

6.01 CANAKINUMAB, Powder for injection 150 mg with solvent Solution for injection 150 mg in 1 mL, Ilaris[®], Novartis Pharmaceuticals Australia Pty Ltd

1 Purpose of application

- 1.1 The submission requested a Section 100 Streamlined Authority listing for canakinumab for the treatment of adults and children with moderate to severe cryopyrin associated periodic syndromes (CAPS). Canakinumab has not been considered by the PBAC previously for this indication.
- 1.2 The submission requested listing for canakinumab on a cost-minimisation basis to anakinra, based on a claim of equivalent effectiveness and safety.

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

Component	Description
Population	Patients with CAPS (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease)
Intervention	Canakinumab, subcutaneous injection once every 8 weeks
Comparator	Anakinra, subcutaneous injection once daily
Outcomes	Disease remission, flare, relapse and symptom scores
Clinical claim	In patients with CAPS, canakinumab is as effective as anakinra in reducing flares and reducing symptoms with a reduced burden of injection administration.

Abbreviations: CAPS, cryopyrin-associated periodic syndrome.

Source: Table 1.1, p22 of the submission

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Canakinumab, 150 mg/1 mL, white solid lyophilisate powder 150 mg for subcutaneous injection	1	2	Public: \$ [REDACTED]	Ilaris [®]
			Private: \$ [REDACTED]	Novartis Pharmaceuticals
Category / Program:	Section 100 (Highly Specialised Drugs Program)			
PBS Indication:	Moderate to severe cryopyrin associated periodic syndromes			
Restriction:	Authority required (STREAMLINED)			
Treatment criteria:	Must be treated by a rheumatologist or in consultation with a rheumatologist; OR Must be treated by a clinical immunologist or in consultation with a clinical immunologist. A diagnosis of CAPS must be documented in the patient's medical records.			

- 2.1 The requested listing was based on the current PBS listing for the comparator, anakinra, with the restriction limiting use to patients with moderate to severe CAPS. No means of identifying patients with moderate to severe disease was proposed in the submission. The ESC recalled that at its November 2014 meeting, the PBAC did

not recommend incorporating any diagnostic criteria to the anakinra listing for the treatment of moderate to severe CAPS. The PBAC noted that there was currently no MBS listing for genetic testing to determine CAPS and that a significant proportion (30-50%) of patients who present clinically with Cutaneous, Articular Syndrome (CINCA)/ Neonatal Onset Multisystem Inflammatory Disease (NOMID) and respond favourable to therapy with IL-1 blocking agents are negative for mutations in the relevant gene. The ESC therefore considered that consistent with anakinra, it would be more appropriate to manage any risk of use beyond the restriction through risk sharing arrangements.

- 2.2 The proposed maximum quantity of one pack (150 mg powder for injection) with two repeats provides approximately 24 weeks (6 months) of treatment for adult and child patients > 40kg. The proposed maximum quantities in the restriction may not be sufficient for treatment of patients requiring higher doses (up to 600 mg every 8 weeks) as specified in the canakinumab Product Information.

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

3 Background

Registration status

- 3.1 TGA status: Canakinumab was approved by the TGA for use in CAPS on 10 May 2010.

Previous PBAC consideration

- 3.2 At the July 2017 PBAC meeting, the PBAC did not recommend amending the Authority Required (STREAMLINED) listing of anakinra for treatment of patients with moderate to severe cryopyrin associated periodic syndromes (CAPS) to be an Authority Required listing. This PBAC outcome does not impact this submission for canakinumab.

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

4 Population and Disease

- 4.1 Cryopyrin-Associated Periodic Syndrome (CAPS) consists of a group of very rare hereditary autoinflammatory diseases, specifically Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Neonatal Onset Multisystem Inflammatory Disease (NOMID, also known as Chronic Infantile Neurological, Cutaneous, Articular Syndrome or CINCA). CAPS is a life-long condition, with recurrent fever episodes accompanied by differing degrees of systemic inflammation. Intermittent, disruptive exacerbations or flares can be triggered at any time by exposure to cool temperatures, stress, exercise or other stimuli. Flares can include fever, fatigue, rash, arthralgia, myalgia, headache and in more severe cases, can lead to serious complications such as hearing loss, blindness and amyloidosis resulting in kidney failure.
- 4.2 The submission positioned canakinumab as an alternative first-line treatment to anakinra. As anakinra is PBS-listed for the treatment of moderate to severe CAPS, the submission proposed that canakinumab would also be restricted to patients with

moderate to severe disease, but did not specify a means of identifying those patients from the total patient pool. The different CAPS phenotypes tend to be considered as increasing in severity of symptoms from FCAS, to MWS, with NOMID generally the most severe disease. However, the submission cautioned that differentiation of severity based on diagnosis should be made on an individual basis and not on phenotype categorisation.

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

5 Comparator

- 5.1 The submission nominated anakinra as the comparator, as it is the only therapy PBS-listed for treatment of CAPS. The ESC considered that anakinra is the appropriate comparator.

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.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 No head-to-head trials of canakinumab and anakinra were identified during the submission; nor were there any studies with a common comparator to enable an indirect comparison. The submission is therefore based on a naive comparison of one randomised placebo-controlled trial of canakinumab (Trial D2304), eight nonrandomised canakinumab studies and six nonrandomised anakinra studies (three of which were associated with the same clinical trial number). The submission also presented a pooled analysis of efficacy and safety of some of the canakinumab studies. The included anakinra studies were previously considered by the PBAC in the November 2014 anakinra submission for treatment of CAPS. An additional three non-randomised, non-comparative studies incorporating patients taking canakinumab or anakinra were also presented.
- 6.4 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Canakinumab randomised trials		
D2304	A three part multi-centre study, with a randomized, double-blind, placebo controlled, withdrawal design in Part II to assess efficacy, safety and tolerability of ACZ885 (interleukin 1 β monoclonal antibody) in patients with Muckle-Wells syndrome. 2009. NCT00465985	Clinical Trial Report, 2009
	Lachmann et al. Use of canakinumab in the cryopyrin-associated periodic syndrome.	NEJM 2009; 360(23): 2416-2425
	Curran. Canakinumab: in patients with cryopyrin-associated periodic syndromes.	BioDrugs 2012; 26(1) 52-9
Canakinumab nonrandomised trials		
D2306	An open label, long-term safety and efficacy study of ACZ885 (interleukin-1 β monoclonal antibody) administered for at least 6 months in patients with the following Cryopyrin-associated periodic syndromes: Familial Cold Auto Inflammatory Syndrome, Muckle-Wells Syndrome or Neonatal Onset Multisystem Inflammatory Disease.	Clinical Study Report, 2010
	Efficacy and Safety of ACZ885 in Patients With the Following Cryopyrin-associated Periodic Syndromes: Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, or Neonatal Onset Multisystem Inflammatory Disease. NCT00685373	Clinicaltrials.gov
	Kuemmerle-Deschner et al. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes.	Annals of the Rheumatic Diseases 2011; 70: 2095-2102
D2307	A one-year open label, multicentre trial to assess efficacy, safety and tolerability of canakinumab (ACZ885) and the efficacy and safety of childhood vaccinations in patients aged 4 years or younger with Cryopyrin Associated Periodic Syndromes (CAPS). NCT01302860	Clinical Study Report, 2015
	A study to check how safe, beneficial and tolerable the drug canakinumab along with childhood vaccines is for patients with cryopyrin associated periodic syndromes.	European Clinical Trials Register
D2307E1	An open-label extension study to assess efficacy, safety and tolerability of canakinumab and the efficacy and safety of childhood vaccinations in patients with Cryopyrin Associated Periodic Syndromes (CAPS). NCT01576367	Clinical Study Report, 2016

Trial ID	Protocol title/ Publication title	Publication citation
	Brogan et al. Efficacy and safety of canakinumab in patients aged one to six years with cryopyrin-associated periodic syndromes: results of an open-label, phase III extension study.	Arthritis and Rheumatology 2017; 68: 3106 – 3108
	Brogan et al. Effectiveness of childhood vaccinations in CAPS patients treated with canakinumab: results from an open-label phase III extension study.	Arthritis and Rheumatology 2017; 68: 4287 – 4288
	Brogan et al. Efficacy and safety of canakinumab in patients with cryopyrin associated periodic syndromes: an open-label phase III extension study.	Annals of the Rheumatic Diseases 2016; 75: 620-621
D2201	A multi-center, open label, 24-month treatment study to establish the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of canakinumab (anti-IL-1 beta antibody) in patients with NOMID / CINCA syndrome	Clinical Study Report, 2012
	Ilaris (canakinumab) efficacy and safety in CAPS patients without confirmed mutation on exon 3 of gene CIAS1 and young CAPS patients with severe neurological (CINCA) phenotype.	EU Clinical Trials Register
D2401	β-Confident – Clinical outcomes and safety: A registry study of Ilaris® (canakinumab) patients.	Clinical Study Report, June 2016
	Clinical Outcomes and Safety: A registry study of Ilaris (canakinumab) patients. NCT01213641	Clinicaltrials.gov
	Tilson et al. Methodological challenges in monitoring new treatments for rare diseases: lessons from the cryopyrin-associated periodic syndrome registry.	Orphanet Journal of Rare Diseases 2013; 8:139
D2308	An open-label, efficacy and safety study of canakinumab (anti-interleukin-1β monoclonal antibody) administered for 6 months (24 weeks) in Japanese patients with the following cryopyrin-associated periodic syndromes: Familial cold inflammatory Syndrome; Muckle-Wells Syndrome or Neonatal Onset Multisystem Inflammatory Disease, followed by an extension phase to provide canakinumab to study patients until it is approved for marketing in Japan.	Clinical Study Report, August 2012
	Imagawa et al. Safety and efficacy of canakinumab in Japanese patients with phenotypes of cryopyrin-associated periodic syndrome as established in the first open-label phase 3 pivotal study (24-week results).	Pediatric Rheumatology 2013; 31: 302-309
Kuemmerle-Deschner	Kuemmerle-Deschner et al. Real-life	Rheumatology 2016; 55: 689 – 696

Trial ID	Protocol title/ Publication title	Publication citation
2016	effectiveness of canakinumab in cryopyrin-associated periodic syndrome.	
	Kuemmerle-Deschner et al. Canakinumab treatment-to-target strategies increase complete response rate in CAPS.	Pediatric Rheumatology 2015; 13: 249
Meta-analysis of nonrandomised canakinumab studies		
Lachmann 2012	Lachmann et al. Efficacy and safety of canakinumab patients with cryopyrin associated periodic syndromes. Results from meta-analysis of 5 studies.	Arthritis and Rheumatism 2012; 64: S321-S322.
	Meta-analysis report of CAPS studies A2102, D2201, D2304, D2306 and D2308.	Internal Novartis Report
Studies with canakinumab and anakinra patients (non-comparative)		
Kuemmerle-Deschner 2013	Kuemmerle-Deschner et al. Treatment of Muckle-Wells syndrome: Analysis of two IL-1-blocking regimens.	Arthritis Research and Therapy 2013; 15(3)
Vitale 2017	Vitale et al. A snapshot on the on-label and off-label use of the interleukin-1 inhibitors in Italy among rheumatologists and pediatric rheumatologists: a nationwide multi-center retrospective observational study.	Frontiers in Pharmacology 2017; 7, DOI: 10.3389/fphar.2016.00380
Wittkowski 2011	Wittkowski et al. MRP8 and MRP14, phagocyte-specific danger signals, are sensitive biomarkers of disease activity in cryopyrin-associated periodic syndromes.	Annals of the Rheumatic Diseases 2011; 70(12): 2075-2081
Anakinra nonrandomised studies		
Goldbach-Mansky 2006 (NCT00069329)	Goldbach-Mansky et al. 2006. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1 β inhibition.	NEJM 2006; 355(6): 581 – 592
	Anakinra to Treat Patients with Neonatal Onset Multisystem Inflammatory Disease. NCT00069329.	Clinicaltrials.gov
	Olivecrona et al. Kineret® (anakinra) controls disease symptoms in patients with severe cryopyrin-associated periodic syndromes (CAPS) up to 5-year follow-up data.	Annals of the Rheumatic Diseases 2013; 72 (Suppl 3).
Sibley 2012 (NCT00069329)	Sibley et al. 2012. Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra. A cohort study to determine three and five – year outcomes.	Arthritis & Rheumatism 2012; 64(7): 2375 – 2386

Trial ID	Protocol title/ Publication title	Publication citation
Kullenberg 2016 (NCT00069329)	Kullenberg et al. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes.	Rheumatology 2016; 55: 1499–1506
	Kullenberg et al. Steroid-sparing effect of anakinra (Kineret®) in the treatment of patients with severe cryopyrin-associated periodic syndromes.	Annals of Rheumatic Disease 2015; 74: 607
Ross 2008	Ross et al. Use of anakinra (Kineret®) in the treatment of familial cold autoinflammatory syndrome with a 16-month follow-up.	Journal of Cutaneous Medicine and Surgery 2008; 12(1): 8–16
Lepore 2010	Lepore et al. Follow-up and quality of life of patients with cryopyrin-associated periodic syndromes treated with anakinra.	The Journal of Pediatrics 2010; 157(2):310–315
	Lasiglie et al. Role of IL-1 beta in the development of human TH17 cells: Lessons from NLPR3 mutated patients.	PLoS ONE 2011; 6(5): e200014
	Caroli et al. Clinical and genetic characterization of Italian patients affected by CINCA syndrome.	Rheumatology 2007; 46: 473–478
	Gattorno et al. Pattern of interleukin-1 β secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with CIAS1 mutations.	Arthritis and Rheumatism 2007; 56(9): 3138–3148
Kuemmerle-Deschner 2011	Kuemmerle-Deschner et al. Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome.	Arthritis and Rheumatism 2011; 63(3) 840–849

Source: Table 2.5, pp39-44 of the submission

- 6.5 The key features of the canakinumab randomised trial (Trial D2304) and the nonrandomised studies are summarised in the table below. The primary outcome for the randomised part of Trial D2304 was the proportion of patients with disease flare, defined as C-reactive protein and/or serum amyloid A values >30 mg/L; and either physician global assessment of autoinflammatory disease activity > minimal; or physician global assessment of autoinflammatory disease activity = minimal, and assessment of skin disease > minimal.

		median 37.5 months			
Kuemmerle-Deschner 2011	12	Single arm observational study, 2 weeks	High	Severe MWS	Response

Abbreviations: CAPS, Cryopyrin-Associated Periodic Syndromes; CNS, central nervous system; FCAS, Familial Cold Autoinflammatory Syndrome; MWS, Muckle-Wells Syndrome; NOMID, Neonatal-Onset Multisystem Inflammatory Disease

Source: compiled during the evaluation from relevant study reports and publications

6.6 With the exception of the randomised, placebo-controlled phase of Trial D2304, all included studies had a high risk of bias, given their single-arm, open-label design. Although the ESC agreed there was a high risk of bias, the ESC considered that the risk of bias may be partially mitigated due to the studies' objective inflammatory biomarker assessments (i.e C-reactive protein and serum amyloid A levels).

6.7 The included canakinumab studies incorporated a greater number of patients with the generally less severe FCAS and MWS phenotypes compared to the anakinra studies.

Comparative effectiveness

6.8 Results are presented below for the key canakinumab Trial D2304 and a summary of key outcomes for the nonrandomised canakinumab and anakinra studies.

6.9 In the randomised phase of Trial D2304, no patients in the canakinumab group experienced disease flare, versus 13/16 (81.3%) in the placebo group. Ten patients in the placebo group met the criteria for clinical relapse, and 12/16 (75.0%) of placebo group patients discontinued from the randomised phase (and moved to open-label canakinumab in Part III of the study) due to unsatisfactory therapeutic effect. At the end of Part III of the study (open-label canakinumab for all participants), 96.8% of patients were without disease relapse.

6.10 Change from the start of the randomised phase (Week 8) of Trial D2304 in inflammatory markers (C-reactive protein and serum Amyloid A) are presented in Table 4. Both treatment groups had increased inflammatory markers from Week 8 to the end of Part II, but the change was statistically significantly smaller in the canakinumab treatment group.

Table 4: Change from start of Part II (week 8) to last assessment in serum protein levels, Trial D2304

Trial D2304	Canakinumab N=15			Placebo N=16			P-value ^a
	Week 8	Last Assessment Part II	Change from week 8	Week 8	Last Assessment Part II	Change from week 8	
CRP, mean (SD)	2.79 (2.18)	3.89 (4.36)	1.10 (3.09)	9.23 (10.67)	29.16 (29.09)	19.93 (24.18)	<0.001
SAA, mean (SD)	7.63 (8.32)	9.90 (11.42)	2.27 (8.60)	23.76 (37.79)	94.85 (141.90)	71.09 (135.64)	0.002

^a p-value is derived from stratified Wilcoxon rank sum test, stratified by cohort for the change from Week 8 (start of Part II). Analysis uses last observation carried forward, intent to treat population.

Abbreviations: CRP, C-reactive protein; SAA, serum amyloid A; SD, standard deviation

Source: Table 2.26, p80; Table 2.27, p82 of the submission.

6.11 Change in disease symptoms during Part II of the trial are presented in Table 5. The physician's global assessment of auto-inflammatory disease activity included arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise and other symptoms related to auto-inflammatory syndrome, and was generally better at the

last assessment in Part II for those patients treated with canakinumab compared to patients treated with placebo. Almost all canakinumab-treated patients reported absence of skin disease at the last assessment in Part II (93.3%) compared to only 31.3% of placebo-treated patients. In Part III of the study (canakinumab treatment), physicians rated all patients' symptoms as 'minimal' or less, regardless of treatment allocation in Part II.

- 6.12 The patient's global assessment of symptoms, assessed by a single question, tended to worsen in Part II of the trial for both treatment groups. At the end of Part II, 66.7% of canakinumab treated patients assessed their symptoms as absent or minimal, compared to 31.3% of placebo-treated patients. However, there were 4 patients in the canakinumab-treated group (26.7%) who reported their symptoms as severe at the end of Part II. In Part III of the study (canakinumab treatment), 86.7% of patients rated their symptoms as absent or minimal. The ESC noted that while there was significant difference in change to physicians' assessment of disease activity between canakinumab and placebo in trial D2304, there was no significant difference in patients' assessment of their own symptoms. However, the ESC considered that the discrepancy between these outcomes were difficult to interpret due to the small number of patients.

Table 5: Global assessment of symptoms, Part II of Trial D2304

Trial D2304	Canakinumab N=15		Placebo N=16		P-value ^a
	Week 8	Last Assessment Part II	Week 8	Last Assessment Part II	
Physician's global assessment of auto-inflammatory disease activity n (%)					
Absent	9 (60.0)	8 (53.3)	8 (50.0)	0 (0.0)	<0.001
Minimal	4 (26.7)	7 (46.7)	8 (50.0)	4 (25.0)	
Mild	2 (13.3)	0 (0.0)	0 (0.0)	8 (50.0)	
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Assessment of skin disease n (%)					
Absent	13 (86.7)	14 (93.3)	13 (81.3)	5 (31.3)	-
Minimal	2 (13.3)	1 (6.7)	3 (18.8)	3 (18.8)	
Mild	0 (0.0)	0 (0.0)	0 (0.0)	5 (31.3)	
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	3 (18.8)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Patient's global assessment of symptoms n (%)					
Absent	9 (60.0)	6 (40.0)	8 (50.0)	0 (0.0)	0.2837
Minimal	4 (26.7)	4 (26.7)	5 (31.3)	5 (31.3)	
Mild	0 (0.0)	1 (6.7)	2 (12.5)	4 (25.0)	
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	6 (37.5)	
Severe	1 (6.7)	4 (26.7)	0 (0.0)	0 (0.0)	

^a p-value is derived from exact permutation test with equally spaced scores, stratified by cohort for the change from Week 8 (start of Part II). Analysis uses last observation carried forward, intent to treat population.

Source: Table 2.26, p80; Table 2.27, p82 of the submission.

- 6.13 Changes in quality of life survey scores during Part II of Trial D2304 were generally similar between treatment groups for all four scales used in the trial (Child Health

Questionnaire-Parent Form, Functional Assessment of Chronic Illness Therapy-Fatigue, SF-36 and Health Assessment Questionnaire), with scores showing little change or worsening for each measure. There was little change to quality of life scores in Part III of the study.

- 6.14 Efficacy outcomes for the nonrandomised canakinumab studies showed similar results to the key canakinumab randomised trial. The majority of patients had a complete response to canakinumab treatment in each study, with low relapse rates in the majority of studies. Response rates tended to be lower for the more severe NOMID phenotype (see Table 6 below).

Table 6: Response and relapse rates, canakinumab nonrandomised studies

Study ID	Complete response, n (%)	Relapse rates, n (%) ^a
D2306 (n=166) - FCAS (n=30) - MWS (n=103) - NOMID (n=32) (response assessed on Day 8)	85/109 (78.0) ^b 29 (96.7) 90 (87.4) 24 (75.0)	14 (8.4) 2 (6.7) 9 (8.7) 3 (9.4)
D2307 (n=17) (one year)	16 (94.1)	4 (25.0)
D2307E (n=17) - FCAS (n=1) - MWS (n=12) - NOMID (n=4) (104 weeks)	17 (100) 1 (100) 12 (100) 4 (100)	1 (5.9) 0 0 1 (25.0)
D2308 (n=19) - MWS (n=7) - NOMID (n=12) (24 weeks)	18 (94.7) 7 (100) 11 (91.7)	4 (22.2) 1 (14.3) 3 (27.3)
D2201 (n=6) - NOMID (n=6) (6 months)	4 (66.7) 4 (66.7)	3 (75.0) 3 (75.0)
Kuemmerle-Deschner 2016 (n=68) - FCAS, FCAS/MWS (n=20) - MWS (n=41) - MWS/NOMID, NOMID (n=7) (median CR 6 (range 0.5-41) months)	49 (72.1) 17 (85.0) 31 (75.6) 1 (14.3)	NR
Pooled analysis D2306/D2308 (n=196) - FCAS (n=38) - MWS (n=110) - NOMID (n=44)	109/128 (85.2) ^b 28 (96.6) 53 (88.3) 28 (73.7)	17 (8.7) 2 (6.7) 8 (7.3) 7 (15.9)

^a Relapse rates were measured in treatment responders only.

^b canakinumab-naïve patients only

Abbreviations: CR, complete response; FCAS, Familial Cold Autoinflammatory Syndrome; MWS, Muckle-Wells Syndrome; NA, not applicable; NOMID, Neonatal-Onset Multisystem Inflammatory Disease; NR, not reported

Source: Compiled during the evaluation using Table 2.34, Table 2.35, p91; Table 2.39, p95; Table 2.50, p106; Table 2.62, p121 of the submission; and relevant study reports.

- 6.15 Physicians' global assessments of disease activity and skin disease, measured in five of the nonrandomised studies, tended to improve over time, with more patients reporting absent or minimal symptoms at study endpoints than at baseline. C-

reactive protein and serum amyloid A levels also improved from baseline to endpoint.

- 6.16 Results of the nonrandomised canakinumab studies were consistent with Trial D2304, with the majority of participants demonstrating a complete response to treatment and few disease flares. Outcomes data for the different CAPS phenotypes appear to indicate a lower response rate for patients with the more severe NOMID phenotype compared to FCAS or MWS phenotypes. However, given the small patient numbers and the open-label, single arm design of these studies, results must be interpreted with caution.
- 6.17 The nonrandomised anakinra studies reported statistically significant improvements in symptoms using a variety of patient and physician assessments of disease activity, as well as inflammatory markers of C-reactive protein and serum amyloid A, at time points ranging from 2 weeks to 3 years. Efficacy outcomes from Goldbach-Mansky (2006) and Sibley (2012) are presented in Table 7.

Table 7: Change from baseline in global diary, physician and patient scores and inflammation markers with anakinra therapy, Goldbach-Mansky 2006 and Sibley 2012

Outcome measure	Goldbach-Mansky 2006, median (IQ range)			Sibley 2012, estimated mean ^c	
	Baseline (N=18)	One month (N=18)	Six Months (N=18)	Baseline (N=26)	3 Years (N=26)
Global diary score, p-value ^a	3.70 (2.16-4.84)	0.79 (0.26-1.25), <0.001	0.26 (0.12-0.70) <0.001	0.8	0.1 <0.001
Parent Global assessment, VAS (mm), p-value ^b	48.5 (23.5-52.0)	10.0 (4.0-28.0) <0.001	5.5 (2.0-8.5) <0.001	40.5	8.3 <0.001
Physician Global assessment, VAS (mm), p-value ^b	16.5 (8.0-32.0)	9.0 (7.0-14.0) <0.001	4.5 (2.0-8.0) <0.001	NR	NR <0.001
CRP, mg/L, p-value	52.9 (40.0-105.0)	9.3 (4.9-19.4) <0.001	4.0 (1.0-9.1) <0.001	57.7	8.7 <0.001
SAA, mg/L, p-value	174 (131-436)	25 (9-97) <0.001	6 (3-16) <0.001	220.4	23.2 <0.001

^a Score ranges from 0 to 20. A decrease in the score indicates an improvement of disease symptoms. P-value is for change from baseline

^b A visual analogue scale was used in which a value of 100mm indicates the worst possible measure for the condition assessed by the test. P-value is for change from baseline

^c Mean values from Sibley (2012) were estimated during the evaluation from graphs included in Sibley 2012 using Web Plot Digitizer software

Abbreviations: CRP, C-reactive protein; DAS, disease activity score; IQ, interquartile; MWS, Muckle-Wells syndrome; NS, not significant; SAA, serum amyloid A; SD, standard deviation; VAS, visual analogue scale.

Source: Goldbach-Mansky 2006; Sibley 2012

- 6.18 In Kuemmerle-Deschner 2011, 12 patients with severe Muckle-Wells Syndrome were treated with anakinra for a median of 11 months. Efficacy was measured after 2 weeks of anakinra therapy (Table 8).

Table 8: Change from baseline in Disease Activity Score and inflammation markers with anakinra therapy, Kuemmerle-Deschner 2011

Outcome measure	Baseline (N=12)	Week 2 (N=12)	Last follow-up visit; median 11 months (N=12)
MWS DAS, mean (SD), p-value ^a	12.8 (2.2)	3.2 (1.0), 0.005	3.9 (3.2), <0.0001
Patient Global assessment, 10cm VAS, mean (SD), p-value ^b	6.3 (2.0)	2.8 (1.6), 0.0005	2.5 (0.8), <0.0001
Physician Global assessment, 10cm VAS, mean (SD), p-value ^b	7.3 (1.1)	1.9 (1.3), 0.0005	1.9 (1.1), <0.0001
CRP, mg/L, mean (SD), p-value	21.1 (13.3)	8.7 (18.6), NS	4.4 (7.0), 0.0005
SAA, mg/L, mean (SD), p-value	36.5 (26.1)	27.5 (70.5), NS	6.6 (5.2), 0.001

^a Score ranges from 0 to 20. A decrease in the score indicates an improvement of disease symptoms. P-value is for change from baseline

^b 0 represents no disease activity and 10 represents maximum disease activity. P-value is for change from baseline

Abbreviations: CRP, C-reactive protein; DAS, disease activity score; MWS, Muckle-Wells syndrome; NS, not significant; SAA, serum amyloid A; SD, standard deviation; VAS, visual analogue scale.

Source: Table 2.77, p140 of the submission, Kuemmerle-Deschner et al 2011.

- 6.19 Ross (2008) reported data from 8 related adult patients with FCAS. Within one day after initiation of anakinra therapy, all 8 patients were free of FCAS-related symptoms, and remained symptom-free during the 4 week treatment period. A statistically significant change in C-reactive protein (-14.38 mg/L, 95%CI -7.35, -21.42) and serum amyloid A levels (results not reported) were observed from the pre-treatment to treatment phase. Statistically significant increases in CRP and SAA were observed after treatment withdrawal.
- 6.20 The primary efficacy outcome for Lepore (2010), an Italian registry study, was the change in clinical manifestations of CAPS before treatment to last follow up. All anakinra-treated patients had immediate clinical response to treatment, with rash, fever, and arthritis disappearing within a few days, and with no relapse during follow-up. Lepore (2010) reported sustained normalisation of inflammatory markers (C-reactive protein and serum amyloid A; data not published).
- 6.21 The majority of patients in the nonrandomised anakinra studies showed improvements from baseline in measures of disease activity and inflammatory markers. However, given the small patient numbers and the open-label, single arm design of these studies, results must be interpreted with caution.

Comparative harms

- 6.22 Adverse events observed in the canakinumab studies were generally mild to moderate and transient. The most commonly reported adverse events were infections (respiratory, wound infections), gastrointestinal symptoms such as abdominal pain or diarrhoea, and headache. There were no treatment-related deaths in any of the canakinumab studies and very few discontinuations due to adverse events.
- 6.23 Adverse events reported in the anakinra studies included localised injection site reactions, as well as infections, gastrointestinal symptoms, headache, and rash. Injection site reactions occurred mostly during the first few weeks of anakinra treatment.

Interpretation of clinical evidence

- 6.24 The submission claimed that canakinumab and anakinra both show effectiveness and show comparable safety profiles in the treatment of CAPS, and can be considered equivalent. The submission added that canakinumab has a significantly reduced injection burden when compared with anakinra for the treatment of CAPS (1 subcutaneous injection every 8 weeks versus 1 subcutaneous injection per day).
- 6.25 There was limited evidence presented in the submission to support the therapeutic conclusion. Although canakinumab and anakinra both show effectiveness in the treatment of CAPS and similar safety profiles, the lack of comparable outcomes meant that it was difficult to draw conclusions in regards to the submission's claim of equivalent efficacy or safety. The ESC agreed that while the clinical evidence for canakinumab presented in the submission supports an effect in the treatment of CAPS, the claim that canakinumab is as effective as anakinra in the treatment of CAPS is uncertain. The ESC noted that as many studies were single arm (with the exception of part II of study D2304), different patient baseline characteristics, different treatment regimens/dosing and different study follow up durations, it was not possible to conduct an indirect comparison of canakinumab and anakinra. The ESC also noted that the patient population of study D2304 (part II) were not treatment naïve and therefore not comparable with the treatment naïve patient populations of the single-arm anakinra studies (Sibley 2012, Goldbach-Mansky 2006 & Kuemmerle-Deschner 2011). Given the objective inflammatory biomarker assessments of C-reactive protein in the trials, the ESC considered it would be informative to have a table of the change from baseline in inflammatory marker CRP from some of the available evidence (canakinumab and anakinra studies, Table 9).

Table 9: Change from baseline in inflammatory marker CRP

	Trial name	Study duration	CRP mg/L at baseline, mean (SD)	CRP mg/L at last assessment, mean (SD)	CRP mg/mL change from baseline, mean (SD)
Canakinumab	D2304 Part II (treatment arm, n=15)	24 weeks	2.79 (2.18) (pts already 8 weeks of canakinumab treatment)	3.89 (4.36)	1.10 (3.09)
	D2304 Part II (placebo arm, n=16)		9.23 (10.67) (pts already 8 weeks of canakinumab treatment)		
	D2306	56 weeks	25.51 (41.19)	5.29 (8.07)	20.22 (NR)
	D2307 / E1	152 weeks	17.9 (40.17)	4.8 (4.6)	13.1 (NR)
	D2308	48 weeks	45.17 (42.70)	14.78 (19.24)	30.39 (NR)
	D2401 – CAPS patients only	48 months	10.1 (17.70)	6.7 (17.08)	3.4 (NR)
	Kuemmerle-Deschner 2013^a	median 50-52 months	23 (21)	2 (3)	21 (NR)
Anakinra	Sibley 2012	3 years	57.7 (NR)	8.7 (NR)	49 (NR)
	Goldbach-Mansky 2006	6 months	52.9 (40-105 IQ range)	4.0 (1.0-9.1 IQ range)	48.9 (NR)
	Kuemmerle-Deschner 2011	11 months	21.1 (13.3)	4.4 (7.0)	16.7 (NR)
	Kuemmerle-Deschner 2013^a	median 50-52 months	21 (13)	4 (5)	17 (NR)

Abbreviations: CRP, C-reactive protein; IQ, interquartile; NR, not reported; SD, standard deviation.
a: Kuemmerle-Deschner 2013: CRP was reported as mg/dL. Values were multiplied by 10 for mg/L
Constructed from Tables 2.5.1, 2.5.6, 2.5.7, 2.5.8, 2.5.10 of the Commentary.

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

Economic analysis

6.26 The equi-effective doses were estimated in the submission as:

- canakinumab 150 mg once every 8 weeks = anakinra 100 mg once daily for eight weeks (5600 mg).

The mean doses of canakinumab and anakinra were calculated by body weight and phenotype, consistent with the recommended dose regimens in the Product Information documents (mean weight × mean dose by phenotype). The distribution of patients between the NOMID and FCAS/MWS genotypes were derived from an Australian prospective epidemiological study of 18 patients (Mehr et al. 2016). The submission derived the mean body weights of patients with each genotype from patient ages reported in Mehr et al. (2016) plotted against Victorian Growth Charts (children) and weight-for-age tables from the Australian Bureau of Statistics (adults). The table below presents the calculation of weighted doses.

Table 10: Calculation of mean canakinumab and anakinra doses

Phenotype	Weight range	Mean patient weight ^a	Recommended dose regimen ^b	Mean dose	Distribution by phenotype ^c	Weighted average dose	Mean dose used in submission
Mean dose of canakinumab (once every 8 weeks)							
FCAS	≥ 40 kg	50.39 kg	150 mg	150 mg	11%	115.8 mg	150 mg
MWS		50.39 kg	150 mg	150 mg	44%		
NOMID	15 - 40 kg	36.50 kg	2 mg/kg	73 mg	44%		
Mean dose of anakinra (once daily)							
FCAS	≥ 10 kg	50.39 kg	1.5 mg/kg	75.6 mg	11%	98.8 mg	100 mg
MWS		50.39 kg	1.5 mg/kg	75.6 mg	44%		
NOMID		36.50 kg	3.5 mg/kg	127.8 mg	44%		

^a See Table 3.2.1, Attachment 3 of the Commentary.

^b Recommended doses from canakinumab and anakinra Product Information

^c Mehr et al. (2016)

Abbreviations: FCAS, familial cold autoinflammatory syndrome; MWS, muckle wells syndrome; NOMID, neonatal onset multisystem inflammatory disease

Source: EXCEL spreadsheet "Section3_CostMin_Ilaris_July17.xlsx", Attachment 8 to the submission

- 6.27 The submission calculated that patients with the NOMID phenotype would receive a mean dose of 2 mg/kg (73 mg), while patients with the FCAS/MWS phenotypes would receive 150 mg, giving a weighted average dose of 115.8 mg once every eight weeks. However, as canakinumab is presented as single use 150 mg vials of powder for injection, the submission assumed one 150 mg vial per patient every eight weeks to account for wastage. This was not consistent with the recommended dose regimen for canakinumab; i.e. dose titration from 150 mg up to 300 mg and then 600 mg (8 weekly) in patients not responding after seven days of therapy. In addition, canakinumab studies with protocols providing for dose escalation in non-responders reported several instances of dose escalation, with overall mean doses greater than 150 mg (or greater than 2 mg/kg for patients under 40 kg).
- 6.28 The ESC considered that the estimated mean weighted doses for canakinumab were underestimated. The ESC noted that in study D2306, the mean doses were 188.9 mg (2.7 mg/kg) for patients with FCAS, 199.8 mg (5.5 mg/kg) for patients with MWS, and 228.9 mg (5.8 mg/kg) for patients with NOMID and in study D2308, the mean doses for patients with MWS and NOMID were 281.25 mg (6 mg/kg). The ESC further noted in the product information that in the pooled efficacy analysis (n=185) of studies D2306 and D2308, 65.6% (84/128) of patients previously not treated with canakinumab achieved complete response at 150 mg (2 mg/kg) while 85.2% (109/128) of patients achieved complete response at any dose. The ESC considered this data suggested that approximately 20% of patients would require doses higher than 150 mg. The ESC assumed in clinical practice that non-responders would go to the highest dose (600 mg) before ceasing.
- 6.29 The submission calculated that patients treated with anakinra would receive a mean dose of 3.5 mg/kg (NOMID phenotype) or 1.5 mg/kg (FCAS/MWS phenotypes), a weighted mean dose of 98.8 mg daily. Similar to canakinumab, the submission assumed one 100 mg syringe per patient daily to account for wastage (5,600 mg over eight weeks). However, Mehr (2016) reported lower doses for patients with the NOMID phenotype (mean 2.5 mg/kg/day compared to 3.5 mg/kg/day used in the

submission) and a maximum dose of 100 mg daily for adults with FCAS/MWS phenotype.

- 6.30 The submission did not claim any additional cost offsets. The submission suggested there may be more frequent injection site reactions associated with the daily dosing of anakinra, but did not provide evidence supporting this claim, or quantify the associated costs. The ESC advised that given the complexity of reconstituting each vial, canakinumab is unlikely to be self-administered by many patients or carers. The ESC considered that although patients may receive initial training to administer the injection, many patients may not be comfortable to repeat all steps involved every eight weeks. The ESC therefore considered there would likely be additional consultation costs with GPs or nurses associated with administering the treatment in some patients. These costs would be appropriate to include in the cost minimisation analysis.
- 6.31 The results of the cost minimisation analysis is summarised in the table below, assuming 6.5 packs per of canakinumab is equivalent to 13.04 packs of anakinra over one year. The cost minimisation analysis presented in the submission included a rounding error in the calculation of the number of doses per year of canakinumab, corrected during the evaluation. The ESC noted that this cost minimisation analysis does not factor in the concerns raised by ESC.

Table 11: Calculation of mean canakinumab and anakinra doses

Drug	Dose	Doses per pack	Packs per year	AEMP (pack)	AEMP per year	Price DPMQ (Public Hosp)	Price DPMQ (Private Hosp)
Anakinra	100 mg	28	█	█	█	\$1,650.00	\$1,697.15
Canakinumab	150 mg	1	█	█	█	█	█
			█	█	█	█	█

^a Rounding error in number of packs per year corrected during the evaluation

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

Source: EXCEL spreadsheet "Section3_CostMin_Illaris_July17.xlsx", Attachment 8 to the submission

Drug cost/patient/year

- 6.32 The cost of canakinumab per patient per year was calculated at \$█ for public hospital use (DPMQ \$█), and \$█ for private hospital use (DPMQ \$█). Costs per year were based on 6.5 scripts per year with 56 days' treatment per script. The equivalent cost of anakinra treatment was calculated to be \$█ per patient per year (\$100 public hospital DPMQ \$█), based on a dose of 100 mg (one pre-filled syringe) per day for 28 days per script, and 13.04 scripts per year. Treatment is ongoing. Cost per patient per year for private hospital use of anakinra is \$█. Costs per patient per year may be greater for both canakinumab and anakinra if dose escalation is required beyond the 150 mg and 100 mg vials or pre-filled syringes provided with each prescription.

Estimated PBS usage & financial implications

- 6.33 This submission was not considered by DUSC. The submission took a market share approach to estimate the usage and financial implications of a PBS listing for canakinumab. The submission used current prescribing patterns for anakinra and an

assumed proportion of uptake for canakinumab to estimate use in the Australian population with CAPS.

6.34 Estimated use and financial implications of a PBS listing for canakinumab are presented in the table below.

Table 12: Estimated use and financial implications

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Estimated canakinumab scripts¹						
Estimated anakinra scripts (5% annual growth rate)	■	■	■	■	■	■
Estimated canakinumab uptake	■	■	■	■	■	■
Canakinumab scripts (1 canakinumab script for every 2 anakinra scripts)	■	■	■	■	■	■
Canakinumab PBS cost	■	■	■	■	■	■
Canakinumab copayments	■	■	■	■	■	■
Canakinumab cost less copayments	■	■	■	■	■	■
Estimated displaced anakinra scripts²						
Displaced anakinra scripts	■	■	■	■	■	■
Anakinra PBS cost	■	■	■	■	■	■
Anakinra copayments	■	■	■	■	■	■
Anakinra cost less copayments	■	■	■	■	■	■
Net changes to the PBS/RPBS						
Net cost to PBS	■	■	■	■	■	■
Net copayments	■	■	■	■	■	■
Net cost to PBS (less copayments)	■	■	■	■	■	■

¹Corrected during the evaluation for error in '2b. Scripts – market' worksheet of "Utilisation-and-cost-model canakinumab for CAPS" Excel workbook (incorrect reference in cell C46 and C58).

² Corrected during the evaluation for error in '4a. Volumes – displaced' worksheet of "Utilisation-and-cost-model canakinumab for CAPS" Excel workbook (estimated script volumes projected from 2017 instead of 2016).

Source: "Utilisation-and-cost-model canakinumab for CAPS" Excel workbook.

The redacted table shows that at year 5, the estimated number of scripts was less than 10,000 per year

6.35 The submission estimated a net saving of less than \$10 million in Year 6, resulting in a total saving of less than \$10 million over the first 6 years of listing. The submission's estimates of utilisation for canakinumab may be underestimated. Both anakinra and canakinumab may be used at higher doses in patients who have not achieved a satisfactory clinical response at lower doses (the canakinumab Product Information states that doses of up to 600 mg every 8 weeks may be used). The relative utilisation of anakinra and canakinumab at higher doses for patients who are inadequately controlled on lower doses is unclear. The Pre-Sub-Committee Response (PSCR, p2) reiterated that based on the number of relevant PBS items for anakinra processed in 2016, approximately 7% (2% of public hospital scripts and 11% of private hospital scripts) of scripts overall are dispensed with more than one vial. The PSCR (p2) stated that if a similar proportion of canakinumab scripts were dispensed with more than one vial, the net impact on the PBS would be less than \$10 million

over five years at the proposed price. As discussed above, the ESC considered the canakinumab product information indicated that approximately 20% of patients would require doses higher than 150 mg.

- 6.36 There were no anticipated impacts on the MBS in the submission. As discussed above, there are likely additional consultation costs with GPs or nurses associated with administering canakinumab, if patients switch treatment, resulting in additional impacts on the MBS.
- 6.37 There is also potential for canakinumab to be used outside of the PBS restriction (such as for the treatment of milder forms of CAPS and systemic juvenile idiopathic arthritis). At the March 2015 PBAC meeting, canakinumab was recommended for listing for the treatment of systemic juvenile idiopathic arthritis, however the recommendation is yet to be implemented.
- 6.38 Overall, the ESC considered that the proposed savings in the submission would unlikely be realised.

Quality use of medicines

- 6.39 No quality use of medicines information was provided in the submission. The ESC noted that anakinra was currently PBS listed in a pre-filled syringe while the requested listing was for a powder for subcutaneous injection form of canakinumab requiring reconstitution. The ESC advised that canakinumab is unlikely to be self-administered by many patients given the requirement to calculate the correct dose according to body weight and the complexity of the steps involved in reconstituting each vial (i.e. the solution is required to be mixed in a specific way and requires careful handling). The ESC considered that although patients and caregivers may receive initial training from physicians to prepare and administer injections, the eight week intervals between doses would likely mean that many patients may not be confident in preparing the injection, particularly given the complexity of the steps.

Financial management – risk sharing arrangements

- 6.40 The submission noted that the anakinra Public Summary Document (November 2014) referred to the implementation of a capping arrangement to ensure PBS expenditure does not exceed agreed limits. The sponsor expects to be asked to sign up to the Deed of Agreement governing the CAPS market in the event that the canakinumab submission is successful.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of canakinumab for the treatment of moderate to severe cryopyrin-associated periodic syndromes (CAPS), on the basis that it should be available only under special arrangements under Section 100. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of canakinumab would be acceptable if it were cost-minimised against anakinra, and if joining the current Risk Sharing

Arrangement for anakinra in the same indication was implemented to contain risks associated with the cost of the drug to the PBS.

- 7.2 The PBAC accepted that anakinra is the appropriate comparator. The PBAC did not accept the equi-effective doses proposed in the submission (anakinra 100 mg once daily for eight weeks and canakinumab 150 mg once every 8 weeks) noting that dose escalations for neither anakinra nor canakinumab were considered. The PBAC also considered it appropriate for the price of canakinumab to be adjusted to account for the likely administration costs for canakinumab.
- 7.3 The PBAC noted that the life-long burden for patients with CAPS. The PBAC considered there was a clinical need for additional treatment options. The PBAC noted that there would be a reduced injection burden for this patient population as the only PBS-subsidised treatment for this condition currently is anakinra, the appropriate comparator in the submission, which is administered as a daily injection. The PBAC however considered that canakinumab and anakinra should not be used in combination and hence recommended that the criterion of 'The treatment must be the sole PBS-subsidised biological medicine for this condition' should be added to the restriction for canakinumab and flowed-on to the restriction for anakinra for CAPS.
- 7.4 The PBAC advised that it was appropriate that the restriction wording for canakinumab be the same as the current listing for anakinra, including an Authority Required (STREAMLINED) listing. The PBAC considered there was a risk of use outside of the restriction with canakinumab as with anakinra. However, as with its July 2017 consideration of amending the Authority Required (STREAMLINED) listing for anakinra to an Authority Required listing, the PBAC considered the proposed streamlined restriction level is appropriate. The PBAC noted that the restriction for anakinra included the administrative note 'This drug is not PBS-subsidised for conditions other than CAPS'. The PBAC considered that this note should also be applied to the restriction for canakinumab. However, noting that canakinumab was recommended for listing for the treatment of systemic juvenile idiopathic arthritis at the March 2015 meeting that is yet to be implemented, the administrative note should be reviewed if canakinumab is listed for this other indication.
- 7.5 The submission proposed a maximum quantity of one pack (150 mg powder for injection) with two repeats provides approximately 24 weeks (6 months) of treatment for adult and child patients greater than 40kg. The PBAC noted that for patients on the intensified dosing regimen of 600 mg every eight weeks or requiring a second dose for unsatisfactory clinical response within 7 days, the proposed maximum quantity and number of repeats would not be sufficient for 24 weeks of treatment. However, for patients less than 40kg, the proposed maximum quantity and number of repeats would lead to a substantial wastage of the 150 mg powder for injection. On balance, the PBAC considered that the proposed maximum quantity and number of repeats was reasonable for the listing. The PBAC further noted that the listing will allow for an increased maximum quantity to be prescribed with prior authority approval from the Department of Human Services.

- 7.6 The PBAC noted the results of the key canakinumab trial D2304 (n=31) indicated that canakinumab was an effective treatment for CAPS (specifically, MWS) compared with placebo in terms of reducing disease flare (81.3% of patients in the placebo group compared to none of the patients in the canakinumab group experienced disease flare) and that these results were also supported by significantly lower levels of inflammatory biomarkers (C-reactive protein and serum amyloid A levels) in the canakinumab group compared to the placebo group. The PBAC further noted that the results of the non-randomised studies consisting of patients with different CAPS phenotypes were also generally supportive of an effect of treatment.
- 7.7 The PBAC acknowledged the limitations of assessing the comparative efficacy between canakinumab and anakinra in the treatment of CAPS based on the clinical evidence presented in the submission. The PBAC noted that the lack of comparator arms in the anakinra studies as well as the difference in outcome measures and patient characteristics. However, noting that the evidence presented supported a treatment effect and challenges in obtaining robust comparative clinical data for such rare conditions, the PBAC considered it would be reasonable to accept the submission's claim of equivalent efficacy in the treatment of CAPS compared to anakinra.
- 7.8 The PBAC noted that no safety data comparing canakinumab with anakinra was presented in the submission. The PBAC noted that the majority of adverse events reported in the canakinumab key trial (D2304) and non-randomised studies were transient and mild to moderate in severity and similar overall to those observed in the anakinra studies. The PBAC considered that based on the adverse events reported in the canakinumab and anakinra studies, the submission's claim of equivalent safety compared to anakinra was reasonable.
- 7.9 The PBAC noted that the proposed equi-effective doses were canakinumab 150 mg once every 8 weeks and anakinra 100 mg once daily for eight weeks (5,600 mg). The PBAC noted that value of 150 mg of canakinumab was more conservative than the calculated weighted average dose of 115.8 mg, albeit the disease phenotype weighting was based on a small number of patients in Mehr et al. 2016. The PBAC agreed with the ESC that the mean dose of canakinumab was underestimated given it did not account for dose escalation. If the mean doses reported in D2306, namely 188.9 mg for patients with FCAS, 199.8 mg for patients with MWS, and 228.9 mg for patients with NOMID, were applied to the calculation, the weighted average dose for canakinumab would be approximately 211 mg. However, modifying the calculation for anakinra with a mean dose 2.5 mg/kg/day rather than 3.5 mg/kg/day, based on Mehr et al. 2016, for patients with the NOMID phenotype and a maximum dose of 100 mg daily for adults with FCAS/MWS phenotype, rather than 75.6 mg, did not significantly change the weighted average dose (96.1 mg compared to 98.8 mg).
- 7.10 The PBAC noted the ESC advice that approximately 20% of patients (based on the results of pooled data from studies D2306 and D2308) would require doses higher than 150 mg. The PBAC also noted the statements in the PSCR that based on the number of relevant PBS items for anakinra processed in 2016, approximately 7% of scripts overall (2% of public hospital scripts and 11% of private hospital scripts) are dispensed with more than one vial and it is very unlikely that the availability of

canakinumab on the PBS would have any influence on the extent to which this occurs. The PBAC considered that the cost-minimisation should take account of the likely use of a higher number of vials in a proportion of both canakinumab and anakinra patients.

- 7.11 The PBAC agreed with the ESC that additional consultations with a physician would be required for administering canakinumab given the complexity of reconstituting each vial. The pre-PBAC response argued that the administration of canakinumab by a physician was unlikely to be a regular occurrence and argued a scenario where the anakinra administration cost would more than offset any additional costs associated with administering canakinumab. The PBAC did agree with the argument in pre-PBAC response that it was reasonable to assume 2% of all 56 injections for anakinra would be administered by a physician, noting the Product Information indicated there are very limited circumstances in clinical practice where a physician may be required to administer the injections for anakinra. The PBAC disagreed with the pre-PBAC response and considered that it was likely that 100% of patients would seek professional aid in administering the injection. The PBAC advised it would be appropriate to include a cost in the cost-minimisation analysis for additional consultations with GPs or nurses for each canakinumab treatment, though independent of dose given, but not for treatment with anakinra. The PBAC considered that this would result in an additional cost to the MBS on listing.
- 7.12 The PBAC recalled that at its November 2014 meeting when it recommended the listing of anakinra for moderate to severe CAPS, it considered there was a risk that anakinra would be used outside the restriction to treat rheumatoid arthritis and mild forms of CAPS. The PBAC also note that the recommended listing of canakinumab for the treatment of systemic juvenile idiopathic arthritis (SJIA) at its March 2015 meeting is yet to be implemented. The PBAC considered there was a risk that canakinumab would be used outside of the proposed PBS restriction, in this case for the treatment of mild forms of CAPS and in SJIA. The PBAC advised that the sponsor of canakinumab should join the existing Risk Share Arrangement for the treatment of CAPS. The PBAC would welcome the implementation of the listing for the treatment of SJIA, but considered, upon this additional listing there was the potential for some use of canakinumab outside the two PBS listings.
- 7.13 Noting its concerns above regarding the proportion of patients requiring a higher dose, the increased risk of use outside the proposed restriction and uptake rates, the PBAC considered that overall the utilisation estimates presented in the submission may be underestimated. The PBAC agreed with the ESC that the proposed savings in the submission would unlikely be realised.
- 7.14 The PBAC advised that canakinumab is not suitable for prescribing by nurse practitioners, as drugs listed under Section 100 (Highly Specialised Drugs Program) are currently out of scope for prescribing by Nurse Practitioners.
- 7.15 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.

- 7.16 The PBAC advised that the Early Supply Rule should not apply to this listing of canakinumab, noting that currently the Rule does not apply to anakinra and that the maximum quantity may not be sufficient for one month supply for patients requiring an intensified dosing regimen.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review, as the listing was recommended.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	Nº. of Rpts	Proprietary Name and Manufacturer
Canakinumab, 150 mg/1 mL, white solid lyophilisate powder 150 mg for subcutaneous injection	1	2	Ilaris® Novartis Pharmaceuticals
Category / Program:	Section 100 (Highly Specialised Drugs Program) Public and Private		
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives		
Severity:	Moderate to severe		
Condition:	cryopyrin associated periodic syndromes (CAPS)		
PBS Indication:	Moderate to severe cryopyrin associated periodic syndromes		
Restriction Level/Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined		
Treatment criteria:	Must be treated by a rheumatologist or in consultation with a rheumatologist; OR Must be treated by a clinical immunologist or in consultation with a clinical immunologist.		
Clinical criteria:	The treatment must be the sole PBS-subsidised biological medicine for this condition.		
Prescribing Instructions:	A diagnosis of CAPS must be documented in the patient's medical records.		
Administrative Advice:	This drug is not PBS-subsidised for conditions other than CAPS.		

Amend the current listing for anakinra for CAPS (10263E and 10264F) as follows (changes are highlighted in italics):

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
ANAKINRA anakinra 100 mg/0.67 mL injection, 28 x 0.67 mL syringes	28	5	Kineret® A. Menarini Australia Pty Limited
Category / Program:	Section 100 (Highly Specialised Drugs Program) Public and Private		
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives		
Severity:	Moderate to severe		
Condition:	cryopyrin associated periodic syndromes (CAPS)		
PBS Indication:	Moderate to severe cryopyrin associated periodic syndromes		
Restriction Level/Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined		
Treatment criteria:	Must be treated by a rheumatologist or in consultation with a rheumatologist; OR Must be treated by a clinical immunologist or in consultation with a clinical immunologist.		
Clinical criteria:	<i>The treatment must be the sole PBS-subsidised biological medicine for this condition.</i>		
Prescribing Instructions:	A diagnosis of CAPS must be documented in the patient's medical records.		
Administrative Advice:	This drug is not PBS-subsidised for conditions other than CAPS.		

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.