5.04 CANAKINUMAB, Solution for injection 150 mg in 1 mL, Ilaris®, Novartis Pharmaceuticals Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required listing for canakinumab, for the treatment of paediatric colchicine-resistant or intolerant familial Mediterranean fever (FMF) patients who continue canakinumab treatment into adulthood (provided they initiated canakinumab treatment before turning 18 years of age).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC), comprised of colchicine at the maximum tolerated dose, symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs), and oral corticosteroids where necessary for protracted febrile myalgia.

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

Component	Description
Population	Paediatric patients with colchicine-resistant or intolerant FMF, continuing treatment into adulthood provided the first dose of canakinumab is received prior to turning 18 years of age.
Intervention	Canakinumab 150 mg or 300 mg subcutaneous injection every 4 or 8 weeks added to BSC.
Comparator	BSC, comprised of colchicine at the highest tolerated dose, and symptomatic treatment with non-steroidal anti-inflammatory drugs and oral corticosteroids.
Outcomes	Complete response, disease flares while on treatment, suppression of acute phase reactants (C-reactive protein and serum amyloid A), health related quality of life, safety.
Clinical claim	In paediatric patients with colchicine-resistant or intolerant FMF, canakinumab plus BSC is more effective than BSC alone, with inferior but tolerable safety.

Source: Table 1.1, p29 of the submission.
Abbreviations: BSC, best supportive care; FMF, familial Mediterranean fever

2 Background

Registration status

2.1 Canakinumab was registered by the TGA on 16 January 2025 for the treatment of various autoinflammatory periodic fever syndromes in adults, adolescents and children aged 2 years and older, including:

- Cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome/familial cold urticaria, Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease/chronic infantile neurological, cutaneous, articular syndrome.
- Tumour necrosis factor receptor associated periodic syndrome (TRAPS).

- Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD).
- Familial Mediterranean fever (FMF). Canakinumab should be given in combination with colchicine, if appropriate.

Previous PBAC consideration

2.2 The PBAC recommended canakinumab for the treatment of systemic juvenile idiopathic arthritis (sJIA) at the March 2015 PBAC meeting and for moderate to severe CAPS at the November 2017 PBAC meeting. However, the submission noted that neither recommendation proceeded to a PBS listing as the sponsor was unable to obtain internal pricing approval post recommendation.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
CANAKINUMAB					
Initial, grandfathered and continuing treatment					
Canakinumab 150 mg in 1 mL, solution for injection, 1	Public hospital: $20,000.00 published price $[redacted] effective price Private hospital: $20,048.88 published price $[redacted] effective price	1	1	5	Ilaris
Balance of supply for initial treatment					
Canakinumab 150 mg in 1 mL, solution for injection, 1	Public hospital: $20,000.00 published price [redacted] effective price Private hospital: $20,048.88 published price $[redacted] effective price	1	1	1	Ilaris

Requested restriction (initial treatment)
Category / Program: Section 100
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
Condition: Colchicine-resistant or intolerant familial mediterranean fever (crFMF)
Indication: Colchicine-resistant or intolerant familial mediterranean fever (crFMF)
Treatment Phase: Initial treatment
Clinical criteria:
Patient must have a documented diagnosis of FMF based on the Tel-Hashomer diagnostic criteria.
AND
Clinical criteria:
Patient must have at least one known MEFV gene exon 10 mutation, confirmed by genetic testing and documented in the patient's medical records.
AND
Clinical criteria:
Patient must have documented evidence of active disease defined as at least one febrile attack per month for at least three months despite maximally tolerated doses of colchicine treatment; OR
Patient must have documented evidence of chronic or recurrent disease activity supported by persistently elevated C-reactive protein or serum amyloid A during the attack-free period for at least three months despite maximally tolerated doses of colchicine treatment; OR
Patient must have a documented contraindication to colchicine therapy or side-effects necessitating discontinuation in addition to persistent clinical flares or subclinical inflammation for at least 3 months as described above.

Treatment criteria:
Must be treated by a medical practitioner who is at least one of: (a) rheumatologist, (b) clinical immunologist, (c) physician experienced in the management of FMF patients, (d) in consultation with one of these prescriber types.
The treatment must be in combination with colchicine unless contraindicated or the patient has documented evidence of having experienced an adverse event necessitating discontinuation.
Population criteria:
Patient must be at least 2 years of age, but yet to turn 18 years of age, at treatment initiation with this drug.
Administrative Advice: No increase in the maximum quantity or number of units above 2 may be authorised. Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Requested restriction (grandfathered patients)
Category / Program: Section 100
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
Condition: Colchicine-resistant or intolerant familial mediterranean fever (crFMF)
Indication: Colchicine-resistant or intolerant familial mediterranean fever (crFMF)
Treatment Phase: Grandfathered patients
Clinical criteria:
Patient must have a documented diagnosis of FMF based on the Tel-Hashomer diagnostic criteria.
AND
Clinical criteria:
Patient must have at least one known MEFV gene exon 10 mutation, confirmed by genetic testing and documented in the patient's medical records.
AND
Clinical criteria:
Patient must have had, prior to initiating non-PBS-subsidised treatment, documented evidence of active disease defined as at least one febrile attack per month for at least three months despite maximally tolerated doses of colchicine treatment; OR
Patient must have had, prior to initiating non-PBS-subsidised treatment, documented evidence of chronic or recurrent disease activity supported by persistently elevated C-reactive protein or serum amyloid A during the attack-free period for at least three months despite maximally tolerated doses of colchicine treatment; OR
Patient must have had, prior to initiating non-PBS-subsidised treatment, a documented contraindication to colchicine therapy or side-effects necessitating discontinuation in addition to persistent clinical flares or subclinical inflammation for at least 3 months as described above.
Treatment criteria:
Must be treated by a medical practitioner who is at least one of: (a) rheumatologist, (b) clinical immunologist, (c) physician experienced in the management of FMF patients, (d) in consultation with one of these prescriber types.
The treatment must be in combination with colchicine unless contraindicated or the patient has documented evidence of having experienced an adverse event necessitating discontinuation.
Population criteria:
Patient must be at least 2 years of age, but yet to turn 18 years of age, at treatment initiation with this drug.
Administrative Advice: No increase in the maximum quantity or number of units above 2 may be authorised. Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Requested restriction (Continuing treatment)
Category / Program: Section 100
Prescriber type: ☒Medical Practitioners

Restriction type: ☒Authority Required (STREAMLINED)
Condition: Colchicine-resistant or intolerant familial mediterranean fever (crFMF)
Indication: Colchicine-resistant or intolerant familial mediterranean fever (crFMF)
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
The treatment must have commenced between the ages of 2 to 17 years inclusive.
Treatment criteria:
Must be treated by a medical practitioner who is at least one of: (a) rheumatologist, (b) clinical immunologist, (c) physician experienced in the management of FMF patients, (d) in consultation with one of these prescriber types.
The treatment must be in combination with colchicine unless contraindicated or the patient has documented evidence of having experienced an adverse event necessitating discontinuation.
Administrative Advice: An increase in the maximum quantity to 2 should be sought for patients requiring a maintenance dose of canakinumab above 150 mg every 4 weeks. No increase in the maximum quantity or number of units above 2 may be authorised.
Requested restriction (Balance of supply for initial treatment)
Category / Program: Section 100
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
Condition: Colchicine-resistant or intolerant familial mediterranean fever (crFMF)
Indication: Colchicine-resistant or intolerant familial mediterranean fever (crFMF)
Treatment Phase: Balance of supply for initial treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
The treatment must have commenced between the ages of 2 to 17 years inclusive.
Treatment criteria:
The treatment must provide no more than the balance of up to 24 weeks treatment available under this restriction.
Must be treated by a medical practitioner who is at least one of: (a) rheumatologist, (b) clinical immunologist, (c) physician experienced in the management of FMF patients, (d) in consultation with one of these prescriber types.
The treatment must be in combination with colchicine unless contraindicated or the patient has documented evidence of having experienced an adverse event necessitating discontinuation.
Administrative Advice: An increase in the maximum quantity to 2 should be sought for patients requiring a maintenance dose of canakinumab above 150 mg every 4 weeks. No increase in the maximum quantity or number of units above 2 may be authorised.

3.1 The submission noted that canakinumab is available as a 150 mg solution and a 150 mg powder, but only the 150 mg solution was proposed for PBS listing.

3.2 The submission proposed a special pricing arrangement with a published approved ex-manufacturer price (AEMP) of $20,000 and an effective AEMP of $[redacted] per 150 mg vial.

3.3 The proposed PBS restrictions were narrower than the TGA indication and the clinical trial evidence presented in the submission, as they proposed to limit treatment to patients under 18 years at treatment initiation. The submission argued that the paediatric population experiences the most significant and disproportionate disease

burden due to the paediatric onset of disease and limited treatment options with tolerable administration and randomised controlled trial (RCT) evidence of efficacy and safety. The evaluation and the ESC considered that it may not be reasonable to limit treatment to paediatric patients, given evidence of clinical benefit was also demonstrated in adult patients in the CLUSTER trial and the TGA indication includes treatment of adult patients. Given the lack of other available PBS listed treatment options for this population the ESC considered that limiting treatment to patients <18 years at initiation is likely to result in equity concerns for those patients >18 years at the time of PBS listing. The PBAC considered that an age-agnostic listing would be appropriate.

3.4 The Pre-PBAC response stated that as the sponsor has limited price flexibility that the decision was made to focus the request for reimbursement on the population with the greatest need. The Response highlighted that both the Australian Parliament and the *Health Technology Assessment Review 2024* consider access to PBS-listed medicine for paediatric patients as a priority.

3.5 The submission argued that the requirement for MEFV exon-10 pathogenic variant-positive disease in the requested restriction would ensure treatment occurs in the cost-effective population and would help to prevent use outside of FMF, in other periodic fever syndromes. The submission noted that not all patients with clinically diagnosed FMF will return a positive MEFV pathogenic variant test. These patients would not be eligible for treatment with canakinumab under the proposed restriction. In addition, authors of a retrospective review of MEFV gene testing in a major Melbourne referral centre (Shan & Mian 2024) noted that the MEFV gene test is not required within any diagnostic criteria for FMF (diagnosis of FMF using the Tel Hashomer criteria is based on a combination of presenting symptoms and response to colchicine), and that genetic testing can be laborious and costly and requires an out-of-pocket payment in Australia. It is unclear whether all Australian patients diagnosed with FMF have received the MEFV gene test. The Pre-Sub-Committee Response (PSCR) stated , “Australian paediatric rheumatologists refer FMF patients to hospitals that offer fee-free genetic testing. Gene testing is recommended for every patient with suspected FMF in the EULAR 2024 guidelines (Ozen et al., 2025). It is appropriate therefore for patients to have their diagnosis confirmed via genetic testing for access to canakinumab”. The PBAC considered it would be appropriate for patients to return a positive MEFV pathogenic variant test and for diagnosis of FMF to be confirmed using the Tel Hashomer criteria prior to accessing canakinumab on the PBS.

3.6 The submission acknowledged that the requested restriction for continuing treatment does not include a definition for adequate response to canakinumab. The submission argued that the key CLUSTER trial demonstrated that 96.6% of patients completed 72 weeks of treatment with canakinumab with one or fewer disease flares, and therefore most of the proposed PBS population would be expected to experience large clinical benefits. Expert opinion from Australian paediatric rheumatologists included in the submission reinforced that they would discontinue treatment in

patients who did not achieve a clinical benefit. The submission noted that should the PBAC agree with this approach, the initial and continuing restrictions could be combined into a single restriction. The ESC noted that in clinical practice serum AA can be useful to detect baseline inflammation in non-symptomatic patients, particularly when C-Reactive Protein (CRP) is normal, but is not routinely measured as the test is only available at a small number of laboratories, whereas CRP testing is widely available and provides an indication of the level of inflammation. The PBAC agreed with the ESC that it would be reasonable for assessment of adequate response to be based on clinician judgement rather than requiring a strict definition.

3.7 The PBAC also considered that prescribing instructions regarding dose reductions and increased should be included to ensure that patients are treated with the minimum effective dose.

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

4 Population and disease

4.1 FMF is the most common of the periodic fever syndromes, a group of rare genetic autoinflammatory diseases characterised by recurrent febrile attacks and severe systemic inflammation. FMF is an autosomal recessive genetic disorder, caused by one or more pathogenic variants in the MEFV gene (Lachmann and Hawkins 2009; Livneh and Langevitz 2000). Onset of disease is typically in the first decade of life with median age of onset of 4 years, and 75% and 90% of patients experiencing their first febrile attack before 10 and 20 years of age, respectively (Kallinich 2015; Georgin-Lavialle 2023), though the ESC noted that diagnosis is often delayed.

4.2 The incidence and prevalence of FMF is highest in countries around the Mediterranean basin and primarily affects individuals of Turkish (prevalence ranging from approximately 1 in 20 to 1 in 35,000 in different regions), Armenian (1 in 500), Non-Ashkenazi Jewish (1 in 500 to 1 in 1,000), Middle Eastern, and Arab descent. However, due to global migration patterns and an increase in recognition and diagnostic sensitivity, more patients in Australia have been diagnosed over time, although there are no published epidemiological data for FMF in Australia. The PBAC noted that within Australia, patients who are culturally and linguistically diverse (CALD) are disproportionately affected by crFMF.

4.3 FMF patients experience recurrent episodes of systemic inflammation ('flares'), which are typically accompanied by fever, and other systemic symptoms associated with peritonitis (inflammation of the lining of the abdomen), pleuritis (inflammation of the lining of the lungs and chest), arthritis and erysipelas-like erythema (a red, swollen skin rash that has an identical appearance to a rash caused by an erysipelas bacterial infection). Flares typically resolve spontaneously within 1-3 days. The frequency of flares is highly variable, even in the same patient, and can range from every few days to several months apart (UpToDate 2025). Between attacks, patients are generally asymptomatic although some patients experience persistent subclinical inflammation.

Persistent inflammation or frequent inflammatory attacks place patients at risk of developing amyloid A (AA) amyloidosis, which occurs due to deposition of insoluble amyloid fibrils in organs. AA amyloidosis commonly leads to renal damage, which may require dialysis or transplant, and is the major cause of early mortality for patients with FMF (Ozeri 2025).

4.4 The standard of care for FMF is daily colchicine, which prevents febrile attacks and the development of secondary amyloidosis by suppressing inflammation. While colchicine is not TGA-indicated for FMF, it has an unrestricted PBS listing and is commonly used for the treatment of FMF in Australia. Other treatments for FMF include NSAIDs and corticosteroids for treatment of acute symptoms.

4.5 A proportion of patients develop resistance and/or intolerance to colchicine treatment (Ozen 2016) and continue to experience one or more febrile attacks despite receiving the maximally tolerated colchicine dose for at least 3 months or have persistent subclinical inflammation (elevated C-reactive protein and serum amyloid A levels between flares).

4.6 Canakinumab was positioned as an add-on therapy to maximum tolerated doses of colchicine in patients aged 2-17 years with FMF who are colchicine-resistant or intolerant, with treatment continued into adulthood. The ESC considered that this positioning was appropriate and noted that colchicine is the first line therapy in all guidelines, is easy to take and often well-tolerated, and is effective in preventing attacks. However, the ESC considered that some patients may cycle through colchicine to access canakinumab without a reasonable trial of colchicine's tolerability and efficacy.

4.7 The recommended dose of canakinumab is 150 mg (or 2 mg/kg for patients with body weight between 7.5 kg and 40 kg) administered by subcutaneous injection every 4 weeks. Increasing the dose of canakinumab from 150 mg to 300 mg (or from 2 mg/kg to 4 mg/kg for body weight between 7.5 kg and 40 kg) every 4 weeks is recommended for patients who do not achieve a treatment response. The submission noted feedback from Australian paediatric rheumatologists indicating that they are likely to increase the dose interval of canakinumab from 4 to 8 weeks following clinical and biochemical remission. The canakinumab product information does not include recommendations for changing the dose interval for the FMF indication.

4.8 The Pre-PBAC response noted that access to canakinumab is available for patients treated at the major academic teaching hospitals (with the sponsor receiving the requested net price), but that patients who are not treated at these hospitals are limited to either BSC, or off-label anakinra if available via individual patient submissions to local hospital drug usage committees.

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

5 Comparator

5.1 The submission nominated BSC as the main comparator, comprising colchicine at the maximum tolerated dose, with NSAIDs and oral corticosteroids where necessary for treatment of acute symptoms and protracted febrile myalgia. The main arguments provided in support of this nomination were that canakinumab is the only TGA-registered medicine for the treatment of FMF, and canakinumab will be used in addition to, rather than replacing colchicine. The ESC agreed with the evaluation that BSC is an appropriate comparator.

5.2 The submission noted feedback from Australian paediatric rheumatologists that some patients with crFMF are currently receiving treatment with anakinra, an interleukin-1 (IL-1) receptor antagonist. The submission argued that anakinra is not a relevant comparator on the basis that it is not TGA-registered for the treatment of FMF, and there is a lack of RCT evidence for anakinra in paediatric patients with crFMF. However, the ESC considered that a comparison of canakinumab versus anakinra may have been informative, as the listing of canakinumab on the PBS would likely lead to substitution among patients who are receiving anakinra treatment that is self-funded, hospital funded or obtained through a compassionate access scheme. The ESC noted that the cost for anakinra on the PBS (for moderate to severe cryopyrin associated periodic syndromes (CAPS)) was $1,146.64 DPMQ (public hospital) compared to $[redacted] DPMQ proposed for canakinumab.

5.3 The Pre-PBAC response maintained that BSC is the only appropriate comparator as it is the treatment that is accessible and affordable to all patients. The Response stated that anakinra has an extremely high needle burden and sub-optimal compliance and efficacy. The PBAC noted that this was consistent with input provided in the written statement from a paediatric rheumatologist (see paragraph 6.1) and input from other healthcare professionals via the Office of Health Technology Assessment Consultation Hub. The Response also stated that a comparison to anakinra would be inappropriate, uncertain and not informative given the different trial endpoints and a lack of data in the requested population.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item, however the sponsor provided a written statement from a paediatric rheumatologist. The rheumatologist discussed FMF, stating that flares can manifest as high-grade fevers for several days and that the condition is often associated with severe abdominal pain and fatigue. The rheumatologist highlighted that poorly controlled FMF affects the ability of children to attend school and interact with family and friends and effective treatment can improve work attendance and

reduce hospital visits in adults. Current access to IL-1 blockade medicines was described as relying on individual patient submissions to local hospital drug usage committees, which leads to pressure on individual hospital budgets and issues with inequity of access to appropriate care. The preferred treatment was stated to be canakinumab, however, the rheumatologist stated that the agent most commonly accessible via drug usage committees is anakinra, which requires daily injections. The rheumatologist described how injection pain and local reactions with anakinra can lead to challenges with compliance that result in suboptimal disease control and less than optimal long term inflammatory outcomes. The rheumatologist highlighted that canakinumab is infrequently dosed and has improved tolerability over anakinra, and stated that having access to canakinumab would align their clinical practice with evidence based international standards of care and prevent predictable harm and crisis drive care.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (11 rheumatologists and immunologists) and organisations (4) via the Office of Health Technology Assessment Consultation Hub.

6.3 Input from individuals and health care professionals highlighted the lack of PBS-listed alternatives to colchicine for patients with crFMF. One paediatric rheumatologist stated that based on local experience that the proportion of patients who do not respond to colchicine with complete remission would be higher than the 5-10% rate reported in international cohorts, and that in addition to that subset, there are also some patients who cannot tolerate colchicine in sufficient doses to prevent inflammation due to gastrointestinal effects. Health care professionals highlighted that treatment with IL-1 receptor antagonists, including canakinumab, for these patients is best practice according to international guidelines, and that currently there is a reliance on ad hoc hospital funding. The input stated that there is a need for equitable access to effective therapy, with one health care professional stating that lack of a PBS-listed anti-IL-1 therapy places “children at risk of undertreatment and creates major challenges during transition to adult public services, where access to hospital-funded biologics is even more constrained”.

6.4 Both parents of individuals with crFMF and health care professionals stated that ongoing and unpredictable flares contribute to stress, anxiety and worry for family members, which affects the overall wellbeing and day-to-day functioning of families. Health care professionals highlighted that recurrent flares can lead to irreversible organ damage, including AA amyloidosis, kidney failure and reduced life expectancy. One clinician who undertook training overseas and saw canakinumab in use for patients with autoinflammatory diseases regularly, believed canakinumab to be a life changing medication.

6.5 Individuals highlighted that flares result in considerable pain, with one individual stating that uncontrolled inflammation has led to recurrent pericarditis and organ

failure. One parent stated that canakinumab has provided predictable disease control and reduced emotional distress associated with less painful injections for their child.

6.6 While input from individuals noted that anakinra injections have provided symptom relief, one individual stated that a monthly injection schedule would be easier and less stressful. Health care professionals reinforced this view, stating that canakinumab is generally well tolerated and associated with less injection-site pain compared to anakinra, highlighting that injection pain can result in missed doses, poorer disease control and more frequent inflammatory flares in children, where the pain of injections is a significant barrier to adherence.

6.7 Health care professionals stated that canakinumab leads to a marked reduction in flares, normalisation of inflammatory markers, prevention of amyloidosis, and better long-term disease suppression control compared with intermittent or poorly tolerated anakinra. While noting the high cost of canakinumab, the input noted that downstream costs of inadequately treated FMF include hospital admissions for acute inflammatory attacks, treatment of complications such as renal failure and amyloidosis, long term disability and loss of workforce participation, and inappropriate use of non-targeted therapies.

6.8 Health care professionals asserted that there is no biological or clinical justification for limiting access to canakinumab by disease subtype when IL-1 is the common pathogenic driver to many autoinflammatory diseases, or by age, given the disease does not fundamentally change when patients transition to adulthood.

6.9 One health care professional highlighted that standard practice in the UK and the USA is to prescribe anakinra plus canakinumab for patients with severe disease.

6.10 All four organisations providing input supported the listing of canakinumab on the PBS.

- The Australasian Society of Clinical Immunology and Allergy stated there is a need for an alternative effective treatment option for patients with colchicine-resistant or intolerant FMF and that PBS listing should improve access for patients. The input further highlighted the considerable cost of consultations for poorly controlled disease.
- The National Paediatric Medicines Forum noted that an alternative to the daily injections of anakinra would assist with compliance.
- Comments received from Juvenile Arthritis Foundation Australia outlined the effectiveness of canakinumab in crFMF and its good tolerability, as well as the positive impact that long term treatment would have on outcomes and quality of life for patients and carers.
- The Australia and New Zealand Forum for AutoInflammatory Diseases stated that while colchicine is effective for many patients, that patients and carers frequently describe the experience of managing colchicine intolerance as particularly distressing, reporting feeling pressured to continue colchicine therapy despite clear adverse effects given the absence of funded alternatives. The input stated that

families have described lack of medical guidance on how to introduce or adjust colchicine therapy and noted that this has left parents to balance disease control against visible harm to their child's well-being. The input further highlighted that ongoing systemic inflammation increases the risk of AA amyloidosis, chronic pain, fatigue and cumulative organ damage and that the impact is particularly significant in childhood and adolescence, when unstable disease can affect physical development, education and psychosocial well-being. Without access to TGA-approved biologic treatments for FMF in Australia, the input highlighted that patients are accessing off-label biologic therapies, and that these have resulted in treatment fatigue and difficulty in maintaining long-term adherence. Based on access to canakinumab through clinical trials, compassionate access programs, or private funding, families have reported improved disease control, reduced flare frequency, and meaningful improvements in daily functioning and quality of life, as well as sustained adherence due to reduced treatment burden. The input stated that it is important for patients to be able to continue treatment into adulthood.

Clinical trials

6.11 The submission was based on one head-to-head trial comparing canakinumab with BSC to BSC alone (n=63 randomised patients; CLUSTER trial).

6.12 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CLUSTER	A randomized, double-blind placebo controlled study of canakinumab in patients with Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/dosing frequency reduction and open-label long term treatment epochs.	Clinical Study Reports, 20 January 2014: Week 16 primary endpoint analysis; Week 40 analysis; Week 112 analysis.
	De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes.	New Eng J Med 2018; 378(20): 1908-1919.
	Koné-Paut I, Piram M, Benseler S, et al. Use of the auto-inflammatory disease activity index to monitor disease activity in patients with colchicine-resistant Familial Mediterranean Fever, Mevalonate Kinase Deficiency, and TRAPS treated with canakinumab.	Joint Bone Spine 2022; 89(6).

Source: Table 2.4, p84 of the submission.

6.13 The key features of the CLUSTER trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Canakinumab plus BSC versus BSC alone						
CLUSTER	63	MC, 4 stage trial with DB, randomised stage (16 weeks), DB, re-randomised stage for responders (24 weeks) plus OL cohort, and long term follow-up (72 weeks)	Unclear	Patients with FMF aged ≥2 years with active disease despite maximum tolerated colchicine therapy	Complete response, PGA, CRP, SAA response, number of flares, HRQoL, adverse events	Number of flares, HRQoL, adverse events

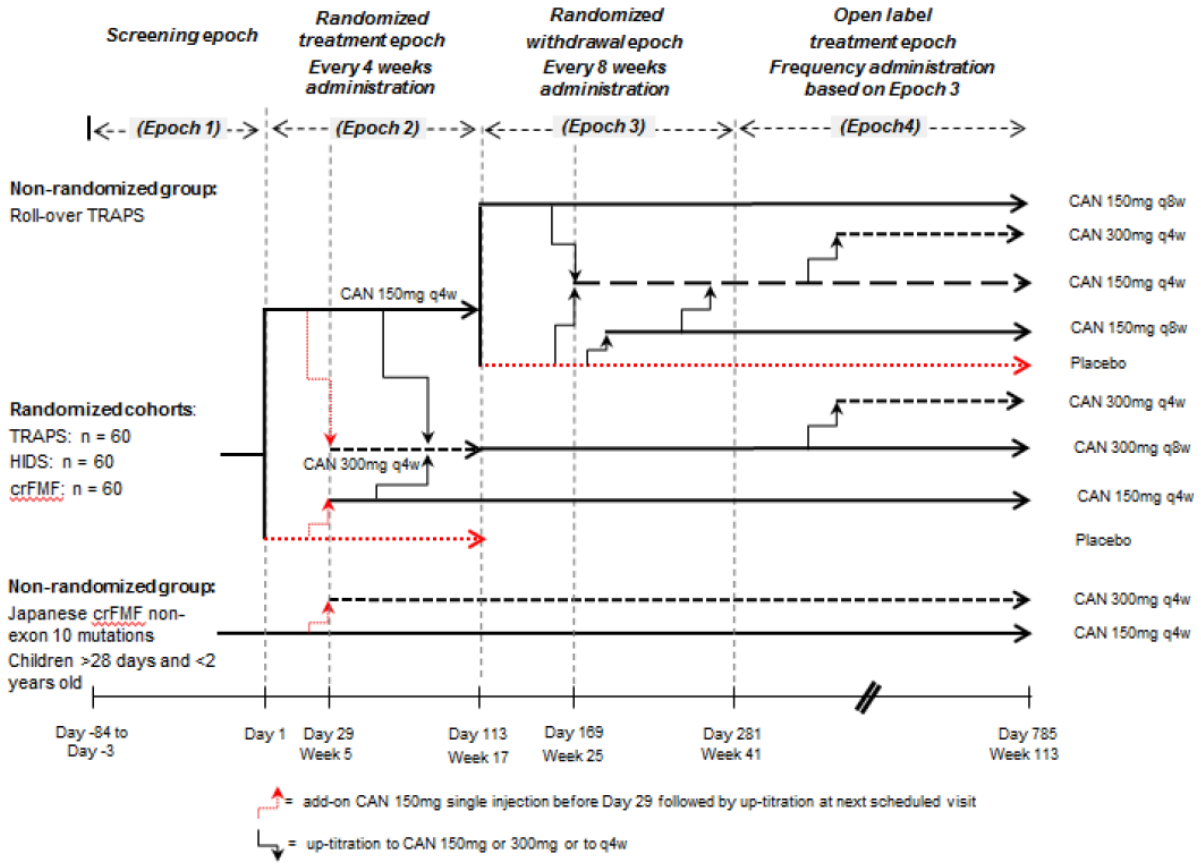
Source: Table 2.10, pp103-104; Table 2.14, pp115-116; Section 2.3, p85 of the submission.

Abbreviations: BSC, best supportive care; CRP, C-reactive protein; DB, double blind; HRQoL, health-related quality of life; MC, multi-centre; OL, open label; PGA, Physician Global Assessment; R, randomised; SAA, serum amyloid A.

6.14 The CLUSTER trial is a multi-stage phase 3 trial comparing canakinumab added to BSC with BSC alone in 3 randomised cohorts of patients with different periodic fever syndromes, including colchicine-resistant FMF. The proposed PBS population aligns with a subgroup of the colchicine-resistant FMF cohort who are aged <18 years, while results from the total colchicine-resistant FMF cohort inform treatment outcomes once these patients continue treatment into adulthood.

6.15 The 4 stages of the CLUSTER trial are summarised in Figure 1.

Figure 1: CLUSTER trial study design



Source: Figure 2.2, p87 of the submission
Abbreviations: CAN, canakinumab; crFMF, colchicine-resistant familial Mediterranean fever; HIDS, hyperimmunoglobulin D syndrome; q4w, every 4 weeks; q8w, every 8 weeks; TRAPS, tumour necrosis factor receptor associated periodic syndrome.

6.16 The trial included a screening stage of up to 12 weeks (Stage 1), during which eligible patients who experienced a disease flare could immediately enter the randomised treatment stage (Stage 2, 16 weeks duration). Patients were randomised to canakinumab 150 mg (or 2 mg/kg for patients with body weight ≤40 kg) every 4 weeks or matched placebo, both with concomitant BSC. Patients whose index flare had resolved remained on their randomised treatment and dosage. There were 2 possible escape options for patients who did not respond to treatment of their index disease

flare: blinded escape from Day 1 to Day 28, where the randomised therapy remained blinded, but patients received a single add-on subcutaneous injection of canakinumab 150 mg (or 2 mg/kg) and were then up-titrated to the ongoing higher dose from Day 29 onwards. This resulted in patients initially randomised to canakinumab 150 mg (or 2 mg/kg) every 4 weeks receiving blinded treatment with canakinumab 300 mg (or 4 mg/kg) every 4 weeks, and patients initially randomised to placebo receiving blinded treatment with canakinumab 150 mg (or 2 mg/kg) plus placebo injection every 4 weeks for the remainder of the randomised phase. If on or after day 29 patients still had disease activity (both clinical and laboratory measures of disease flare), patients randomised to canakinumab moved to open-label treatment with canakinumab 300 mg every 4 weeks, and patients randomised to placebo moved to open-label treatment with canakinumab 150 mg every 4 weeks (with the option to increase to 300 mg every 4 weeks if needed). Patients who had already received blinded escape prior to Day 29 and who required a second up-titration on or after Day 29 were also eligible to move to open label up-titrated doses. However, patients were not permitted to exceed the maximum canakinumab dose of 300 mg every 4 weeks.

6.17 In Stage 3 (dose tapering/withdrawal phase), patients who were initially randomised to the canakinumab arm whose index flare had resolved and who did not have an additional disease flare in Stage 2 (canakinumab responders) were re-randomised to canakinumab 150 mg (or 2 mg/kg) or placebo every 8 weeks for 24 weeks to assess the potential for canakinumab to maintain clinical efficacy at a reduced dosing frequency or complete withdrawal. Patients randomised to placebo who did not have an additional disease flare in Stage 2 were considered placebo responders and were withdrawn from study treatment. Patients who required any up-titration or crossed over from placebo to canakinumab treatment during Stage 2 were switched to open label 8-weekly dosing at their current escape dose of 150 mg or 300 mg but were allowed to revert to 4-weekly dosing in the event of a re-flare. In the event of a disease flare less than 8 weeks into Stage 3, patients re-randomised to placebo were switched to open label canakinumab 150 mg every 4 weeks, while a flare after 8 weeks resulted in a switch to open label canakinumab 150 mg every 8 weeks. Patients re-randomised to canakinumab 150 mg every 8 weeks who had a disease flare reverted to open label canakinumab 150 mg every 4 weeks.

6.18 Stage 4 of the CLUSTER trial was an open-label long-term safety follow-up (72 weeks duration), with up-titration of canakinumab permitted on disease flare to a maximum of 300 mg every 4 weeks. Patients already receiving canakinumab in Stage 3 continued their dosing regimen into Stage 4, while placebo-treated patients attended scheduled visits but did not receive ongoing investigational treatments. Patients who re-flared during Stage 4 received open-label canakinumab 150 mg every 8 weeks, with up-titration as required. No down titration was permitted during Stage 4.

6.19 Overall, the CLUSTER trial had an uncertain risk of bias due to the study design that incorporated treatment switching from placebo to canakinumab or dose up-titration in the canakinumab arm. The submission argued that the incorporation of treatment

switching into the CLUSTER trial addressed the ethical implications of withholding an effective treatment from patients with a rare disease and high clinical unmet need. The primary and secondary outcomes were designed so that placebo patients who crossed over to canakinumab due to a new flare, and canakinumab patients who required up titration due to a re-flare were considered as non-responders. However, for exploratory efficacy and safety outcomes, results were presented by treatment sequence (e.g., placebo (no flare), or placebo to canakinumab 150 mg every 4 weeks), and no analyses were conducted to measure a comparative treatment effect between canakinumab and BSC. In addition, there was the potential for treatment unmasking (patient awareness of treatment allocation) due to the disappearance of symptoms whilst treated with canakinumab. While the key primary and secondary outcomes assessed in the trial were objective laboratory measures or assessed by physicians, measures of health-related quality of life were patient reported and may have been influenced by patient awareness of treatment allocation.

6.20 Randomised patients in the CLUSTER trial were predominantly White (85.7%), had a mean age of 22 years, and there were slightly more males than females enrolled (54.0%). All patients had a confirmed pathogenic variant, with the M694V variant recorded in most patients (85.7%; 68.3% homozygous, 17.5% heterozygous). Mean time since first symptoms was 16 years, with patients experiencing an average of 24 disease flares per year. Most patients were assessed as having moderate (57.1%) or severe (28.6%) disease according to the Physician Global Assessment of disease. Of the randomised patients in Stage 2, only 29 patients (46.1%) were representative of the proposed PBS population (paediatric patients aged 2-17 years).

6.21 There were some differences noted between treatment arms within and across the paediatric and adult subgroups. The mean number of flares per year in paediatric canakinumab patients (27.4) was similar to adult canakinumab patients (28.4) and adult placebo patients (24.2), however patients in the paediatric placebo group reported a lower mean number of flares per year (16.3). The average duration of each flare was lower in the paediatric canakinumab group (2.3 days) compared to the paediatric placebo group (3.5 days), and the adult canakinumab (3.6 days) and the adult placebo groups (3.8 days). There was a greater proportion of males in the paediatric canakinumab arm (71.4%) compared to the adult canakinumab arm (41.2%). All patients in the paediatric canakinumab arm had the M694V variant, compared to 80% in the paediatric placebo arm, 94.1% in the adult canakinumab arm and 70.6% in the adult placebo arm. Proportions of patients with mild, moderate or severe disease as measured by the Physician Global Assessment were similar between age groups. Subgroups analysed during the trial, including paediatric and adult age groups, were not stratified at randomisation, and no statistical adjustments for multiple comparisons were reported.

6.22 Patients in the canakinumab arm had a longer mean time since first symptoms (17.1 years) compared to the placebo arm (15.1 years), had a higher mean number of flares per year (27.9 versus 20.5), higher mean C-reactive protein values at baseline

(163.9 versus 118.2 mg/L), higher mean serum amyloid A values at baseline (1,684.8 versus 865.4 mg/L), and were more likely to have 'severe' disease measured with the Physician Global Assessment (35.5% versus 21.9%). The submission argued that these differences favoured the placebo arm for efficacy outcomes.

6.23 Almost all patients randomised to placebo during Stage 2 did not respond to treatment of their index disease flare and moved to canakinumab treatment during the 16-week randomised phase, with 27 (84.4%) switching to canakinumab 150 mg every 4 weeks, including 5 patients (15.6%) who required further up-titration to canakinumab 300 mg every 4 weeks. There were 10 (32.2%) patients in the canakinumab arm who required up-titration to 300 mg every 4 weeks due to disease activity in the randomised stage.

6.24 In the paediatric subgroup, 12/15 patients in the placebo arm (80%) switched to canakinumab treatment, including 2 patients (13.3%) who required up-titration to canakinumab 300 mg every 4 weeks (or weight-based equivalent dose). In the canakinumab arm, 4/14 paediatric patients (28.6%) had their dose up-titrated during the randomised stage. Similar results were observed in the adult age group, with 15/17 (88.2%) patients in the placebo arm switching to canakinumab (including 3 (17.6%) up-titrated), and 6/17 (35.3%) patients in the canakinumab arm requiring dose up-titration.

6.25 The submission noted that the CLUSTER trial only reported the number of flares on treatment and the proportion of patients who achieved a complete response, whereas the target clinical endpoints in the model are the development of AA amyloidosis and end-stage renal disease. The submission assessed the relationship between FMF disease flares and the development of AA amyloidosis and end-stage renal disease, providing responses to components of the surrogate to target clinical outcomes framework. The ESC considered that it is reasonable to assume that the reduction of inflammation would lead to lower SAA and reduced deposition of AA amyloid over time. The ESC noted that guidelines (EULAR/PReS 2024[1]) highlight that AA amyloidosis is due to ongoing inflammation which is not adequately suppressed.

Comparative effectiveness

6.26 Results for the primary outcome, the proportion of patients with a complete response at the end of the 16-week randomised phase (Stage 2), and key secondary outcomes or the full analysis set and subgroup analyses by paediatric/adult patients are summarised in Table 4.

[1]EULAR/PReS endorsed recommendations for the management of familial Mediterranean fever (FMF): 2024 update. Ozen, Seza et al. Annals of the Rheumatic Diseases, Volume 84, Issue 6, 899 - 909

Table 4: Results for the primary and key secondary outcomes from Stage 2 of the CLUSTER trial, full analysis set and subgroups by age

Population	Canakinumab	Placebo	OR (95% CI)
Primary outcome – patients with complete response [a] at Week 16, n/N (%)			
Full analysis set	19/31 (61.3)	2/32 (6.3)	**23.75 (4.38, 227.53)**
Age <18 years	10/14 (71.4)	1/15 (6.7)	35.00 (2.88, 1,622.69)
Age ≥18 years	9/17 (52.9)	1/17 (5.9)	18.00 (1.77, 836.71)
Secondary outcome – patients with PGA <2 at Week 16, n/N (%)			
Full analysis set	20/31 (64.5)	3/32 (9.4)	**16.96 (4.15, 69.21)**
Age <18 years	10/14 (71.4)	2/15 (13.3)	12.67 (1.59, 185.72)
Age ≥18 years	10/17 (58.8)	1/17 (5.9)	22.13 (2.32, 1,164.24)
Secondary outcome - patients with CRP ≤10 mg/L at Week 16, n (%)			
Full analysis set	21/31 (67.7)	2/32 (6.3)	**29.78 (5.86, 151.31)**
Age <18 years	10/14 (71.4)	1/15 (6.7)	2.66 (0.91, ∞)
Age ≥18 years	11/17 (64.7)	1/17 (5.9)	6.60 (1.85, ∞)
Secondary outcome - patients with SAA ≤10 mg/L at Week 16, n (%)			
Full analysis set	8/31 (25.8)	0/32 (0)	17.46 (0.92, 332.92)
Age <18 years	4/14 (28.6)	0/15 (0)	1.19 (0.30, ∞)
Age ≥18 years	4/17 (23.5)	0/17 (0)	0.40 (0.02, ∞)

Source: Table 2.59, p187; Table 2.60, pp188-189 of the submission.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; PGA, Physician Global Assessment; OR, odds ratio; SAA, serum amyloid A.

Bold indicates statistically significant results. Statistical significance (one-sided) was measured at the 0.025 level based on the logistic regression model with treatment group and baseline PGA, CRP or SAA as explanatory variables.

Note: Subgroup comparison between treatment groups was performed using a logistic regression model with treatment group and baseline values as explanatory variables. Fisher exact test was used if exact logistic regression is not estimable. Tests for treatment effect interaction were not reported.

[a] Complete response was defined as a resolution of the index flare at Day 15 (Physician Global Assessment score <2 and C-reactive protein within normal range ≤10 mg/L or reduction ≥70% from baseline) with no new disease flares over 16 weeks of treatment. A new flare following the resolution of the index flare was defined as the simultaneous occurrence of a Physician Global Assessment score ≥2 (clinical flare) and C-reactive protein ≥30 mg/L (serological flare) from the time of resolution of the index flare.

6.27 A statistically significantly greater proportion of patients in the canakinumab arm achieved a complete response at Week 16 compared to placebo (OR 23.75, 95% CI 4.38, 227.53). Results for the individual components of Physician Global Assessment and C-reactive protein response were consistent with the primary outcome. Fewer patients overall met the threshold for serum amyloid A response (with the difference between treatment arms not reaching statistical significance at the 2.5% level), however all responders were in the canakinumab arm. Results for the primary and key secondary outcomes in the paediatric and adult subgroups were consistent with the full analysis set for all outcomes, with canakinumab treated patients more likely to respond on all measures compared to the placebo arm. The submission noted that the difference between treatment arms for the primary outcome of complete response was greater in the paediatric subgroup compared to the adult subgroup, with a greater proportion of paediatric patients showing a complete response with canakinumab treatment compared to the adult subgroup. Small patient numbers mean that results of subgroup analyses should be interpreted with caution. Tests for treatment effect interaction were not reported.

6.28 The absence of new flares at Week 40 was the only secondary outcome assessed in Stage 3 of the CLUSTER trial. All patients analysed for this outcome were canakinumab responders in Stage 2 who were re-randomised to canakinumab 150 mg (or 2 mg/kg)

every 8 weeks (n=9), or to placebo (n=10). In the re-randomised canakinumab arm, 7 patients (77.8%) maintained a clinically meaningful response (absence of new flares) at Week 40, compared to 3 patients in the re-randomised placebo arm (30%; OR 8.17, 95% CI 0.75, 113.44). Patients needing dose escalation in the canakinumab arm, patients who crossed over from placebo to canakinumab, and patients who discontinued from the study for any reason during Stage 3 were considered non-responders. Due to the hierarchical structure of outcome assessment, the difference between treatment arms was not analysed statistically (i.e., as there was no statistically significant difference between treatment arms in Stage 2 for serum amyloid A response). The clinical study report also noted that the number of patients in each group was small, and that the results should be interpreted with caution.

6.29 Patient-reported outcomes were measured during Stages 2 and 3 of the CLUSTER trial as exploratory outcomes. The submission noted that comparisons between canakinumab and placebo were limited due to the high proportion of patients randomised to placebo who switched to canakinumab during the trial, with no statistical analyses for a comparative treatment effect conducted. The submission argued that results in the placebo arm for patients who did not cross over to canakinumab in Stage 3 may overestimate any treatment effect as these patients represent only those who completed Stage 2 with no flare.

6.30 Changes in median scores from baseline to the end of Stage 2 for key health-related quality of life measures (AIDAI, SF-12 physical component score, CHQ-P50 physical component score and the Sheehan Disability Scale global functional impairment score) are summarised in Table 5. As comparisons between treatment arms are not informative due to treatment switching, results are grouped by ‘no flare’ (patients who did not receive add-on doses or up-titration or patients who stayed on their randomised treatment regimen), and ‘≥1 flare’ (patients who received add on dose or up-titration, or patients who did not stay on their randomised treatment regimen at the end of Stage 2), as included in the CLUSTER clinical trial report.

Table 5: Change from baseline to Week 16/17 in key health-related quality of life measures by flare/no flare during Stage 2, CLUSTER trial

	Randomised to canakinumab 150 mg every 4 weeks			Placebo to canakinumab 150 mg every 4 weeks (≥1 flare)
	All randomised to canakinumab	No up-titration (no flare)	150 mg to 300 mg every 4 weeks (≥1 flare)	
Median AIDAI score [a]				
N	31	21	10	22
Baseline	2.38	1.75	2.69	2.50
Week 2 (change)	0.76 (−1.16)	0.64 (−1.31)	1.23 (−0.67)	1.83 (−0.66)
Week 5 (change)	0.60 (−1.50)	0.60 (−1.27)	0.52 (−1.63)	0.00 (−1.25)
Week 16 median (change)	0.43 (−1.71)	0.16 (−1.37)	0.80 (−2.14)	0.07 (−2.00)
Median SF-12 physical component score (>18 years of age at baseline) [b]				
N	17	11	6	11
Baseline	38.74	37.91	41.31	36.46
Day 29 (change)	45.87 (10.39)	47.54 (11.83)	45.38 (8.56)	42.97 (10.40)
Week 17 (change)	47.76 (6.69)	48.30 (9.07)	42.70 (−1.72)	53.41 (12.79)
Median CHQ-PF50 physical component score (>5 to <18 years of age at baseline, completed by parent) [c]				
N	12	9	3	10
Baseline	24.8	26.8	13.2	23.5
Day 29 (change)	48.6 (24.4)	49.8 (23.4)	47.4 (34.2)	38.7 (7.7)
Week 17 (change)	43.1 (22.8)	43.3 (17.7)	40.6 (27.1)	50.6 (15.0)
Median SDS v3, global functional impairment [d]				
N	27	21	10	22
Baseline	15.0	15.0	20.0	18.0
Week 17 (change)	7.0 (-8.0)	5.0 (-10.0)	18.0 (-2.0)	4.0 (-14.0)

Source: Table 2.37, pp152-153; Table 2.40, pp158-159; Table 2.4.2, pp162-164 of the submission.

Abbreviations: AIDAI, Auto-Inflammatory Diseases Activity Index; CHQ-PF50, Child Health Questionnaire – Parent Form 50; SDS, Sheehan Disability Scale; SF-12, SF-12 health survey.

Note: In the CLUSTER trial, 'no flare' was defined as patients who did not receive an add-on dose or any up-titration or patients who stayed on their randomised treatment regimen, and '≥1 flare' was defined as patients who received an add-on dose or up-titration or patients who did not stay on their randomised treatment regimen at the end of Stage 2.

Note: Canakinumab 150/300 mg also refers to canakinumab 2/4 mg/kg in patients weighing ≤40 kg. Results for placebo to canakinumab 300 mg are not shown due to the small number of evaluable patients. Median change from baseline is presented for each study week and was calculated only for patients with both baseline and post-baseline values. Week 16 results were used for the AIDAI measure due to small number of patients with available results in Week 17.

[a] AIDAI scores are based on the sum of all 'Yes' responses from 12 items: (a) fever, ≥38°C; (b) overall symptoms; (c) abdominal pain; (d) nausea/vomiting; (e) diarrhoea; (f) headaches; (g) chest pain; (h) painful nodes; (i) arthralgia or myalgia; (j) swelling of the joints; (k) eye manifestations; (l) skin rash ('pain relief drugs taken' item not included). Higher scores are indicative of more auto-inflammatory disease activity.

[b] The SF-12 measures the impact of disease on overall quality of life and consists of eight subscales (physical function, pain, general and mental health, vitality, social function, physical and emotional health) which can be aggregated to derive a physical-component summary score (PCS) and a mental-component summary score (MCS). Scores are determined with the use of norm-based methods which standardise scores based on an assessment of the general U.S. population free of chronic conditions. Scores above 50 indicate better than average health, scores below 50 indicate below average health with a change of 3 to 5 points typically suggesting a clinically meaningful improvement or decline, depending on population norms.

[c] The CHQ-P50 questionnaire measures the following concepts: physical functioning, role/social emotional, role/social behaviour, role/social physical, bodily pain, general behaviour, mental health, self-esteem, general health perception, change in health, parental impact – emotional, parental impact – time, family activities, and family cohesion. The CLUSTER clinical study report noted that a change from baseline of 2, 5, and 8 points in CHQ-P50 physical and psychological component summary scores corresponds to a small, moderate and large treatment effect, respectively. Higher scores indicate better or more positive health states.

[d] Three items from the SDS are summed up into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired).

6.31 Results from the health-related quality of life measures suggest an improvement in auto-inflammatory disease activity, a decrease in functional impairment and an

improvement in health-related quality of life from baseline to the end of Stage 2 in all patients treated with canakinumab, including those switching from placebo to canakinumab during the stage.

Comparative harms

6.32 The submission noted that the extensive crossover of placebo patients to canakinumab treatment in the randomised and re-randomised groups in Stages 2 and 3 of the CLUSTER trial precludes a meaningful comparison of harms between canakinumab and placebo. Adverse events by stage for patients receiving any dose of canakinumab are summarised in Table 6.

Table 6: Key adverse events by CLUSTER trial stage, any patients treated with at least one dose of canakinumab

Adverse event type	Stage 2, n (%) N = 58	Stage 3, n (%) N = 59	Stage 4, n (%) N = 60
Any adverse event	47 (81.0)	47 (85.5)	57 (95.0)
Any serious adverse event	5 (8.6)	5 (9.1)	13 (21.7)
Adverse event related to study drug	19 (32.8)	13 (23.6)	19 (31.7)
Adverse event leading to discontinuation	0 (0)	0 (0)	1 (1.7)
Deaths	0 (0)	0 (0)	0 (0)
Commonly reported adverse events (at least 10% of patients in at least one Stage)			
Familial Mediterranean fever [a]	13 (22.4)	13 (23.6)	19 (31.7)
Injection site reaction	8 (13.8)	5 (9.1)	2 (3.3)
Diarrhoea	7 (12.1)	2 (3.6)	7 (11.7)
Abdominal Pain	6 (10.3)	5 (9.1)	12 (20.0)
Headache	6 (10.3)	7 (12.7)	12 (20.0)
Nasopharyngitis	6 (10.3)	NR	NR
Upper respiratory tract infection	5 (8.6)	5 (9.1)	9 (15.0)
Pyrexia	3 (5.2)	5 (9.1)	11 (18.3)
Nausea	NR	NR	6 (10.0)
Influenza	1 (1.7)	4 (7.3)	8 (13.3)
Urinary tract infection	NR	4 (7.3)	8 (13.3)
Gastroenteritis	NR	4 (7.3)	7 (11.7)
Pharyngitis	1 (1.7)	NR	7 (11.7)
Back pain	NR	3 (5.5)	11 (18.3)
Arthralgia	2 (3.4)	4 (7.3)	10 (16.7)
Myalgia	1 (1.7)	2 (3.6)	6 (10.0)
Oropharyngeal pain	NR	NR	7 (11.7)

Source: Table 2.48, p174; Table 2.49, pp174-175 of the submission; Table 12.4, CLUSTER 16 Week clinical study report; Table 14.3.1-1.1b, CLUSTER 40 Week clinical study report; Table 12.4, CLUSTER 112 Week clinical study report; Tables 14.3.1-1.1c to 14.3.1-1.9c, CLUSTER 112 Week clinical study report, CSR Tables.

Abbreviations: FMF, familial Mediterranean fever; NR, not reported

Note: An event that occurred in any patient who took at least 1 dose of canakinumab in Epoch 2 is included even if the event occurred when the patient was on placebo.

[a] Adverse events of FMF were reported by investigators based on their assessment of the patient and these may not correspond to the definition of disease flares pre-specified in the trial protocol (i.e., Physician Global Assessment score ≥2 and C-reactive protein ≥30 mg/L).

6.33 Across the entire treatment period (Stages 2-4), 96.7% of patients who received at least one dose of canakinumab had at least one adverse event, with an exposure-adjusted event rate per 100 patient-days of 1.66. The most frequently affected primary system organ class was infections and infestations (85.2%), followed by gastrointestinal disorders (60.7%), musculoskeletal and connective tissue disorders

(55.7%), general disorders and administration site conditions (49.2%), and congenital, familial and genetic disorders (41.0%, all events of FMF). The CLUSTER study reports noted that many of the commonly reported adverse events were related to known disease symptoms.

6.34 For the entire treatment period (Stages 2-4), 52 patients (85.2%) treated with at least one dose of canakinumab had an adverse event of infections and infestations. The most common infections were upper respiratory tract infection (21.3%), influenza (18.0%), gastroenteritis (16.4%), urinary tract infection (16.4%), pharyngitis (31.1%), tonsillitis (13.1%) and viral upper respiratory tract infection (13.1%). None of the infection events were considered to be opportunistic infections after adjudication by an independent committee.

6.35 A small proportion of patients treated with any canakinumab experienced a serious adverse event, including 5 patients (8.6%) in Stage 2 (reported events included ascites, bile duct stone, FMF, granulomatous liver disease, hepatic cirrhosis, obesity, pharyngotonsillitis and umbilical hernia). Ten patients reported serious adverse events during Stage 3 (5 of which occurred while the patient was receiving placebo). Three episodes of FMF, reported by 2 patients, were considered disease-related and were regarded as severe. One patient receiving canakinumab 8-weekly had 2 serious adverse events of infection (cellulitis and pelvic abscess). In Stage 4, 6 patients (10.0%) experienced serious adverse events of infections and infestations, 3 patients reported gastrointestinal disorders (5.0%), two each (3.3%) reported musculoskeletal or respiratory disorders, and one each experienced congestive heart failure, FMF, thyroiditis, pyrexia, schizophrenia, and pyoderma gangrenosum.

6.36 There were no discontinuations due to adverse events during Stages 2 and 3. One patient discontinued treatment in Stage 4 due to pyoderma gangrenosum. There were no deaths during any stage of the trial.

Benefits/harms

6.37 The evidence presented in the submission did not allow for a quantitative comparison of the benefits and the harms of canakinumab and BSC versus BSC alone. Accordingly, a benefits/harms table was not presented.

Clinical claim

6.38 The submission described canakinumab, when added to BSC, as superior in terms of effectiveness and inferior in terms of safety compared to BSC alone. This claim was adequately supported by the evidence presented in the submission. However, the evaluation considered the following issues should be considered:

- The magnitude of benefit attributable to canakinumab rather than ongoing colchicine treatment is unclear given the majority of patients moved from placebo to canakinumab treatment during the randomised phases of the trial.

- It was not possible to assess comparative efficacy for exploratory outcomes, including health-related quality of life.
- No clinical trial data assessing the impact of canakinumab treatment on the development of AA amyloidosis was available. However, the ESC considered that it is reasonable to assume that the reduction of inflammation would lead to lower SAA and reduced deposition of AA amyloid over time (see paragraph 6.25).

6.39 Regarding the magnitude of benefit, the Pre-PBAC Response stated that Complete Response (the primary endpoint of CLUSTER) is the ultimate treatment goal for crFMF and the strongest predictor of patient wellbeing, noting that this is unaffected by treatment crossover. The Response noted that Complete Response can be wholly attributed to canakinumab since 0/26 patients (0%) with protocol-mandated colchicine treatment attained a Complete Response, compared to 18/29 patients (62%) treated with added canakinumab. The Response stated that compared to BSC, canakinumab treatment leads to a 65% absolute increase in the number of paediatric patients achieving a Complete Response.

6.40 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data but that the magnitude of benefit was uncertain, mainly due to crossover from placebo to canakinumab in the CLUSTER trial.

6.41 The PBAC considered that the claim of inferior but manageable comparative safety was reasonable.

Economic analysis

6.42 The submission presented a modelled economic evaluation of canakinumab plus BSC versus BSC alone for the treatment of paediatric patients with FMF who are intolerant or resistant to colchicine. The economic evaluation was based on the results of the CLUSTER trial with additional modelled data. The economic evaluation was presented as a stepped cost-effectiveness/cost-utility analysis, based on a Monte Carlo microsimulation model.

Table 7: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Canakinumab plus BSC versus BSC
Time horizon	70 years in the base case versus up to 112 weeks of follow-up in the CLUSTER trial.
Outcomes	Proportion of patients with response, proportion of patients with complete response, number of flares avoided, time spent in response state, life years, quality-adjusted life years.
Methods used to generate results	Monte Carlo microsimulation.
Health states	No AA amyloidosis (flare, no flare), AA amyloidosis (flare, no flare), pre-dialysis (flare, no flare), dialysis (flare, no flare), kidney transplant (flare, no flare), post kidney transplant (flare, no flare), death.
Cycle length	1 week

Component	Summary
Transition probabilities	Probability of flare in the canakinumab + BSC arm (patients on canakinumab treatment): Gamma distribution fitted to the mean number and standard distribution of flares among paediatric and adult patients on canakinumab treatment in the CLUSTER trial. Flares assumed to last for one model cycle. Probability of flare for patients in the BSC arm and patients in the canakinumab + BSC arm who discontinue canakinumab: Gamma distribution fitted to the mean number and standard distribution of flares at baseline among paediatric patients in the CLUSTER trial. Flares assumed to last for one model cycle. No AA amyloidosis to AA amyloidosis health state (patients who do not have chronic inflammation): Based on the proportion of patients without evidence of chronic inflammation who developed amyloidosis in a study conducted by Varan et al. (2019). No AA amyloidosis to AA amyloidosis health state (patients with chronic inflammation): Lognormal distribution fitted to the odds ratio comparing the risk of AA amyloidosis development in patients with chronic inflammation versus no chronic information reported by Varan et al. (2019). AA amyloidosis to pre-dialysis health state: Based on the proportion of patients with AA amyloidosis progressing to dialysis in a study conducted by Ahbap et al. (2014). Pre-dialysis to dialysis health state: All patients assumed to move to the dialysis health state after 1 cycle in the pre-dialysis health state. Dialysis to kidney transplant health state: Gamma distribution fitted to the mean wait time for kidney transplant in Australia in 2006 (National Clinical Taskforce on Organ and Tissue Donation; 2008). Kidney transplant to post kidney transplant health state: All patients assumed to move to the post kidney transplant health state after 1 cycle in the kidney transplant health state. Transition to death health state: No AA amyloidosis health state mortality based on Gendelman et al. (2020); AA amyloidosis health state mortality based on Ahbap et al. (2014); pre-dialysis and dialysis health state mortality based on Hudson et al. (2025); kidney transplant and post kidney transplant mortality based on Green et al. (2007).
Health related quality of life	No AA amyloidosis, no flare: Individual SF-12 physical and mental component scores among adults who achieved a complete response in the CLUSTER trial were mapped to an EQ 5D-3L utility using a published algorithm (Sullivan et al., 2006). No AA amyloidosis, flare: Mean SF-10 scores among paediatric patients and mean SF-12 scores among adult patients with colchicine-resistant FMF experiencing a disease flare reported by Kuemmerle-Deschner et al. (2020) were mapped to an EQ-5D-3L utility using a published algorithm (Sullivan et al., 2006). AA amyloidosis health state: Assumed to be the average of the utilities included for the no AA amyloidosis with flare and pre-dialysis health states. Pre-dialysis, dialysis and kidney transplant health states: Based on utilities among patients with IgA nephropathy derived in a study conducted by Zhou et al. (2024) using the time trade-off method. Post kidney transplant health state: Based on estimated EQ-5D-3L utility among patients with a history of renal transplantation derived from a study conducted by Lee et al. (2005).
Costs	Canakinumab treatment cost: Based on the proposed effective DMPQ for canakinumab. Persistence estimated from treatment utilisation in Stages 3 and 4 of the CLUSTER trial. Adherence assumed to be 100%. BSC treatment cost: Assumed no cost associated with BSC.

Component	Summary
	Flare cost: Based on specified AR-DRGs (inpatient hospitalisation), AECC codes (emergency department visits) and MBS items (specialist visit, UEC, FBC, ferritin level). No AA amyloidosis health state: Based on specified MBS costs (specialist attendance, UEC, FBC, ferritin level). AA amyloidosis health state: Based on specified AR-DRGs (inpatient hospitalisation), AECC codes (emergency department visits), MBS (renal biopsy, renal ultrasound, GP visits) and PBS items (telmisartan, frusemide, empagliflozin, fluvastatin, patiromer). Pre-dialysis health state: Based on specified AR-DRGs (inpatient hospitalisation), MBS (urine albumin/creatinine ratio, eGFR, UEC, HbA1c, fasting lipids, FBC, GP visits) and PBS items (difelikefalin, epoetin alfa). Dialysis health state: Based on specified AR-DRGs (inpatient hospitalisation), MBS (urine albumin/creatinine ratio, eGFR, UEC, HbA1c, fasting lipids, FBC, GP visits) and PBS items (difelikefalin, epoetin alfa). Kidney transplant health state: Based on specified AR-DRGs (inpatient hospitalisation) and MBS costs (urine albumin/creatinine ratio, eGFR, UEC, HbA1c, fasting lipids, FBC, GP visits). Post kidney transplant health state: Based on specified AR-DRGs (inpatient hospitalisation) and MBS costs (urine albumin/creatinine ratio, eGFR, UEC, HbA1c, fasting lipids, FBC, GP visits).

Source: Constructed during the evaluation with reference to the Section 3 economic model Excel workbook.
Abbreviations: AA, amyloid A; AECC, Australian Emergency Care Classification; AR-DRG, Australian Refined Diagnosis Related Groups; BSC, best supportive care; DPMQ, dispensed price for maximum quantity; eGFR, estimated glomerular filtration rate; FBC, full blood count; FMF, familial Mediterranean fever; GP, general practitioner; HbA1c, glycosylated haemoglobin; IgA, immunoglobulin A; MBS, Medicare Benefits Schedule; SF-10, Short Form-10 Health Survey; SF-12, Short Form-12 Health Survey; UEC, urea electrolytes creatinine.

6.43 The economic model was a Monte Carlo microsimulation constructed in Microsoft Excel. Each cycle, two random numbers between 0 and 1 were generated using the Excel rand() function. Events and/or health state transitions each cycle were assumed to occur if the predefined weekly probability of the event/transition was lower than the random number. Use of the same random number for multiple possible events each cycle resulted in correlation of some events/transitions in a given cycle, as the probability for multiple events and/or transitions may have been lower than the random number generated in a given cycle. For example, patients in the BSC arm who develop AA amyloidosis due to chronic inflammation almost invariably moved into the pre-dialysis health state in the same cycle, as the probability for pre-dialysis was typically higher than the probability of developing AA amyloidosis (and the model did not preclude patients from moving to pre-dialysis in the same cycle that AA amyloidosis occurred).

6.44 Individual patient characteristics (sex, age, weight, baseline flares) were simulated for patients by randomly drawing values from distributions fitted to the baseline characteristics of paediatric patients in the CLUSTER trial. The patient distributions were informed by sparse data, with only 29 patients included in the paediatric cohort.

6.45 The submission stated that a microsimulation Monte Carlo model was used given the heterogeneity observed in the CLUSTER trial, for essential patient and treatment characteristics which affect the rate of disease progression, and which prevent an 'average' patient from being modelled via a standard cohort approach. The ESC noted

the submission's argument that the model approach was intended to capture patient characteristics, but considered that it was not justified in the context of being informed by sparse data from only 29 paediatric patients. The ESC considered that a Markov Cohort model would have been a preferable approach. The Pre-PBAC Response reasserted that use of a Monte Carlo model is consistent with the PBAC Guidelines (v5.0), which recognise microsimulation as appropriate when patient-level heterogeneity materially affects outcomes. The Response stated that patients experience flare-driven treatment changes and that each patient's unique flare risk creates a distinct treatment trajectory. The Response stated that the model includes several conservative assumptions and that there is less than 10% variability, which demonstrates real-world heterogeneity and not model instability. The Response maintained the economic evaluation is fit for decision making and stated that would not be possible to address remaining uncertainties in a revised economic model.

6.46 In the absence of data on flare outcomes among patients in the BSC arm (due to high numbers of patients crossing over to receive canakinumab treatment in the CLUSTER trial), the flare rate among patients in the BSC arm was assumed to be the same as at baseline (mean of 22.4 flares per year). It is unclear whether the baseline flare rates among patients who participated in the trial will reflect the baseline flares rate among patients in the proposed PBS population. There were limited details provided on how baseline flare activity, which was collected as part of the baseline demographic and disease characteristics, was defined.

6.47 The submission assumed that a reduction in the number of flares associated with canakinumab treatment would be associated with a reduction in the risk of developing AA amyloidosis and the subsequent development of end-stage renal disease.

6.48 In the economic model, the rate of AA amyloidosis development among patients with and without chronic inflammation were derived from Varan et al. (2019). Varan et al. conducted a retrospective study of medical records for a cohort of patients with FMF treated at a tertiary hospital in Türkiye. Patients were included in the study if they had a confirmed diagnosis of FMF (based on Tel Hashomer criteria) and had regular follow-up (defined as the presence of at least three clinical visits per year) for ≥5 years. Among 146 patients with no diagnosis of amyloidosis at baseline (mean age 37.5 years; 69.2% female), 37 (25.3%) had evidence of chronic inflammation (defined as persistent elevation of C-reactive protein levels during attack-free periods above the upper limit of normal, which was evident at all consecutive visits by an individual patient). Amyloidosis was diagnosed in 5 patients during the 5-year follow-up period, including 4/37 patients (10.8%) with evidence of chronic inflammation and 1/109 patients (0.9%) without evidence of chronic inflammation.

6.49 While there appears to be a relationship between inflammation associated with FMF and the development of AA amyloidosis/renal impairment, it is unclear whether the economic model adequately reflects the natural history of AA amyloidosis development among patients with FMF.

6.50 The following additional issues were noted during the evaluation:

- The mean age of patients included in the Varan et al. (2019) study was 37.5 years (age range: 21 to 65 years). The results of the study may not be applicable to the proposed PBS population (paediatric patients). The rate of amyloidosis development among paediatric patients is likely to be lower than for adult patients.
- The submission assumed that a threshold of >3.25 flares per year was required for the development of AA amyloidosis. However, there was a lack of available evidence to enable the relationship between the number of flares per year and the time to development of AA amyloidosis to be characterised.
- Amyloidosis could develop in any cycle of the model (i.e., if the random number was higher than the pre-defined probability of developing AA amyloidosis), whereas in clinical practice, damage due to AA amyloidosis would accumulate over time and be diagnosed later in the disease course.
- The degree to which colchicine (used by the majority of patients in the CLUSTER trial and in the proposed PBS population) mitigates the development of AA amyloidosis and associated renal complications is unclear.
- The probability of transitioning from the AA amyloidosis to the pre-dialysis/dialysis health state was estimated based on the proportion of patients with AA amyloidosis progressing to dialysis in a study conducted by Ahbap et al. (2014). The Ahbap et al. estimate lacked applicability to the proposed PBS population, as the population included in the study consisted of adult patients and the study was not limited to patients with AA amyloidosis associated with FMF.

6.51 Overall, the ESC considered that the assumption that reduced flares would lead to a reduction in the risk of AA amyloidosis and development of end-stage renal disease was clinically reasonable, however quantifying the magnitude of changes in long term outcomes was highly uncertain.

6.52 The health state utility for patients in the no AA amyloidosis health state was derived from an analysis of SF-12 data from the CLUSTER trial. Physical component and mental component scores among adult patients who achieved a complete response in Stage 2 of the trial were mapped to an EQ-5D-3L utility using a mapping algorithm published by Sullivan et al. (2006). The applicability of the adult quality of life data to the proposed paediatric population is unclear.

6.53 Utilities for paediatric patients with no AA amyloidosis experiencing a disease flare were based on SF-10 physical and mental component scores for 'on-flare' reported by Kuemmerle-Deschner et al., mapped to an EQ-5D-3L utility using the algorithm published by Sullivan et al. (2006). The ESC considered that it was incorrect to map paediatric SF-10 results to an EQ-5D-3L utility using the Sullivan et al. algorithm, as the algorithm is for use with SF-12 data only, and SF-10 represents a different quality of

life instrument with a different scoring methodology. There was a large difference between the utility obtained by mapping the SF-10 data (0.590; based on paediatric data) and the utility obtained by mapping SF-12 data reported by Kuemmerle-Deschner et al. (0.730; based on adult data) using the Sullivan et al. algorithm. The PSCR acknowledged that the Sullivan et al. algorithm was developed for SF-12 data but considered the approach a pragmatic methodological choice given that no validated SF-10 to EQ-5D algorithm exists. The submission did not adequately justify the use of external data to inform the flare utility, given that SF-12 physical and mental component scores among adults on Day 1 of the randomised phase of the trial were available (i.e., when patients were experiencing the index flare). The PSCR stated that the trial-based flare utilities reflect an adult population and were confounded by the use of canakinumab rescue doses that would have artificially reduced flare severity compared to the true burden in a BSC setting. Additionally, the flare utility was applied for the full 1-week model cycle despite the average duration of flares typically being <7 days. The PSCR stated that while the mean flare duration in the trial was <7 days, it was implausible that a patient would immediately return to their full baseline quality of life. As such, the PSCR asserted that it was reasonable to apply the flare disutility for a week to capture the impact of symptoms beyond the flare duration. The ESC noted that no data were presented to characterise the frequency and severity of prodromal/postdromal flare symptoms and considered that it is unlikely to be reasonable to apply the full disutility associated with flares on days in which patients are experiencing prodromal/postdromal symptoms.

6.54 The utility for patients in the AA amyloidosis health state was assumed to be the average of the utilities included for patients with flare and the utility for the pre-dialysis health state. This assumption was not adequately justified.

6.55 Costs included in the model were predominantly based on sponsor assumptions and were considered to be highly uncertain:

- The assumption that hospital attendance (inpatient hospitalisation or emergency department attendance) would be required for 74.1% of all flares for all patients lacked face validity and is likely to have substantially overestimated costs associated with flare. The PSCR argued that FMF flares in children are indistinguishable from symptoms of life-threatening bacterial infections and that presenting symptoms warrant immediate referral to an emergency department according to Australian hospital guidelines. However, the ESC considered that patients with an established diagnosis of FMF would be less likely to attend hospital if they develop FMF flare symptoms.
- Costs associated with flare management were assumed to be additive to health state costs, which the ESC considered resulted in a high likelihood that costs associated with hospitalisation, emergency department attendance, pathology and GP management were double counted.

- All patients in the canakinumab plus BSC arm of the model were assumed to initiate canakinumab at a dose of 150 mg (or 2 mg/kg up to 150 mg) every 4 weeks. Patients who experience a flare receive an additional dose of canakinumab 150 mg (or 2 mg/kg up to 150 mg) in the next cycle. Patients who remain flare free for 16 consecutive weeks switch to canakinumab treatment every 8 weeks. Patients on canakinumab 8-weekly treatment who experience a flare revert to 4-weekly dosing. In the model base case, maintenance canakinumab doses of 300 mg every 4 weeks were not included. The submission assumed that patients who switch to 8-weekly canakinumab dosing would have the same risk of flares as patients on 4-weekly dosing. The ESC noted this assumption was uncertain. The ESC considered that by excluding the 300 mg maintenance dose, the model is likely to have underestimated the costs associated with canakinumab treatment.

6.56 In the base case, patients who develop amyloidosis are assumed to discontinue canakinumab treatment at the time of amyloidosis diagnosis. This assumption was not reasonable given that the proposed restriction does not require treatment discontinuation if patients are diagnosed with AA amyloidosis, and patients are likely to remain on canakinumab treatment to prevent flare recurrence and potentially reduce the rate of AA amyloidosis progression.

6.57 The submission assumed that 2.86% of patients would discontinue treatment with canakinumab each year. It is unclear whether the assumed discontinuation rate, which resulted in a relatively high number of discontinued patients over the 70-year time horizon, will reflect treatment utilisation in clinical practice, given that patients in the PBS population would be able to reinitiate treatment later.

6.58 Table 8 summarises the key drivers of the economic model. The ESC noted that there were a high number of key drivers, all of which favoured canakinumab.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Canakinumab dosing assumptions	It is unclear whether the dosing assumptions included in the model will reflect dosing of canakinumab in Australian clinical practice, particularly given differences in dosing recommendations between the canakinumab product information and clinical guidelines. Refer para 6.55.	High, favours canakinumab
Canakinumab treatment persistence	Patients who develop amyloidosis are assumed to discontinue canakinumab treatment at the time of amyloidosis diagnosis and 2.86% of patients were assumed to discontinue treatment with canakinumab each year. Refer para 6.56-6.57	High, favours canakinumab
Extrapolation	There was a substantial amount of uncertainty associated with the extrapolation of clinical trial data relating to flare rates and adverse events for up to 70 years. It is unclear whether the model adequately captured the relationship between flares/underlying chronic inflammation and the development of AA amyloidosis and subsequent renal complications. Refer para 6.49-6.51	High, favours canakinumab
Flare costs	Largely based on sponsor assumptions, with a high likelihood of double counting. Refer para 6.41	High, favours canakinumab
Utilities	It was incorrect to map paediatric SF-10 results to an EQ-5D-3L utility using the Sullivan et al. algorithm, as the Sullivan et al. algorithm is for use with SF-12 data only. The submission did not adequately justify the use of external data to inform the flare utility. It would be preferable to derive flare and no flare utilities from the same source to ensure consistency between the quality of life measures. Refer para 6.38	Moderate, favours canakinumab
Baseline flare rate	The flare rate among patients in the BSC arm was assumed to be the same as at baseline (22.4 flares per year). Refer Para 6.32	Moderate, favours canakinumab

Source: Constructed during the evaluation based on Section 3 pp211-260 of the submission and the Section 3 economic model Excel workbook.

Abbreviations: 3L, 3 level; AA, amyloid A; AECC, Australian Emergency Care Classification; AR-DRG, Australian Refined Diagnosis Related Group; BSC, best supportive care; SF-10, Short-Form 10-item Health Survey; SF-12, Short-Form 12-item Health Survey.

6.59 The steps and results of the economic evaluation as presented in the submission are in Table 9.

Table 9: Steps in the economic evaluation

Step	Description	Incremental Cost	Incremental Outcome	Cost/Outcome
Step 1a	Modelled analysis over 16 weeks including treatment costs only, undiscounted.	$[redacted]	0.7042	$[redacted][1] per responder [a]
Step 1b	As for Step 1a.	$[redacted]	0.5504	$[redacted][2] per complete response [b]
Step 2a	Time horizon increased to 1 year, all costs included.	$[redacted]	21.5	$[redacted][3] per flare avoided
Step 2b	As for Step 2a.	$[redacted]	0.77	$[redacted][2] per responder-year [c]
Step 3	Time horizon increased to 70 years, discounting of all costs and outcomes.	$[redacted]	1.10	$[redacted][4] per life year gained
Step 4	As for Step 3, with inclusion of health state utilities.	$[redacted]	2.15	$[redacted][5] per QALY gained

Source: Table 3.9, p255 of the submission.
Abbreviations: QALY, quality-adjusted life year.
[a] Based on the number of patients who did not experience a disease flare during Stage 2 of the CLUSTER trial.
[b] Resolution of the index flare at Day 15 and no new disease flares over 16 weeks of treatment during Stage 2 of the CLUSTER trial.
[c] Based on the proportion of patients who did not experience a disease flare over the initial year of treatment.
The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*
[2] *$95,000 to < $115,000*
[3] *$0 to < $5,000*
[4] *$455,000 to < $555,000*
[5] *$255,000 to < $355,000*

6.60 Table 10 presents the results of the economic evaluation (obtained using 1 run of 1,000 simulated patients).

Table 10: Results of the economic evaluation

Component	Canakinumab + BSC	BSC	Increment
Costs	$[redacted]	$967,202	$[redacted]
Life years gained	16.426	15.323	1.104
QALYs	13.165	11.014	2.151
Incremental cost per life year gained			**$[redacted][1]**
Incremental cost per QALY gained (base case)			**$[redacted][2]**

Source: 'Results' tab of the updated Section 3 economic model Excel workbook provided during the evaluation.
Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.
The redacted values correspond to the following ranges:
[1] *$455,000 to < $555,000*
[2] *$255,000 to < $355,000*

6.61 The results of the microsimulation were associated with a high degree of variability (ranging from $255,000 to < $355,000 to $255,000 to < $355,000 per QALY gained based on 10 runs of 1,000 simulated patients) and remained unstable even when substantially higher numbers (i.e., up to 15,000 simulated patients) were used. The variability in the modelled results made it difficult to reproduce the sponsor's base case ICER, which was at the lower end of the range, and to interpret the results of sensitivity analyses. The model did not include functionality to use a seed to model sensitivity analyses using the same sets of 1,000 patient characteristics and random numbers. Additionally, run times for the model were relatively long (approximately 25 minutes per 1,000 simulated patients), which impacted the ability to assess model functionality and limited the number of sensitivity analyses that could be conducted

during the evaluation. The PSCR claimed that the results of the economic model stabilise and converge with a sufficient number of simulations. However, the ESC disagreed with this this statement, noting results did not stabilise and converge even with 15,000 simulations, which takes approximately 6 hours to run. The ESC was of a view that the lack of ability to seed the model severely limited its usefulness for PBAC decision making, as it was not possible to adequately characterise the uncertainty related to key assumptions and variables. The Pre-PBAC Response stated, "While a seed function would improve reproducibility for small-effect analyses, its absence is largely consequential only when tested parameters do not meaningfully impact the model's results".

6.62 For every patient treated with canakinumab + BSC versus BSC and followed for up to 70 years, the economic model estimated that there would be:

- An additional 1.1 years of life.
- An additional 2.2 quality-adjusted years of life.
- Additional active treatment costs of $[redacted], additional adverse event costs of $297, a reduction in flare management costs of $495,957, a reduction in pre-dialysis/dialysis costs of $74,763, and a reduction in kidney transplant/post kidney transplant costs of $20,676.

6.63 The model appeared to be sensitive to a number of different inputs, including changes in the discount rate, the inclusion of adult patients, removal of treatment discontinuations, exclusion of dose down-titration to 8-weekly, assumption of lower baseline flare rates, alternative health state utilities; and correction of errors associated with canakinumab flare rates and the application of the subsequent amyloidosis cost. However, the results of the sensitivity analyses should be interpreted with caution due to the underlying variability in the modelled results.

6.64 The Pre-PBAC Response noted that the cost per responder (no flares) using a 16-week time horizon, trial based only and with only treatment costs included, was estimated to be $75,000 to < $95,000 per responder. The Response also provided estimates of the additional school days attended per year, savings in lost income for patients and carers, educational outcomes associated with canakinumab treatment.

Drug cost/patient/year

6.65 Due to the structure of the CLUSTER trial, which included multiple treatment phases with cross over of patients between treatment arms, the mean dose of canakinumab in the trial could not be estimated. Patients received canakinumab for up to 112 weeks.

6.66 Costs associated with canakinumab treatment in the economic model were based on the average canakinumab utilisation among 1,000 simulated patients. Due to the structure of the model, the underlying mean dose among the 1,000 simulated patients

could not be ascertained. Based on the proposed effective DPMQ of $[redacted] (23.14%/76.86% public/private hospital split) per 1 x 150 mg vial, the cost per patient per year for patients receiving canakinumab 150 mg every 4 weeks was $[redacted]. The cost per patient per year for patients receiving canakinumab 150 mg every 8 weeks was $[redacted]. The submission assumed 100% treatment adherence and an annual treatment discontinuation rate of 2.86%.

6.67 Costs for canakinumab in the financial estimates were based on 6-monthly treatment periods, in which all patients receive a base dose of canakinumab 150 mg (or 2 mg/kg for body weight ≤40 kg) every 4 weeks. In addition, a fixed proportion of patients (36.27% during initial treatment, and 15.43% during each 6-month continuing period) were assumed to experience a disease flare and receive a single additional canakinumab 150 mg (or 2 mg/kg for body weight ≤40 kg) top-up dose, while the remaining patients had their base dose frequency adjusted after 16 weeks to every 8 weeks. This resulted in 11.68 scripts (with 1 x 150 mg canakinumab vial) per patient per year for initiating and 9.77 scripts per patient per year for continuing patients. Based on the proposed effective DPMQ of $[redacted] (23.14%/76.86% public/private hospital split), the cost per patient per year for initial treatment was $[redacted]. The cost per patient per year for continuing patients was $[redacted]. The submission assumed 100% treatment adherence and an annual treatment discontinuation rate of 2.86%.

6.68 The PBAC considered that the assumptions regarding dosing applied in the financial estimates were not well-justified as patients experiencing flares on treatment were assumed to receive top up doses rather than increasing to a 300 mg (or 4 mg/kg) maintenance dose. The PBAC considered that calculation of the cost per patient for canakinumab should assume:

- All patients initiate treatment on a dose of 1 vial every 4 weeks for the first 6 months.
- For subsequent treatment dosing should be assumed to be consistent with utilisation for patients on canakinumab at the end of Stage 3 of the CLUSTER trial.
- Annual discontinuation of 2.86% per year.

Table 11: Cost per patient calculations

	Number of vials	Cost [d]
First 6 months (1 vial every 4 weeks) [a]	6.52	$[redacted]
Subsequent 6 months [b]	5.12	$[redacted]
Total first year	11.64	$[redacted]
Total subsequent year [b,c]	10.23	$[redacted]

a Assumes 1 vial per 4 weeks
b Assumes 58.8% 150 mg Q8W, 23.5% 150 mg Q4W, 9.8% 300 mg Q8W and 7.8% 300 mg Q4W
c Includes annual discontinuation of 2.86%
d Based on a cost per vial of $[redacted] as proposed in the submission

Estimated PBS usage & financial implications

6.69 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact of listing canakinumab for the treatment of paediatric patients with FMF who are intolerant or resistant to colchicine.

6.70 Table 12 presents the key inputs used to derive the financial estimates.

Table 12: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Incident/ prevalent patients	[redacted][1] prevalent patients in Year 1 of listing; [redacted][1] incident patients per year	Review of two Victorian Children's Hospital databases detailed in a clinician letter from an Australian paediatric rheumatologist. There were [redacted][1] FMF patients recorded in the database over 15 years, with prevalence estimated at [redacted] per 100,000 people based on the Victorian population under the age of 19 years (1.065 million); and incidence of [redacted] patients per 100,000 people based on the same population, divided by 15 (years of data collection).	The number of cases in the database may be an underestimate of total patient numbers given that some patients may be managed in other healthcare settings (e.g., private rheumatology clinics). It is unclear whether patient numbers from Victorian children's hospitals are representative of prevalence and incidence in other areas of Australia. It was not possible to determine whether the incidence of FMF in Australia has changed over time based on the data provided in the submission. The PSCR acknowledged that there are no data available to reliably inform the number of patients in other healthcare settings, differences in incidence rates over time, or differences in cultural demographics across Australia.
Proportion of patients with colchicine resistance or intolerance	15.2%	Bustaffa (2025) – an observational study of 876 patients with FMF; with 15.2% sourced from the proportion of patients treated with IL-1 inhibitors.	It is unclear whether the proportion of patients receiving IL-1 inhibitors is representative of the rate of colchicine resistance or intolerance. Other published estimates report rates of between 5% and 10% (e.g., Ter Haar 2013; Haslak 2025). The submission tested the impact of changes to this proportion in sensitivity analyses.
Treatment utilisation			
Uptake rate	[redacted]%	Assumption, reflecting high unmet clinical need and severe symptom burden. Paediatric rheumatologists advised they would treat all of their paediatric patients with canakinumab.	While high uptake of canakinumab is likely in the context of high unmet clinical need, [redacted]% uptake is unlikely to be realised in clinical practice. The PBAC considered that uptake in

Data	Value	Source	Comment
			an adult population is likely to be lower, approximately [redacted]%.
Discontinuation rate	2.86% per year	The submission estimated a treatment discontinuation rate of 2.86% per year by converting the number of treatment discontinuations in the CLUSTER trial over 112 weeks to an annual rate. The discontinuation rate was applied to the prevalent population only (on the basis that the number of incident and grandfathered patients was too low for the discontinuation rate to change the number of patients treated each year).	It is unclear if discontinuations in the trial setting would be representative of treatment persistence in clinical practice. The submission did not include any treatment discontinuations due to achieving disease remission (as described in Section 1 of the submission). The proposed restrictions for canakinumab do not propose a stopping rule or definition of a response to continue treatment.
Proportion of patients with disease flare (used to determine canakinumab dose regimens)	Initial: 36.27% Continuing: 15.43%	Derived from individual patient data for the paediatric population of the CLUSTER trial (Stage 2 for flares during initial treatment, and Stage 4 for flares during continuing treatment), with probabilities of experiencing a flare calculated for 6-monthly treatment cycles (6 months of initial treatment followed by continuing treatment in 6-monthly periods). Patients with flares received an additional top-up dose while patients without a flare had their dose frequency reduced from 4-weekly to 8-weekly until the end of each 6-month period (see below).	Calculating the estimated number of canakinumab scripts based on 6-month periods with a fixed proportion of patients in each cycle experiencing a flare with a dose top-up, or no flare with a reduction in treatment frequency after 16 weeks, resulted in all down-titrated patients returning to the base dose at the start of the next 6 month period, rather than continuing on reduced dose frequency, which is unlikely to reflect use in clinical practice.
Scripts dispensed [a]	Yr 1: [redacted][1] Yr 2: [redacted][1] Yr 3: [redacted][1] Yr 4: [redacted][1] Yr 5: [redacted][1] Yr 6: [redacted][1]	The base dose regimen for all patients was canakinumab 150 mg (or 2 mg/kg) every 4 weeks (13.04 vials per patient per year). For each 6-month period, a single top up dose of 150 mg or 2 mg/kg (1 vial) was added for the proportion of patients who experienced a flare during that period. For the remaining proportion of patients who did not experience a flare during the 6-month period, the base dose was reduced after 16 weeks to 8-weekly frequency for the remainder of the 6-month period.	The PBAC considered the assumption that patients experiencing flares on treatment would receive top up doses rather than increasing to a 300 mg (or 4 mg/kg) maintenance dose was not reasonable. The exclusion of the 300 mg maintenance dose from the financial impact estimates is likely to underestimate the costs associated with canakinumab treatment. The PBAC considered that dosing should reflect the patient dosing at the end of Stage 3 of the CLUSTER trial to account for dosing adjustments: 150 mg Q8W: 30/51 (59%) 150 mg Q4W: 12/51 (24%) 300 mg Q8W: 5/51 (10%) 300 mg Q4W: 4/51 (8%)

Source: Table 4.1, pp262-264 of the submission.

Abbreviations: ABS, Australian Bureau of Statistics; CAPS, Cryopyrin-associated autoinflammatory periodic syndromes; FMF, familial Mediterranean fever; GP, general practitioner; IL, interleukin; MBS, Medicare Benefits Schedule; Yr, year

[a] The submission's utilisation estimates also included calculations of the number of vials required to achieve the higher canakinumab dose of 300 mg (or 4 mg/kg for patients with body weight 40 kg and under). Patients with a lower body weight are able to achieve the higher canakinumab dose with only one 150 mg vial. However, the submission's utilisation estimates for each patient group ('1 vial' versus '2 vials' required for the higher canakinumab dose) were the same, as no-one in the submission's financial estimates receives the higher dose, rather, the proportion of patients experiencing a flare receive one additional 'top up' dose of canakinumab 150 mg (or 2 mg/kg).

The redacted values correspond to the following ranges:

[1] < 500

6.71 Table 13 presents the estimated use and financial implications of listing canakinumab on the PBS.

Table 13: Estimated utilisation and net cost of canakinumab to the PBS (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost of canakinumab to the PBS						
Total patients [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total script numbers [b]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Net PBS/RPBS cost	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to MBS [c]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net cost to PBS/RPBS/MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]

Source: Table 4.2, pp265-266; Table 4.4, p266; Table 4.12, p271; Table 4.20, p278 of the submission; UCM – Ilaris crFMF PBAC Submission Excel workbook, Attachment 6 of the submission.

[a] Assumes [redacted]% uptake of canakinumab, with 2.86% discontinuations per year applied to prevalent patients only, and includes < 500 grandfathered patients added to each year of listing

[b] Script numbers were estimated based on an initial 6 months of treatment then continuing treatment split into 6 monthly periods. Within each period, all patients started treatment on canakinumab 150 mg (or 2 mg/kg for patients with body weight ≤ 40 kg; equivalent to 1 vial/script) every 4 weeks. A single top up dose of 150 mg (or 2 mg/kg; 1 vial/script) was added for the proportion of patients who experienced a flare during that period (36.27% during initial treatment, and 15.43% during each 6-month continuing period), based on individual patient flare data whilst on canakinumab treatment from the CLUSTER trial. For the remaining patients who did not experience a disease flare, after 16 weeks at the base dose, the dose frequency was reduced from 4-weekly to 8-weekly for the remainder of the 6-month period. At the start of the next 6-month period, all patients reverted to the base dose and the probability of flare/no flare and associated top up/reduced doses was calculated again.

[c] Changes to MBS item utilisation (MBS item number) with a PBS listing for canakinumab included: increased testing for tuberculosis (69471) and full blood count (65070), one administration of canakinumab (13950, parenteral canakinumab administration) with the remaining treatment assumed to be self- administered by the patient or carer, increased GP visits for treatment of infection adverse events (23), reduced specialist consultations due to reduced emergency room visits and monitoring requirements (104) with reduced requirements for testing of: C-reactive protein level (66512), full blood count (65070) and ferritin level (66593).

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *$0 to < $10 million*

[3] *net cost saving*

6.72 Based on the submission estimates the net cost to the PBS/MBS of listing canakinumab for paediatric patients with crFMF was $0 to < $10 million in Year 1 of listing, increasing to $0 to < $10 million in Year 6, a cumulative total of $30 million to < $40 million over the first 6 years of listing.

6.73 The evaluation considered the estimated utilisation of canakinumab was uncertain for the following reasons:

- The number of prevalent and incident patients with FMF may be underestimated, as the hospital databases used to inform the prevalence and incidence estimates may not account for patients managed in other healthcare settings (e.g., private rheumatology clinics). However, it is unclear whether the prevalence and incidence among patients included in the hospital databases of the two Victorian children's hospitals are representative of the prevalence and incidence in the wider Australian population due to differences in population demographics. Additionally, it was not possible to determine whether the incidence of FMF in Australia has changed over time based on the data provided in the submission.

- The addition of grandfathered patients to the estimated eligible population was not reasonable given that they would already be captured in the prevalent patient pool. The PSCR stated that the grandfathered patients were included to capture paediatric patients who initiated non-PBS canakinumab, but who are now over 18 years of age.
- It is unclear whether the proportion of patients receiving IL-1 inhibitors in the Bustaffa (2025) study is a reasonable proxy for the rate of colchicine resistance or intolerance. Other published estimates report rates of colchicine resistance/intolerance of 5% to 10% (e.g., Ter Haar 2013; Haslak 2025). The ESC considered that the proportion of patients with colchicine intolerance could be substantially higher than estimated, and that there was a risk that with the availability of canakinumab on the PBS that the proportion of patients deemed to be intolerant to colchicine may increase.
- It is unclear whether the dosing assumptions used in the submission to derive the number of scripts per year will reflect dosing of canakinumab in Australian clinical practice, particularly given differences in dosing recommendations between the canakinumab product information and clinical guidelines.
- The assumption that patients experiencing flares on treatment would receive top up doses rather than increasing to a 300 mg (or 4 mg/kg) maintenance dose was not reasonable and is likely to underestimate the costs associated with canakinumab treatment.

6.74 The PSCR presented revised financial estimates, having 1) corrected the proportion of each 6-monthly cycle that patients will be on the base dose or down-titrated, so that patients who remain flare-free in the subsequent 6-month cycle will remain on the down-titrated dose regimen, and 2) changed the assumption that the proportion of adverse events requiring a GP visit would be 100% rather than 25%. The revised financials estimated a slightly reduced net cost to the PBS/MBS of listing canakinumab for paediatric colchicine-resistant FMF $0 to < $10 million in Year 1 of listing, increasing to $0 to < $10 million in Year 6). The PSCR also presented sensitivity analyses examining the impact of colchicine resistance/intolerance estimates and assuming no down-titration to the base dose (see Table 14).

Table 14: Revised financial estimates – sensitivity analyses presented in the PSCR

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Colchicine resistant/intolerance: 4.2%	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Colchicine resistant/intolerance: 18.8%	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
No down-titration	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]

The redacted values correspond to the following ranges:

[1] $0 to < $10 million

Quality Use of Medicines

6.75 The submission stated that targeted education for clinicians will be implemented to improve awareness and the accurate diagnosis of colchicine-resistant FMF, including genetic testing. To support the correct use of canakinumab, the sponsor will provide patient and carer education on administration technique and monitoring for side effects.

Financial Management – Risk Sharing Arrangements

6.76 The ESC noted that the PBAC may wish to consider the need for a Risk Sharing Arrangement to mitigate the risk of 1) increasing numbers of colchicine intolerant patients given the availability of a PBS-listed alternative, 2) use of higher and more frequent dosing of canakinumab than estimated, and 3) the cost to the Government given the uncertainty around the incidence and prevalence of FMF.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Highly Specialised Drugs Program) listing of canakinumab for the treatment of treatment of colchicine-resistant or intolerant familial Mediterranean fever (FMF). The PBAC noted the high unmet need for effective treatments for this rare disease with a high impact on quality of life and poor life expectancy and considered that it would be appropriate for treatment to be available for both children and adults with crFMF. The PBAC considered that the claim of superior effectiveness for canakinumab over standard care was reasonable, noting that treatment with canakinumab was associated with a reduction in febrile attacks in a high proportion of patients. Although longer-term effects remain uncertain, the PBAC noted that there was biological plausibility that the demonstrated reduction in serum amyloid would lead to reduced kidney failure. The PBAC considered that the cost-effectiveness of canakinumab was uncertain due to the limited data informing the economic model, but that in the context of this life-limiting disease in a small number of patients, canakinumab would be considered cost-effective with a reduction in the annual treatment cost. The PBAC noted that this recommendation was in line with other treatments for rare diseases funded on the PBS, accounting for clinical need, available evidence, nature of the benefits and size of the patient population. The PBAC considered that a risk sharing arrangement would be required to manage the uncertainty associated with the long-term clinical benefit for canakinumab and the uncertain dosing and duration of therapy.

7.2 The PBAC considered there is a high clinical need for new therapies for FMF, noting the severity of symptoms and impact on patient quality of life and life expectancy. The PBAC noted that there are no PBS-listed treatment options for patients who are intolerant or resistant to maximally tolerated doses of colchicine (crFMF). The PBAC noted the input from clinicians regarding anakinra, which has a very high needle

burden that may result in issues with adherence and efficacy, and is funded via local hospital drug committees, meaning it is not available to all patients.

7.3 The PBAC noted that FMF is a rare disease that disproportionately affects culturally and linguistically diverse groups. The PBAC noted that colchicine is effective in 80 to 90% of patients and considered that canakinumab is appropriately positioned for patients with crFMF. The PBAC considered that canakinumab should be used in combination with the maximum tolerated dose of colchicine unless it is contraindicated.

7.4 The PBAC noted the strong consumer support for the listing of canakinumab, with comments received reflecting the debilitating nature of the disease, the lack of effective treatments, the pressure for patients to continue colchicine therapy despite clear adverse effects, and the lack of justification for limiting canakinumab by age, given the disease does not fundamentally change when patients transition to adulthood.

7.5 The PBAC noted that the submission requested limiting canakinumab to patients who initiated treatment prior to 18 years of age. However, given the high clinical need and demonstrated efficacy of canakinumab in both paediatric and adult patients, the Committee considered that the listing should be age agnostic. The PBAC considered that over time it is likely that newly diagnosed crFMF patients will initiate treatment in childhood.

7.6 The PBAC accepted the submission's proposed comparator of BSC. The PBAC considered that while anakinra is being used to treat crFMF for some patients in Australia, that it is not a suitable comparator given it is not reliably available or widely used for this condition in Australia.

7.7 The PBAC noted that the results of the CLUSTER trial indicated that canakinumab was highly effective at reducing disease flare and markers of subclinical inflammation (CRP and SAA), with a complete response rate across both paediatric and adult patients of 61.3% for canakinumab at week 16 compared to 6.3% for placebo. The PBAC noted that persistence on treatment in the trial was very high and that most placebo patients crossed over to canakinumab in the randomised withdrawal (Stage 3) and open label (Stage 4) phases. The PBAC considered that the reduction of inflammation would lead to lower SAA and reduced AA amyloidosis and renal disease over time.

7.8 The PBAC considered that the data presented supported the submission's claim that canakinumab has superior effectiveness to BSC, but that the high crossover from placebo to canakinumab in the trial and the lack of longer term clinically relevant outcomes (AA amyloidosis and renal disease) made it difficult to determine the magnitude of benefit. The PBAC considered that while comparative harms were hard to quantify given the high crossover from placebo to canakinumab in the trial, that the submission's claim of inferior safety to BSC was reasonable.

7.9 The PBAC noted the economic evaluation presented a stepped cost-effectiveness/cost-utility analysis, based on a Monte Carlo microsimulation model. The PBAC noted the sponsor's argument that the model was intended to capture patient characteristics, however, considered that the limited trial data informing the model (given the rare indication) resulted in a high level of uncertainty in the modelled costs and outcomes. Further, the PBAC noted the model relied on a number of assumptions and data sources that may not be reasonable or applicable to the patient population, with key drivers of the model favouring canakinumab. The PBAC considered that the resulting incremental cost per life year gained for canakinumab compared to BSC was high and likely to be underestimated. The PBAC agreed with the ESC that the model structure was not reliable for decision-making. However, given the paucity of data available for this rare condition, the PBAC acknowledged that revising the model structure or inputs is unlikely to resolve the uncertainty associated with the modelled outcomes. The PBAC noted that the cost per responder (no flares) using a 16-week time horizon, direct trial outcomes and treatment costs only, was estimated to be $75,000 to < $95,000 and the cost per responder-year (all costs included) was estimated to be $95,000 to < $115,000. The cost per flare avoided was estimated to be $0 to < $5,000 over a 1 year time horizon.

7.10 The PBAC reflected on previous determinations made for other rare diseases where no effective alternative therapies were available. The PBAC compared the available evidence, nature of the benefits, ICERs, numbers of patients expected to be treated, and the cost per patient per year for canakinumab at the proposed price, with other high-cost treatments for rare diseases funded on the PBS. The PBAC considered that in the context of this rare and life-limiting disease, and with consideration of the potential impacts on quality of life and the expected longer-term reduction in kidney failure, the cost per responder for canakinumab would be considered acceptable with an annual treatment cost of $[redacted] for the first year of treatment, noting that costs may be lower in subsequent years due to reducing dosing and discontinuation. In providing this advice the PBAC also noted that the magnitude of benefit for canakinumab may be somewhat less in patients initiating treatment in adulthood compared with paediatric patients, and that the approach to dosing used in Australian clinical practice is uncertain. The PBAC considered that calculation of the annual treatment cost per patient should assume dosing as per the end of Stage 3 of the CLUSTER trial, to reflect the proportion with increased dosing due to flares and dose reductions in patients with ongoing response to treatment (see Table 11).

7.11 The PBAC noted that the submission used an epidemiological approach to estimate the utilisation and financial impact of listing canakinumab for the treatment of paediatric patients with FMF who are intolerant or resistant to colchicine. The PBAC noted that the prevalence of FMF in Australia and the proportion of patients resistant or intolerant to colchicine is uncertain, with limited Australian data available. The PBAC considered that, given its recommendation to include treatment of adult patients, the estimates should account for use in prevalent adult crFMF patients. The

Committee considered that it would be reasonable to use the proportion of paediatric/adult patients in the CLUSTER trial (46.1% paediatric patients) as a proxy to adjust the estimates of adult patients. The PBAC noted that, to avoid double-counting, grandfathered patients should not be included in addition to these adjustments. The PBAC considered that as adults may have more mild disease than children, uptake may be lower and should be reduced from [redacted]% in children to [redacted]% for adults. The PBAC considered that exclusion of the 300 mg maintenance dose was not reasonable and that the dosing assumed in the financial estimates should be consistent with the cost per patient calculations (see paragraph 7.10 and Table 11), with adjustment for lower dosing in paediatric patients with body weight between 7.5 kg and 40 kg. The Committee further considered that the submission's estimate of a 100% compliance rate may be overestimated and that there could also be extended tapering of doses and 'on-demand treatment' (use only where the patient is having a flare).

7.12 The PBAC considered the prevalence of FMF, the proportion of patients who are resistant or intolerant to colchicine, and the likely dose and dosing frequency to be uncertain. The PBAC considered that a Risk Share Agreement (RSA) would be essential to mitigate the risk that patient numbers or utilisation of canakinumab are substantially higher than expected. The Committee considered an RSA with a rebate of [redacted]% for use beyond the caps would be appropriate given the high cost of treatment.

7.13 The PBAC noted that the submission had requested grandfathering provisions for patients previously treated on canakinumab and considered it would be appropriate for the restrictions to allow anti-IL-1 biologic treated crFMF patients meeting or having previously met initial treatment criteria to access treatment on the PBS.

7.14 The PBAC noted that not all clinically diagnosed FMF patients will have a positive *MEFV* pathogenic variant identified, but considered that it would be reasonable to limit use of canakinumab to patients with at least one known *MEFV* pathogenic variant to ensure treatment is limited to patients likely to benefit.

7.15 The submission proposed a maximum quantity of one pack (150 mg injection) with 5 repeats, which provides approximately 24 weeks (6 months) of treatment for patients treated with canakinumab 150 mg every 4 weeks or canakinumab 300 mg every 8 weeks. The PBAC considered the maximum pack size and repeats requested to be reasonable, noting that authorities for increased maximum quantities, up to a maximum of 2, may be authorised under the continuing listing and that a balance of supply restriction would enable patients who require dose escalation to access additional quantities to complete an initial 24 week treatment course. The PBAC considered that down titration of dose should be encouraged for patients who are adequately responding to treatment, and recommended adding Prescribing Instructions to prompt prescribers to consider dose reduction in suitable patients.

7.16 The PBAC considered that an Authority (online/telephone) approval would be appropriate for initial treatment (including patients reinitiating treatment after a break of more than 12 months), and for balance of supply requests for dose escalation

to 300 mg every 4 weeks for flare. The PBAC considered that for continuing treatment an Authority required (STREAMLINED) approval would be appropriate.

7.17 The PBAC noted that in the clinical trial complete response was defined as resolution of the index flare (including PGA<2 and CRP normalised to ≤10 mg/L or reduction ≥70% from baseline) and no new disease flares at 16 weeks. The PBAC noted that this was a stringent requirement for assessing response, and was met in the majority of patients treated with canakinumab in the trial. The PBAC considered that based on secondary outcomes in the trial a high proportion of patients would be expected to have a clinically meaningful response to treatment. The PBAC noted that in crFMF patients who did not have a complete response, the annualised number of flares per patient reduced from a baseline of 32.5 to 1.2 with canakinumab treatment. The PBAC considered that the restrictions should require that patients have adequately responded to canakinumab to continue treatment and that it would be reasonable for the response to treatment to be based on clinical judgement, which would include consideration of reduction in flares and/or improvement of CRP/SAA levels.

7.18 The PBAC advised that patients must be treated by either a rheumatologist, clinical immunologist, paediatrician or specialist physician experienced in the management of FMF patients. The PBAC advised that canakinumab is not suitable for prescribing by nurse practitioners.

7.19 The PBAC advised that, under subsection 101(3BA) of the *National Health Act 1953* canakinumab should not be treated as interchangeable on an individual patient basis with any other drugs.

7.20 The PBAC considered that the Early Supply Rule should not apply to this listing of canakinumab noting that the maximum quantity may not be sufficient for one month supply for patients requiring a higher dosing regimen to manage flares.

7.21 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for canakinumab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over BSC based on the result from the CLUSTER trial;

b) The treatment is expected to address a high and urgent unmet clinical need because there are no other PBS listed therapies for this condition; and

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initial

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
CANAKINUMAB					
Canakinumab 150 mg injection, 1 vial	NEW/HSD Public MP	1	1	5	Ilaris
Canakinumab 150 mg injection, 1 vial	NEW/ HSD Private MP	1	1	5	Ilaris

Concept ID (for internal Dept. use)	**Category / Program:** ☒Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/online PBS Authorities system)
	Authority type: Complex Authority Required (CAR)
	Prescribing rule level:
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
Restriction Summary [new1] / Treatment of Concept: [new1A]	
	Indication: Familial Mediterranean fever (FMF)
	Treatment Phase: Initial treatment (New patients; or Recommencement of treatment in a new treatment cycle following a break of at least 12 months in PBS subsidised therapy with this medicine)
	Clinical criteria:
	Patient must not have received prior PBS-subsidised treatment with this drug for this condition
	OR
	Clinical criteria:
	Patient must have had a break in treatment of at least 12 months from the most recently prescribed PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have a documented diagnosis of familial Mediterranean fever (FMF) based on the Tel-Hashomer diagnostic criteria.
	AND
	Clinical criteria:
	Patient must have at least one known *MEFV* gene exon 10 pathogenic variant, confirmed by genetic testing

	AND
	Clinical criteria:
	Patient must have/have had prior to anti-IL-1 biologic treatment either of: (i) experienced at least one febrile attack per month for at least three months (ii) persistently elevated C-reactive protein (CRP) and/or serum amyloid A (SAA), during the attack-free period for at least three months, despite treatment with the maximally tolerated doses of colchicine treatment; OR
	Patient must have/have had prior to anti-IL-1 biologic treatment either of: (i) experienced at least one febrile attack per month for at least three months (ii) persistently elevated C-reactive protein (CRP) and/or serum amyloid A (SAA), during the attack-free period for at least three months, in the presence of an intolerance/contraindication of a severity requiring treatment discontinuation to colchicine
	AND
	Treatment criteria:
	Must be treated by a medical practitioner with expertise in the management of FMF who is either a: (i) rheumatologist (ii) clinical immunologist (iii) specialist paediatrician, (iv) specialist physician
	Treatment criteria:
	The treatment must be in combination with colchicine unless contraindicated or cannot be tolerated.
	Prescribing Instructions: If colchicine is contraindicated or cannot be tolerated, details of the contraindication or intolerance including severity to colchicine must be documented in the patient's medical records. The maximum tolerated dose of colchicine must also be documented in the patient's medical records, if applicable.
	Prescribing Instructions: At the time of the authority application, medical practitioners should request the appropriate quantity of vials to provide the recommended starting dose of 150 mg, or 2 mg per kg for patients weighing <40 kg every 4 weeks as per the TGA approved PI.
	Prescribing Instructions: The following information must be documented in the patient's medical records: (a) If applicable, the C-reactive protein (CRP) result and date of result (b) If applicable, the serum amyloid A (SAA) result and date of result. (c) The date, pathology provider name and any unique identifying serial number/code that links the genetic test result to the patient. (d) The number of febrile attacks per month within the three months prior to initiating an IL-1 receptor agonist for this condition. (e) If applicable, details of any contraindications/intolerances. (f) If applicable, the maximum tolerated dose of colchicine. (g) The Tel-Hashomer diagnostic criteria for diagnosis of FMF.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

Maintenance

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
CANAKINUMAB					
Canakinumab 150 mg injection, 1 vial	NEW/HSD Public MP	1	1	5	Ilaris
Canakinumab 150 mg injection, 1 vial	NEW/ HSD Private MP	1	1	5	Ilaris

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: Medical Practitioners
	Restriction type: ☒ Authority Required (streamlined)
	Authority type: Complex Authority Required (CAR)
	Prescribing rule level:
	Administrative Advice: Authorities for increased maximum quantities, up to a maximum of 2, may be authorised for patients requiring a maintenance dose of canakinumab above 150 mg every 4 weeks.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
Restriction Summary [new2] / Treatment of Concept: [new2A]	
	Indication: Familial Mediterranean fever (FMF)
	Treatment Phase: Maintenance treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have demonstrated or maintained an adequate response while receiving treatment with this drug.
	AND
	Treatment criteria:
	Must be treated by a medical practitioner with expertise in the management of FMF who is either a: (i) rheumatologist (ii) clinical immunologist (iii) specialist paediatrician (iv) specialist physician
	Treatment criteria:
	The treatment must be in combination with colchicine unless contraindicated or cannot be tolerated.
	Prescribing Instructions: Patients with clinical and biochemical remission for a period of 6-12 months should consider dose reduction by decreasing the dose, increasing the dose interval or discontinuation. Maintenance therapy with 150 mg (or 2mg/kg for patients weighing ≤ 40 kg) every 8 weeks should be considered for suitable patients.
	Prescribing Instructions:

	A patient who has demonstrated an adequate response following at least 24 weeks of PBS-subsidised treatment with this drug for this condition and has had a break in therapy of less than 12 months, is eligible to continue to receive PBS-subsidised treatment with this drug under the 'maintenance' treatment phase. Where a patient has had a treatment break the length of the break is measured from the date the most recent treatment was stopped to the date of the application for further treatment.

Balance of Supply

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
CANAKINUMAB					
Canakinumab 150 mg injection, 1 vial	NEW/HSD Public MP	1	1	~~50~~	ilaris
Canakinumab 150 mg injection, 1 vial	NEW/ HSD Private MP	1	1	~~5~~0	Ilaris

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/electronic)
	Authority type: Complex Authority Required (CAR)
	Prescribing rule level:
	Administrative Advice: Authorities for increased maximum quantities, up to a maximum of 2, may be authorised.
Restriction Summary [new3] / Treatment of Concept: [new3A]	
	Indication: Familial Mediterranean fever (FMF)
	Treatment Phase: Balance of supply
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under Initial treatment to complete 24 weeks of treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 24 weeks of treatment under this restriction.
	AND
	Treatment criteria:
	Must be treated by a medical practitioner with expertise in the management of FMF who is either a: (i) rheumatologist (ii) clinical immunologist (iii) specialist paediatrician (iv) specialist physician
	Treatment criteria:

	The treatment must be in combination with colchicine unless contraindicated or not tolerated.
	Prescribing Instructions: For initial treatment where a patient requires a maintenance dose above 150 mg every 4 weeks, authority approvals may be granted for sufficient vials with sufficient repeats for the balance of up to 24 weeks treatment. Where there is a current, approved PBS prescription with valid repeat prescriptions specified (i.e. where the maintenance dose has increased), mark the prescription that is intended for no further supply as 'Cancelled'.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
	Prescribing Instructions: Up to a maximum of 4 repeats will be authorised under this restriction

The proposed restriction contains a diagnostic tool; however, it does not serve to incorporate a document by reference.

Diagnostic tool	Purpose and use in the Instrument	Reason this reference does not serve to incorporate a document
Tel-Hashomer diagnostic criteria	A widely used clinical guideline for diagnosing FMF requiring specific combinations of major and minor symptoms like fever, abdominal pain, joint pain, and skin rashes (erysipelas-like erythema), alongside a good response to colchicine or FMF in a relative, to establish a diagnosis, often supported by genetic testing for *MEFV* gene mutations. A diagnosis generally needs two major criteria, or one major plus two minor criteria, or sometimes one major plus one minor for a probable diagnosis, helping doctors identify FMF even when genetic tests are inconclusive	The Tel-Hashomer criteria is a clinical guideline helping clinicians differentiate FMF from other periodic fever syndromes. The criteria therefore does not constitute a written record of information that must be referred to in order to determine whether statutory conditions have been met.

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.