per cycle health sector costs for a patient on BSC were 3.6 times higher in the supplier model than in the base-case Pharmac model.

Table 14. Annual health sector utilisation & costs per patient

Event	Best Supportive Care			Biologic treatment			Sources
	Annual number of units per patient	Cost per unit	Cost per patient	Annual number of units per patient	Cost per unit	Cost per patient	
System costs							
Inpatient days	1.104	$1,200	$1,324.76	0.264	$1,200	$316.39	Utilisation estimated from ICD discharge data* Cost estimate from the 2018 cost spreadsheet for CUAs (average inpatient medical ward cost)
ED admissions	0.026	$370	$9.62	0.04	$370	$14.80	Utilisation from Fonia et al., 2010 Cost estimate from the 2018 cost spreadsheet for CUAs (emergency room visit)
Outpatient admissions	3.22	$350	$1,127.00	3.25	$350	$1,137.50	Fonia et al., 2010 2018 cost spreadsheet for CUAs (initial consultation with physician)
Phototherapy treatment	2.72	$155.46	$422.85	0.26	$155.46	$40.42	Fonia et al., 2010 2018 cost spreadsheet for CUAs (dermatology UV treatment)
Total system costs	**-**	**-**	**$2,884.23**	**-**	**-**	**$1,509.11**	**-**
Pharmaceutical costs							
Acitretin	2,025mg	$0.0300	$60.75	253mg	$0.0300	$7.58	Fonia et al., 2010 NZ Pharmaceutical Schedule
Ciclosporin	31,445mg	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)(ba)(i);	10,625mg	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)(ba)(i);	Fonia et al., 2010 Ciclosporin confidential agreement
Methotrexate	310mg	$0.0420	$13.02	238mg	$0.0420	$10.00	Fonia et al., 2010 NZ Pharmaceutical Schedule
Total pharmaceutical costs	**-**	**-**	s9(2)(b)(ii);	**-**	**-**	s9(2)(b)(ii);	**-**
Total costs per patient	**-**	**-**	s9(2)(b)(ii); s9(2)(ba)	**-**	**-**	s9(2)(b)(ii); s9(2)(ba)(i);	**-**

*Number of patients aged 20+ discharged with a primary diagnosis of psoriasis in FY2018 (2,897) divided by the estimated number of people with severe psoriasis in New Zealand (2,624)

These annual costs per patient translate to costs per cycle of:

- s9(2)(b)(ii)); for patients on BSC
- s9(2)(b) for patients on biologic treatment

Two assumptions made the supplier health sector costs estimates much higher than in the Pharmac analysis:

- The supplier assumed patients on BSC required 6.49 inpatient days per annum based on the Fonia et al., 2010 study. This assumption was considered to be unreasonably high, given the comparatively small number of ICD discharges under a primary diagnosis of psoriasis. Therefore, Pharmac staff considered it was appropriate to estimate hospitalisations based on the number of discharges as this would be more relevant to the NZ context.
    - In the base case of the Pharmac model, the number of inpatient days for patients on biologic treatment was estimated using the number of inpatient days for patients on BSC as estimated using ICD discharge data (1.104) and the relativity between inpatient days for patients on BSC (6.49) and those on biologic treatment (1.55) in the supplier model (i.e. 1.104 * (1.55 / 6.49) = 0.264).
    - The supplier assumption was included in sensitivity analysis.
- The supplier assumed that patients also took 24,262 mg of dimethyl fumarate per annum, resulting in an annual cost of $3,610.40. This assumption has been omitted from the Pharmac model since dimethyl fumarate is not listed for psoriasis in New Zealand.

4.5.4 Adverse Event Costs

Costs associated with adverse events from treatment have been estimated using the rates of the three most common adverse events and the cost to the health system of an adverse event occurring. The adverse events considered in this analysis were non-melanoma skin cancer (NMSC), malignancies other than non-melanoma skin cancer and severe infections.

The rates and costs used are from the supplier model, which itself sourced these costs from the phase 3 trials (ULtIMMa-1/2, IMMvent, IMMhance), amongst other sources. Pharmac did not undertake its own research (other than a brief assessment of the sources used in the supplier model) due to the magnitude of adverse event costs being very small relative to overall costs of treatment.

Note that no disutility from adverse events was assumed due to the short-term nature of these events. This assumption is consistent with the supplier analysis.

AE rates and costs for each biologic are presented in Table 15 below. There are no AE costs for patients on BSC since this will already be captured in higher rates of hospitalisation etc. There may be a small amount of double counting the costs of AEs for patients on biologic

treatment, since the system costs detailed in Table 14 are likely to be driven to some extent by adverse events.

Table 15: Adverse event rates and costs by biologic treatment

Biologic	Adverse events			Total costs
	Non-melanoma skin cancer (NMSC)	Malignancies other than NMSC	Severe infections	
Rate of AEs per patient year				
Risankizumab	0.00613	0.00545	0.01975	-
Adalimumab	0.00960	0.00980	0.05190	-
Secukinumab	0.00000	0.00200	0.01500	-
Etanercept	0.03540	0.00123	0.05130	-
Cost by type of AE				
Cost per AE	$1,206	$5,535	$5,672	-
Cost by AE per patient year for each biologic				
Risankizumab	$7	$30	$112	**$150**
Adalimumab	$12	$54	$294	**$360**
Secukinumab	$0	$11	$85	**$96**
Etanercept	$43	$7	$291	**$340**
First use of adalimumab/ secukinumab	$6	$33	$190	**$228**
Second use of adalimumab/ secukinumab	$6	$33	$190	**$228**

Finally, annual costs were converted into costs per cycle by dividing by two.

4.5.5 Costs in the model

In each cycle of the model, costs are accrued based on the proportion of patients on each treatment and the corresponding per cycle costs of that treatment. These costs are made up of four components: Pharmaceutical costs, pharmacy margin, health sector costs and adverse event costs.

For instance, for patients on Risankizumab, costs per cycle would be:

$$Cost\ per\ cycle = cPharmaceutical_{Ris} + cMargin_{Ris} + cSector_{Bio} + cAE_{Ris}$$

For patients on BSC, costs are only comprised entirely of health sector costs:

$$Cost\ per\ cycle = cSector_{BSC}$$

Total costs per cycle for each treatment are presented in Table 16 below.

Table 16: Total costs of treatment per cycle

Treatment	Total costs: First six-monthly cycle	Total costs: Subsequent six-monthly cycles
Risankizumab	s9(2)(b)(ii);	s9(2)(b)(ii); s9(2)
First use of adalimumab/ secukinumab (50:50 weighting)	s9(2)(b)(ii); s9(2)(ba)(i));	s9(2)(b)(ii)); s9(2)(ba)(i));
Second use of adalimumab/ secukinumab (50:50 weighting)	s9(2)(b)(ii)); s9(2)(ba)(i));	s9(2)(b)(ii)); s9(2)(ba)(i));
Etanercept	s9(2)(b)(ii));	s9(2)(b)(ii));
Best supportive care (BSC)		s9(2)(b)(ii));

4.6 Cost-Effectiveness Results

The discounted lifetime incremental cost of listing Risankizumab is estimated to be s9(2)(b)(ii)); if listed first-line and s9(2)(b) if listed second-line. The discounted lifetime incremental QALY gain of listing is estimated to be 0.65 for first-line and 0.63 for second-line. Therefore, the key base-case cost-utility results are as follows:

- ICER: s9(2)(b) first-line and s9(2)(b) second-line
- QALYs per $m: s9(2) first-line and s9(2) second-line

Second-line listing is more cost-effective since only patients who do not respond to the cheaper first-line treatment (adalimumab or secukinumab) proceed to Risankizumab – resulting in significantly lower costs and only slightly fewer QALYs gained. The core CUA results are summarised in Table 17 below.

Table 17. Cost-Effectiveness Summary results

	Risankizumab listed	Current treatment paradigm	Incremental QALYs/costs
First-line			
QALYs	s9(2)(b)	s9(2)(b)	0.65
Cost	s9(2)(b)		s9(2)(b)
QALYs per $m	-	-	s9(2)(b)
Second-line			
QALYs	s9(2)(b)	s9(2)(b)	0.63
Cost	s9(2)(b)		s9(2)(b)
QALYs per $m	-	-	s9(2)(b)

4.7 Sensitivity Analysis

In order to test the robustness of the model results and examine the extent to which the cost-effectiveness of risankizumab depends on specific assumptions, the following parameters were varied in sensitivity analysis:

- *Risankizumab pharmaceutical cost*: Net price of Risankizumab falls by 30% e.g. in negotiations with supplier
- *Inpatient admissions for patients on BSC and biologics*: Supplier assumptions used for both groups
- *Treatment efficacy*: Supplier NMA values used for all transition probabilities
- *Higher utility for PASI 100 response*: Difference between PASI 75 and PASI 90 utilities used as the difference between PASI 90 and PASI 100. This sensitivity was included to account for the possibility that the supplier regression line was not well suited to utilities closer to 1.
- *Long-term discontinuation rates for each biologic*: Rates from cohort study used without adjusting to NZ adalimumab dispensing data
- *Long-term discontinuation rates for risankizumab only*: Risankizumab discontinuation varied with higher and lower rates
- *Proportion of patients using adalimumab as first biologic*: The proportion of people using adalimumab as their first-line biologic other than risankizumab assumed to further decline relative to secukinumab. The values used in sensitivity analysis were 40% adalimumab, 60% secukinumab.
- *Proportion of patients taking etanercept before proceeding to BSC:* Varied with higher and lower rates.

The results of the sensitivity analysis are presented in Table 18 below.

Table 18. Sensitivity Analysis

Input	Base-Case Value	Alternate value(s)	Range QALYs per $m
First-line			
Base Case	-	-	s9(2)(b)(ii);
Risankizumab pharmaceutical cost price reduction	0%	-30%	s9(2)(b)(ii); s9(2)(ba)(i);
Inpatient admissions per annum: On biologics & BSC	0.26, 1.10	1.55, 6.49	s9(2)(b)(ii); s9(2)(ba)(i);
Treatment efficacy	Various	Various	s9(2)(b)(ii);
PASI 100 utility	[redacted]	[redacted]	s9(2)(b)(ii);
Long-term discontinuation rates (all)	Various	Various	s9(2)(b)(ii);
Long-term discontinuation rates (Risankizumab only)	Cycles 3-4: 9.5% Cycles 5+: 6.3%	Cycles 3-4: 6.3-9.5% Cycles 5+: 6.3-9.5%	s9(2)(b)(ii); s9(2)(ba)(i);
Proportion using adalimumab first	50%	40%	s9(2)(b)(ii);
Proportion taking etanercept	50%	25-75%	s9(2)(b)(ii);
Second-line			
Base Case	-	-	s9(2)(b)(ii);
Risankizumab pharmaceutical cost	0%	-30%	s9(2)(b)(ii);
Inpatient admissions per cycle: On biologics & BSC	0.26, 1.10	1.55, 6.49	s9(2)(b)(ii); s9(2)(ba)(i);
Treatment efficacy	Various	Various	s9(2)(b)(ii);
PASI 100 utility	0.9170	0.941	s9(2)(b)(ii);
Long-term discontinuation rates (all)	Various	Various	s9(2)(b)(ii);
Long-term discontinuation rates (Risankizumab only)	Cycles 3-4: 9.5% Cycles 5+: 6.3%	Cycles 3-4: 6.3-9.5% Cycles 5+: 6.3-9.5%	s9(2)(b)(ii); s9(2)(ba)(i);
Proportion using adalimumab first	50%	40%	s9(2)(b)(ii);
Proportion taking etanercept	50%	25-75%	s9(2)(b)(ii);

The sensitivity analysis shows that the model is relatively insensitive to most input parameters, with a few exceptions: the net price of Risankizumab, the number of inpatient admissions and, to a lesser extent, the choice of PASI 100 utility value and the long-term discontinuation rate of biologics.

4.8 Summary of Overall Cost-Effectiveness

As outlined above, the base-case QALY per $m estimate is s9(2) **for first-line listing** and s9(2) **for second-line listing**. Accounting for the results of the sensitivity analysis, the likely cost-effectiveness range is estimated to be s9(2)(b) **QALYs per $m for first-line** and s9(2)(b) **QALYs per $m for second-line listing.** This range captures all sensitivity ranges in Table 18, with the exception of the 30% drop in the net price of Risankizumab, which has been estimated for commercial purposes only, and should not be used for decision-making due to the significant uncertainty surrounding commercial negotiations.

5. Budget Impact Analysis

5.1 Summary of Budget Impact

The 5-year net present value (NPV) to the Pharmaceutical Schedule of funding Risankizumab first-line is estimated to be s9(2)(b)(ii); while the cost of funding Risankizumab second-line is estimated to be s9(2)(b)(ii); The cost of the first 12 months is estimated to be s9(2)(b) first-line and s9(2)(b) second-line.

Listing Risankizumab is estimated to result in a small saving to the wider health system of s9(2)(b) (first-line listing) to s9(2)(b)(ii); (second-line). All NPV calculations use a discount rate of 8%.

The cost of funding Risankizumab is s9(2)(b)(ii); s9(2)(ba)(i)); s9(2)(j)) s9(2)(b)(ii); s9(2)(ba)(i)); s9(2)(j)) s9(2)(b)(ii); s9(2)(ba)(i)); The small amount of savings to the health system are generated via the displacement of infliximab (which requires an infusion) and the reduced number of patients on BSC requiring inpatient admission.

5.2 Patient Numbers

Baseline patient numbers were estimated based on dispensing data for biologics funded for the treatment of plaque psoriasis. The breakdown of the existing market is shown in Table 19 below.

Table 19:, Current biologic market share, year ending October 2021[6]

Biologic	Market share	Patients on treatment
Adalimumab	42.8%	547
Secukinumab	46.0%	587
Etanercept	7.4%	94
Infliximab	3.8%	49
Total market	**100%**	**1,277**

Patient numbers were forecast based on multiple assumptions around market growth, uptake and displacement of currently used biologics. These assumptions are summarised in Table 20 below, and the resulting market share breakdowns for first- and second-line listing are provided in Figure 5 and Figure 6, respectively.

[6] Special Authority database

Table 20: Patient number assumptions

Assumption	Description	First-line	Second-line
Background growth in biologic market	Growth in the biologic market that occurs in the status quo scenario i.e., if Risankizumab is not funded. Estimated to be 12.5% per annum based on the average growth in patient numbers in FY2018 and FY2022 (to date)	Applied after the first three years following risankizumab listing (years 4 and 5 in the BIA model)	Applied after the first three years following risankizumab listing (years 4 and 5 in the BIA model)
Growth in market when a new biologic is introduced	Growth in the biologic market that occurs when a new biologic is listed i.e. if Risankizumab is funded. This growth rate is higher than the background rate since patients who have exhausted other biologic options have another treatment alternative.	23.6% p.a. based on the average growth in patient numbers FY2019-2021 (the 3 years following secukinumab listing).	As per first-line but adjusted down to 20% p.a. to account for the second-line requirement.
Uptake of risankizumab	The uptake of Risankizumab in terms of market share. This rate is based on a weighted average of the secukinumab uptake and an equal market share (i.e. split into thirds by adalimumab, risankizumab and secukinumab). More weight (75%) was given to the secukinumab uptake scenario since it was deemed to be more likely than the even split.	Rises to 46.9% market share by third year of listing	As per first-line but capped at 30% following clinical advice
Displacement of other biologics	Etanercept and infliximab are displaced first, based on advice received in the hot topic presentation on 3 November 2021. Patients are likely to switch off these two biologics because: • They are both clinically inferior to Risankizumab • Risankizumab represents a different mechanism of action to adalimumab, whereas etanercept does not • Infliximab is an infusion whereas Risankizumab is a subcutaneous injection	See Figure 5 for a breakdown of the estimated market share when Risankizumab is listed first-line	See Figure 6 for a breakdown of the estimated market share when Risankizumab is listed second-line

	The rest of the market share taken up by Risankizumab is split evenly from the adalimumab and secukinumab shares.		

Figure 5: Market share forecast with Risankizumab listed first-line

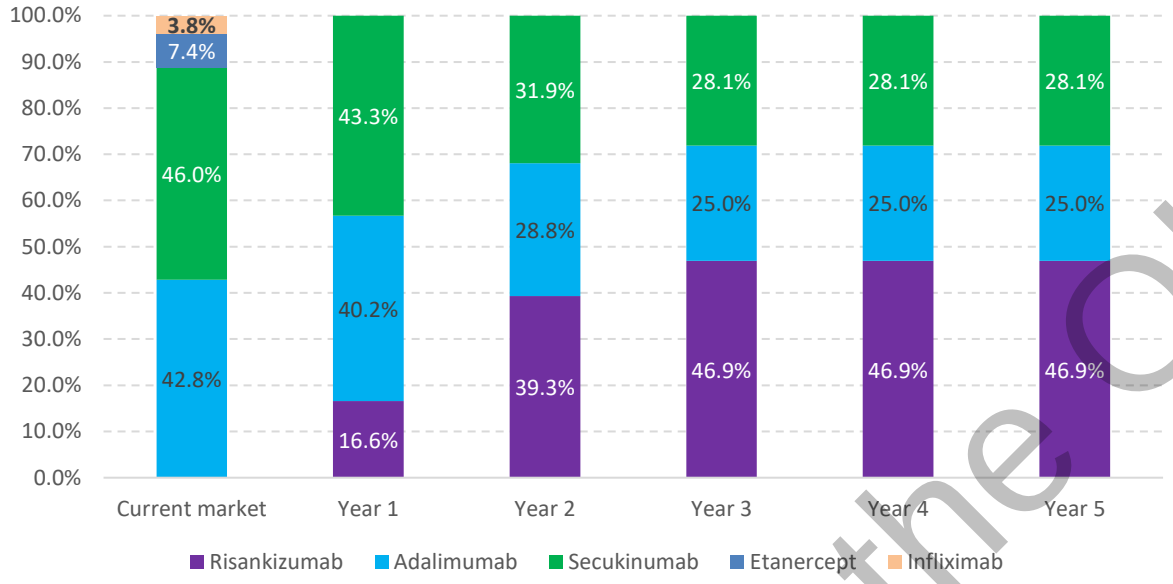
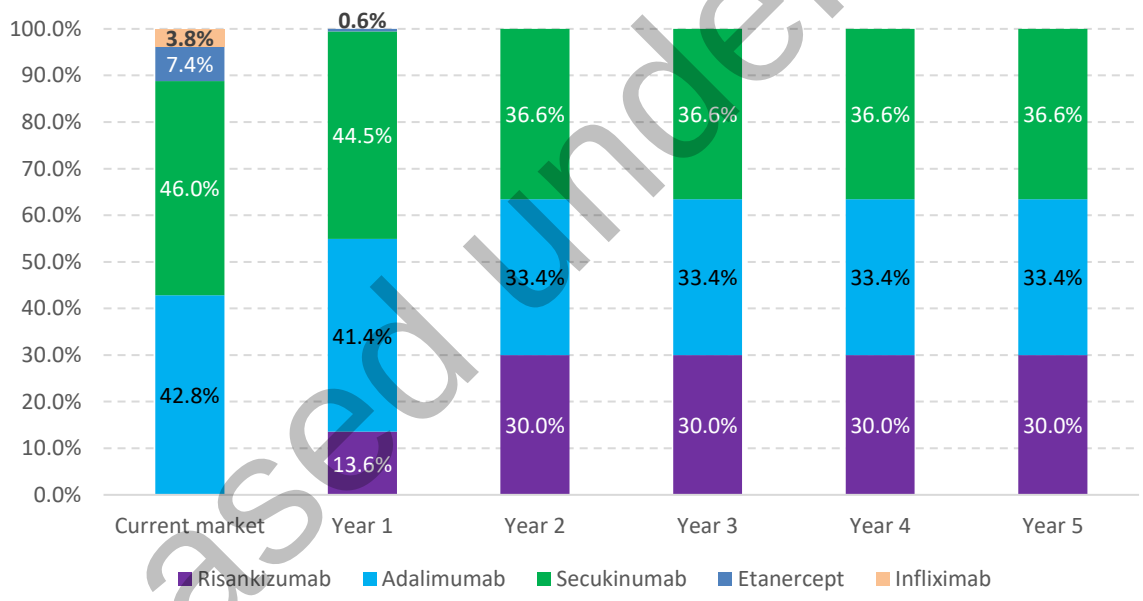


Figure 6: Market share forecast with Risankizumab listed second-line



The estimated patient numbers corresponding to the above growth and market share assumptions are presented in Table 21 below.

Table 21. Estimated Patient Numbers on each biologic treatment

Biologic	Year				
	1	2	3	4	5
First-line					
Risankizumab	261	767	1,132	1,274	1,433
Adalimumab	634	562	603	678	763
Secukinumab	683	623	678	763	859
Etanercept	-	-	-	-	-

Infliximab	-	-	-	-	-
Total patients	**1,579**	**1,952**	**2,413**	**2,715**	**3,055**
Second-line					
Risankizumab	208	552	662	745	838
Adalimumab	634	615	738	830	934
Secukinumab	682	672	807	908	1,022
Etanercept	9	-	-	-	-
Infliximab	-	-	-	-	-
Total patients	**1,532**	**1,839**	**2,207**	**2,483**	**2,794**

5.3 Net Budget Impact to Pharmaceutical Schedule

This section outlines the net impact to the combined pharmaceutical budget (CPB) over 5 years. The annual cost to the CPB was estimated based on:

- The number of patients on each treatment, including BSC. BSC patient numbers were based on the growth in the biologic market. The maximum number of patients on biologic treatment (across the 5 years with Risankizumab first-line listing) is assumed to be the number of people who are on either BSC or biologics. The number of people estimated to be on BSC is then this number less the number of patients currently on biologic treatment.
    - For instance, the maximum size of the biologic market is 3,055, in year 5 of first-line listing. In year 5 of second-line listing, the number of patients on biologic treatment is 2,794. Therefore, it is estimated that there would be 261 patients on BSC (3,055 – 2,794) in the 5th year of second-line listing.
- The per-patient pharmaceutical cost of each biologic (see section 4.5.1) – adjusted to be annual rather than per cycle. Note that costs are higher in the first year due to greater dosing frequency.
- The additional pharmaceutical costs per-patient associated with biologic and BSC treatment (see section 4.5.3)

The impact to the CPB is displayed in Table 22 below, which outlines the cost of listing Risankizumab, the costs if no change is made to the schedule (status quo) and the incremental cost of listing (listing Risankizumab minus status quo).

Table 22. Net Budget Impact to the Pharmaceutical Schedule ($m)

Item	Year					NPV
	1	2	3	4	5	
First-line						
Cost to CPB if Risankizumab listed	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	-
Cost of Status Quo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Incremental cost of listing	s9(2)(b)	s9(2)(b)	s9(2)(b)	s9(2)(b)	s9(2)(b)	s9(2)(b)
Second-line						
Cost to CPB if Risankizumab listed	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	-
Cost of Status Quo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Incremental cost of listing	s9(2)(b)	s9(2)	s9(2)(b)	s9(2)(b)	s9(2)(b)	s9(2)(b)

5.4 Net Budget Impact to DHBs

The net budget impact to the health sector has been estimated based on:

- The number of patients on each treatment, including BSC
- The annual cost per patient, made up of:
  - System costs (see section 4.5.3)
  - AE costs (see section 4.5.4)
  - Pharmacy margin (see section 4.5.5)

The cost to the wider health sector is summarised in Table 23 below.

Table 23. Net Budget Impact to wider health sector

Item	Year					NPV
	1	2	3	4	5	
First-line						
Cost to health sector if Risankizumab listed	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	-
Cost of Status Quo	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	-
Incremental cost to sector	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
Second-line						
Cost to CPB if Risankizumab listed	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	-
Cost of Status Quo	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	-
Incremental cost to sector	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);

The small amount of savings to the health system are generated via the displacement of infliximab (which requires an infusion) and the reduced number of patients on BSC. Second-line listing results in greater savings to the health sector because:

- Both listing options displace infliximab, which has much higher health sector costs than Risankizumab
- Second-line listing displaces fewer patients from adalimumab and secukinumab, which incur slightly lower health sector costs than Risankizumab.