5.05 CANAKINUMAB
150 mg vial, subcutaneous injection; Ilaris®; Novartis Pharmaceuticals Pty Ltd

1 Purpose of Application

1.1 The major submission sought an Authority Required (Written only) listing (PBS category/program unspecified) for the treatment of systemic juvenile idiopathic arthritis (sJIA) in patients meeting certain criteria.

2 Requested listing

2.1 The submission's requested listing is shown in abbreviated form below:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
CANAKINUMAB					
Initial 1 Treatment Powder for injection, 150 mg /1 mL	1+	3	$[redacted]	Ilaris®	NV
Continuing Treatment Powder for injection, 150 mg/1 mL	1+	5	$[redacted]	Ilaris®	NV
Initial 2 Treatment Powder for injection, 150 mg /1 mL	1	3	$[redacted]	Ilaris®	NV

Abbreviated restriction

Treatment phase: Initial 1 (new patient or patient recommencing after a break of more than 12 months)	
Condition	Systemic juvenile idiopathic arthritis
Restriction	Authority Required (Written Only)
Treatment criteria	Initial treatment by a rheumatologist or patients must be undergoing treatment under the supervision of a rheumatology treatment centre
Clinical criteria	Patient has been diagnosed with systemic juvenile idiopathic arthritis AND either i) Failure to achieve an adequate response to the following treatment regimen: Oral or parenteral methotrexate at a dose of at least 15 mg per square meter weekly, alone or in combination with oral or intra-articular corticosteroids for a minimum of 3 months; OR ii) Severe intolerance of, or toxicity due to methotrexate OR iii) Has refractory symptoms demonstrated by An inability to decrease and maintain the dose of prednisolone (or equivalent) below 0.5 mg per kg per day following a minimum of 2 months of therapy AND Has not received PBS- subsidised treatment with canakinumab for this condition in the previous 12 months
Prescriber Instructions	Maximum of 16 weeks of treatment authorised under this restriction.

+Canakinumab is registered in quantities of 1 or 4, with or without diluent. The information provided in the Table is based on a single vial which is the most likely quantity to be described

Treatment phase: Initial 2 (retrial or recommencement of treatment after a break of less than 12 months)	
Condition	Systemic juvenile idiopathic arthritis
Restriction	Authority Required
Treatment criteria	Must be treated by a rheumatologist or patients must be undergoing treatment under the supervision of a rheumatology treatment centre.
Clinical criteria	a. Patient has been diagnosed with systemic juvenile idiopathic arthritis; AND b. Has received PBS-subsidised treatment with canakinumab for this condition in the previous 12 months; AND c. Has not failed PBS-subsidised therapy with canakinumab for this condition more than once in the current treatment cycle.

Treatment phase: Continuing Treatment	
Condition	Systemic juvenile idiopathic arthritis
Restriction	Authority Required
Treatment criteria	Must be treated by a rheumatologist or patients must be undergoing treatment under the supervision of a rheumatology treatment centre.
Clinical criteria	a. Patient has been diagnosed with systemic juvenile idiopathic arthritis; AND b. Has demonstrated an adequate response to treatment with canakinumab
Adequate response	An adequate response to treatment is defined as: a. In a patient with refractory systemic symptoms: i. Absence of fever greater than 38 degrees Celsius in the preceding seven (7) days; AND/OR ii. A reduction in the CRP level by at least 30% from baseline; AND/OR iii. A reduction in the dose of corticosteroid by at least 30% from baseline

2.2 In summary, the submission stated that the proposed restrictions were based on those currently used for tocilizumab for the sJIA indication. The main change to the tocilizumab restriction proposed was the removal of the requirement for patients to be under the care of a paediatric rheumatologist to allow adult rheumatologists to continue the care of sJIA patients into adulthood. The submission considered that removal of subsidy for treatment due to age represents inequity in access. The submission suggested further additional changes to the tocilizumab restriction, including the three criteria based on differences between canakinumab and tocilizumab administration and the most recent treatment guidelines for sJIA. As is stated in the tocilizumab indication, the restriction required patients to have had an inadequate response to therapy with methotrexate.

2.3 The submission omitted to specify what type of PBS Schedule listing is proposed. Given that the comparator, tocilizumab, is a Section 100 Highly Specialised Drug, listing canakinumab as an Authority Required benefit in the Section 100 Highly Specialised Drugs Program would appear appropriate.

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

3 Background

3.1 Canakinumab was approved for registration by the TGA for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients aged 2 years and older at the 298th ACPM meeting on 6 June 2014.

3.2 This was the first consideration by the PBAC to list canakinumab on the PBS.

4 Clinical place for the proposed therapy

4.1 Systemic juvenile idiopathic arthritis is a disease that is diagnosed before 16 years of age and is a diagnosis of exclusion. Clinical guidelines identify three clinical phenotypes; 1) active systemic features and varying degrees of synovitis; 2) no active systemic features and varying degrees of active synovitis (polyarticular presentation); and 3) features concerning for macrophage activation syndrome (MAS). PBS listing was requested for the first clinical phenotype, systemic disease (although the submission dropped the word 'active'), but the second phenotype (polyarticular disease) was excluded from the requested restriction. Phenotype 3 was not included in the requested listing for either canakinumab or the comparator tocilizumab.

4.2 Canakinumab was proposed for the treatment of children and adults with a diagnosis of sJIA, without a polyarticular presentation, who have failed to respond to previous treatment with methotrexate, non-steroidal anti-inflammatories or glucocorticoids.

5 Comparator

5.1 Tocilizumab was the nominated main comparator. The submission included secondary comparisons against etanercept and adalimumab on the basis that they served as comparators for the tocilizumab submission. The ESC considered the comparison against tocilizumab the most relevant.

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 No consumer comments were received for this item.

Clinical trials

6.3 The submission was based on an indirect comparison of canakinumab 4 mg/kg with tocilizumab (dosed at 12 mg/kg for patients weighing <30 kg and 8 mg/ kg for patients weighing >30 kg) in treatment naïve patients (naïve to the intervention) using placebo as a common comparator. In addition the submission provided an indirect comparison of canakinumab 4 mg/kg with etanercept and adalimumab using placebo as the common comparator.

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

Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Canakinumab		
2301 Ruperto	A randomized, double-blind, placebo controlled, withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Arthritis (sJIA) and active systemic manifestations. Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis.	 *New England Journal of Medicine*. 2012, 36 (25): 2396-2405.
2305 Ruperto	A randomised, double-blind, placebo controlled, single dose study to assess the initial efficacy of canakinumab (ACZ885) with respect to the adapted ACR Paediatric 30 criteria in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations. Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis.	 *New England Journal of Medicine.* 2012, 36 (25): 2396-2405.
Tocilizumab		
De Benedetti	Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis.	*New England Journal of Medicine*. 2012. 367(25): 2385-2395.
Yokota	Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial.	*The Lancet*, 2008. 371; 998-1006
Etanercept		
Lovell	Etanercept in children with polyarticular juvenile rheumatoid arthritis.	*New England Journal of Medicine*. 2000. 342(11):763-769
Adalimumab		
Lovell	Adalimumab with or without methotrexate in juvenile rheumatoid arthritis.	*New England Journal of Medicine*. 2008. 359(8):810-820
Otten	Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons	*Annals of the Rheumatic Diseases*. 2013. 72 (11): 1806-1812.

Source: Table 11, p44-45 of the submission

6.5 The Yokota (2008) tocilizumab trial was excluded during the evaluation due to inapplicability (non-matching population and dose).

6.6 The key features of the randomised trials included in the indirect comparisons are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Canakinumab vs. placebo					
Trial 2305	84	R, DB 29 days	Low	sJIA Treatment naive	Response to ACR Pedi 30
Trial 2301	100	R, OL/DB >80mths*	Low	Responders to initial treatment	Proportion without flare
Tocilizumab vs. placebo					
De Benedetti, 2012	112	R, DB 12 weeks	Low	sJIA Treatment naive	Response to ACR Pedi 30
Etanercept vs placebo					
Lovell, 2000	51	R, OL/DB 16 weeks*	Low	Responders to initial treatment	Proportion without flare
Adalimumab vs placebo					
Lovell, 2008	133	R, OL/DB 32 weeks*	Low	Responders to initial treatment	Proportion without flare
Meta-analysis					
Otten, 2013	196	Included De Benedetti 2012; and Ruperto, 2012 (trial 2305); Assessed ACR Pedi 30			

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.
Source: compiled during the evaluation N/A=not applicable *Duration refers to DB phase

6.7 The ESC questioned the evaluation's assessment of the risk of bias for Trial 2301 as being 'low'. Trial 2301 was a two part withdrawal trial. In part 1 of the trial, all patients were treated with open-label canakinumab. Part 1 of the trial included 77 patients from trial 2305 who were responders and had rolled over into Trial 2301. Responders from part 1 (patients with ACR30 response and who also tapered treatment with glucocorticoids) then moved into part 2, the double-blind withdrawal phase. Outcomes analysed from Trial 2301 were based on the withdrawal phase. For Trial 2301 in particular, the PBAC agreed with the ESC and considered that there is high potential for bias in favour of canakinumab. The flow of trial subjects through the trial design made it difficult to estimate a true difference in treatment effect between canakinumab and placebo. However, it was noted that the evidence from the "withdrawal" trial does not contribute to the non-inferiority claim of canakinumab vs tocilizumab.

6.8 Lovell (2000) for the etanercept vs placebo comparison and Lovell (2008) for adalimumab vs placebo used the same two-part withdrawal trial design as Trial 2031 and so would also be considered to be at high risk of bias.

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

Comparative effectiveness

6.9 The table below presents a summary of the indirect comparisons in the submission reporting odds ratios (OR) as a measure of association. The main indirect comparisons were those of canakinumab versus tocilizumab with respect to the ACR Pedi 30 response. Additional comparisons included canakinumab versus adalimumab with respect to the ACR Pedi 30 response; and canakinumab versus etanercept and adalimumab with respect to the proportion of patients having a disease flare.

Results of the indirect comparisons presented in the submission

Canakinumab			Comparator			
Treatment effect OR (95% CI)	Canakinumab *n* with event/*N* (%)	Placebo *n* with event/*N* (%)	Placebo *n* with event/*N* (%)	Comparator *n* with event/*N* (%)	Treatment effect OR (95% CI)	Indirect OR (95% CI)
Canakinumab (trial 2305) vs tocilizumab (De Benedetti 2012) - proportion of the JIA ACR Pedi 30 responders						
47.57 (12.82-176.55)	36/43 (83.7)*	4/41 (9.8)*	9/37 (24)†	64/75 (85)†	18.10 (6.75-48.55)	2.63 (0.51-13.56)
Canakinumab (trial 2305) vs adalimumab (Lovell 2008) - proportion of the JIA ACR Pedi 30 responders						
47.57 (12.82-176.55)	36/43 (83.7)*	4/41 (9.8)*	23/65° (35.4)	41/68° (60.3)	2.77 (1.37-5.6)	17.17 (3.9-76.1)
Canakinumab (trial 2301) vs etanercept (Lovell 2000) – proportion with flare event						
0.26 (0.11-0.62)	11/50 (22)	26/50 (52)	21/26 (80.8)	7/25 (28)	0.09 (0.03-0.34)	2.89 (0.65-12.82)
Canakinumab (trial 2305) vs etanercept (Lovell 2000) – proportion with flare event						
0.02 (0.01-0.1)	3/43(6.9)	31/41(75.6)	21/26 (80.8)	7/25 (28)	0.09 (0.03-0.34)	0.22 (0.04-1.2)
Canakinumab (trial 2305+trial 2301) vs etanercept (Lovell 2000) – proportion with flare event						
0.08 (0.01-0.87)	14/93 (15.1)	57/91(62.4)	21/26 (80.8)	7/25 (28)	0.09 (0.03-0.34)	0.89 (0.07-11.3)
Canakinumab(trial 2301) vs adalimumab (Lovell 2008) – proportion with flare event						
0.26 (0.11-0.62)	11/50 (22)	26/50 (52)	44/65° (67.7)	27/68° (39.7)	0.31 (0.15-0.64)	0.84 (0.27-2.59)
Canakinumab(trial 2305) vs adalimumab (Lovell 2008) – proportion with flare event						
0.02 (0.01-0.1)	3/43(6.9)	31/41(75.6)	44/65° (67.7)	27/68° (39.7)	0.31 (0.15-0.64)	0.065 (0.017-0.25)
Canakinumab (trial 2305+trial 2301) vs adalimumab (Lovell 2008) – proportion with flare event						
0.08 (0.01-0.87)	14/93 (15.1)	57/91(62.4)	44/65° (67.7)	27/68° (39.7)	0.31 (0.15-0.64)	0.26 (0.025-2.7)

CI = confidence interval; *n* = number with event; *N* = number in group; OR = odds ratio

* ACR Pedi 30 response at Day 15.

† ACR Pedi 30 response at 12 weeks

° combined subgroups with and without MXT

6.10 The submission presented an indirect comparison of populations in which treatment naïve patients (with respect to the intervention) treated with canakinumab (Trial 2305) were compared to treatment naïve patients receiving tocilizumab (De Benedetti, 2012). However, the evaluation identified concerns with this comparison because:

- the trials were significantly different in duration: 29 days versus 12 weeks; and

- the populations were very heterogeneous with respect to exposure to previous treatments, duration of disease and active joint count.

6.11 The table below presents the indirect comparison of canakinumab and tocilizumab in treatment naïve patients, using placebo as a common reference, for the proportion of patients who achieved an ACR Pedi 30 response. This analysis was conducted during the evaluation. The evaluation advised that the large time difference between the observations points in the two trials (15 days in 2305 canakinumab trial vs 12 weeks in tocilizumab trial) made the outcomes difficult to compare because it was not possible to determine if the response in the canakinumab trial is maintained at 12 weeks.

Results of the indirect comparison proportion of JIA ACR Pedi 30 responders

Trial ID	Canakinumab 2305			Tocilizumab (De Benedetti 2012)			Indirect RR (95% CI)
	Treatment effect RR (95% CI)	Canak'b *n* with event/*N* (%)	Placebo *n* with event/*N* (%)	Placebo *n* with event/*N* (%)	Tocil'b *n* with event/*N* (%)	Treatment effect RR (95% CI)	
Canakinumab 2305 vs Tocilizumab (De Benedetti 2012)	*8.58 (3.35-21.97)*	*36/43 (83.7)**	*4/41 (9.8)**	*9/37 (24)*†*	*64/75 (85)*†*	*3.50 (1.97-6.24)*	*2.45 (0.81-7.39)*

CI = confidence interval; *n* = number with event; *N* = number in group; RR = relative risk

* ACR Pedi 30 response at Day 15.

† ACR Pedi 30 response at 12 weeks.

6.12 The table below presents indirect comparisons of canakinumab and the secondary comparators etanercept and adalimumab. The table shows the proportion of patients who had a disease flare in the population who responded to original treatment and who were randomised to treatment or placebo.

Results of the indirect comparison proportion of patients with flare event in the population of treatment responders

Canakinumab 2301			Comparator			Indirect RR (95% CI)
Treatment effect RR (95% CI)	Canakinumab *n* with event/*N* (%)	Placebo *n* with event/*N* (%)	Placebo *n* with event/*N* (%)	Etanercept *n* with event/*N* (%)	Treatment effect RR (95% CI)	
Canakinumab (trial 2301) vs, etanercept (Lovell 2000) - proportion with flare event						
0.42 (0.24-0.76)	*11/50 (22)*	*26/50 (52)*	*21/26 (80.8)*	*7/25 (28)*	*0.35 (0.18-0.67)*	*1.2 (0.5-2.88)*
Canakinumab (trial 2301) vs adalimumab (Lovell 2008) - proportion with flare event						
0.42 (0.24-0.76)	*11/50 (22)*	*26/50 (52)*	*44/65* (60)*	*27/68* (35)*	*0.59 (0.42-0.82)*	*0.71 (0.37-1.4)*

CI = confidence interval; *n* = number with event; *N* = number in group; RR = relative risk

*combined subgroups with and without MXT

6.13 The ESC considered that there was potential for bias in each of the trials given that all trials were two-part withdrawal trials with an initial single-arm open label phase in which all patients received active treatment, and responders moved on to the double-blind withdrawal phase. In addition, as noted in the submission some patients in the etanercept trial (approximately 30%) had sJIA but the majority were not the

appropriate population for comparison and in the adalimumab trial no patients were specifically identified as having sJIA.

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

Comparative harms

6.14 The submission did not provide any statistical comparisons of adverse events (AEs) between canakinumab and tocilizumab or canakinumab and etanercept and adalimumab. The submission claimed that the trials were difficult to compare as they were of differing lengths and placebo-treated patients were not in the trial for as long as treated patients, making comparison difficult. The submission concluded that on balance, canakinumab did not have a different adverse event profile to other bDMARDs. The evaluation advised that this conclusion could not be supported given the underlying heterogeneity in the populations, the small sample sizes of all trials and the short duration of the 2305 trial.

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

Clinical claim

6.15 The submission did not make a direct clinical claim and instead provided a summary of results across the comparisons presented. The submission cited no statistically significant differences between canakinumab and tocilizumab for the ACR 30 Pedi response, while canakinumab was found to be better than adalimumab for this outcome. The submission added that canakinumab was shown to have similar efficacy for reducing disease flare when compared with etanercept and adalimumab. While the results of indirect comparisons indicated that there are no statistically significant differences between canakinumab and these comparators for efficacy outcomes, there was no identified non-inferiority margin and importantly, there was heterogeneity in the populations as well as differences in designs and durations of the trials that limited the reliability of the analyses.

6.16 For adverse events, the submission stated that the adverse event profiles of the drugs are difficult to compare using statistical methods but it appeared that the adverse event rates for canakinumab were comparable to other drugs in the submission. The differences in trial populations, trial designs and durations also made it difficult to assess differences in safety.

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

Economic analysis

6.17 The submission sought listing on the basis of cost-minimisation compared with tocilizumab.

6.18 The equi-effective doses were estimated as canakinumab 220.95 mg every 4 weeks and tocilizumab 704.58 mg for 4 weeks. To derive the equi-effective dose the submission assumed a normal distribution for body weights and used parameters from the RCTs for tocilizumab and canakinumab.

6.19 The assumption underlying the calculation of equi-effective doses of a normal distribution of body weights in this population was questionable because the weight distribution was right skewed and thus the estimated cost of canakinumab treatment was poorly supported.

6.20 The PSCR presented an alternate method of calculating the equi-effective dose of canakinumab and tocilizumab. This alternate method applies gender specific weight-for-age data for the Australian population to the age distributions reported in the canakinumab and tocilizumab trials. This method results in a higher therapeutic relativity (3.70) than the corrected 3.25 estimated in the submission. This relativity produced a higher cost-minimised price per vial ($[redacted]) compared to that estimated in the submission ($[redacted]). The PSCR maintained the method used in the submission is the more conservative option for deriving dose relativities and price. However, the ESC considered that neither approach was well supported by the trial data.

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

Drug cost/patient/year: $[redacted]–$[redacted]

6.21 A patient who is less than 37.5 kg (at the recommended dosing of 4 mg/kg) requires 1 vial of 150 mg every 4 weeks, at a cost of $[redacted]. Patients >37.5 kg require 2 vials of 150 mg, so the cost will be $[redacted]. The course of the disease will depend on whether the patient responds to treatment. A patient of <37.5 kg who continues to respond and is treated for the entire year will have 13 cycles at a total cost of $[redacted] and for those requiring 2 vials per treatment the total cost will be $[redacted].

Estimated PBS usage & financial implications

6.22 This submission was not considered by DUSC.

6.23 The submission used a market share approach to estimate the extent of use and financial implications of the requested listing for canakinumab.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/MBS					
Net cost to PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS (saving)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated total net cost					
Net cost to PBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Assuming 13 scripts per year as estimated by the submission.

Source: Table E.4 (cma).1, p50 of the submission

6.24 The redacted table above shows that the uptake of canakinumab is expected to range from one third to three quarters of the total market for SJIA in the first five years of the listing. The number of patients expected to be treated with canakinumab ranges from 25-100 each year, in the first five years of the listing.

6.25 The financial estimates presented in the submission may not have been accurate as they were based on the tocilizumab market, which included patients with polyarticular disease and was excluded from the requested canakinumab listing.

6.26 The submission did not include the cost of canakinumab to the PBS for patients older than 18 years.

6.27 At year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than $10 million per year and the net cost to the MBS/PBS would be less than $10 million per year due to savings in the MBS.

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

7 PBAC Outcome

7.1 The PBAC recommended canakinumab as a Section 100 (Highly Specialised Drugs Program) Authority Required listing for the treatment of systemic juvenile idiopathic arthritis in patients meeting certain criteria on a cost-minimisation basis with tocilizumab. The equi-effective doses were determined to be canakinumab dosed at 4 mg/kg every 4 weeks is equivalent to tocilizumab dosed at either 8 mg/kg (for patients weighing greater than 30 kg) or 12 mg/kg (for patients weighing less than 30 kg) every 2 weeks.

7.2 The submission's clinical placement of canakinumab as a treatment for children and adults with a diagnosis of sJIA, without a polyarticular presentation, who have failed to respond to previous treatment with methotrexate, non-steroidal anti-inflammatories or glucocorticoids represented an alternative treatment to tocilizumab, etanercept and adalimumab. The PBAC noted that anakinra may also sometimes be prescribed for this indication. Tocilizumab, etanercept and adalimumab are all currently PBS-listed for the indication of 'severe active juvenile arthritis'. One of these three drugs was therefore likely to be replaced in practice by canakinumab and considered to be the comparator for the submission.

7.3 The submission's nomination of tocilizumab as the main comparator and presentation of secondary comparisons against etanercept and adalimumab was considered appropriate by the PBAC.

7.4 The PBAC noted the ESC's concerns about the high risk of bias in Trial 2301 favouring canakinumab and resulting from the design and movement of subjects through the trial. The PBAC further noted concerns identified by the evaluation relating to the significant differences in treatment duration in the trials (e.g. 29 days versus 12 weeks), a high level of heterogeneity with respect to exposure to prior treatments, duration of disease and active joint count. Whilst these issues were valid

concerns identified by the evaluation and ESC, the PBAC considered that the nature of these concerns were not too dissimilar to those encountered in previous juvenile idiopathic arthritis submission trial data for other drugs. In turn, the PBAC acknowledged the difficulties in conducting trials in children and small patient populations and was therefore prepared to balance the quality of the trial design against the proposed listing context of an uncommon disease in a small, paediatric population that would be managed by specialist prescribers in a tertiary healthcare setting.

7.5 In the absence of the submission making a direct clinical claim, the PBAC observed that there were no statistically significant differences between canakinumab and tocilizumab for the ACR 30 Pedi response, while results for canakinumab appeared more favourable than adalimumab for this outcome. Canakinumab was also observed to have similar efficacy in reducing disease flare when compared with etanercept and adalimumab. The PBAC therefore considered that canakinumab is likely to be non-inferior to tocilizumab. For adverse events, the PBAC noted that the adverse event profiles of the drugs were difficult to compare using statistical methods but considered that the adverse event rates for canakinumab were likely to be comparable to other drugs in the submission.

7.6 Following on from the view that canakinumab is likely to be non-inferior to tocilizumab, the PBAC accepted the cost-minimisation analysis approach to the economic analysis. The main difficulty arising from the cost-minimisation analysis was the determination of equi-effective doses between canakinumab and tocilizumab due to tocilizumab's variable dosing by weight and whether a patient is below or over 30 kg. The submission assumed a normal distribution of body weight in its calculation of equi-effective doses. As weight was not normally distributed (skewed to the right) in the trials, the evaluation advised that the calculated equi-effective doses may not be realised in clinical practice. The ESC and PBAC noted that the Pre-Sub-Committee Response (PSCR) provided another method of calculating the equi-effective doses, which resulted in a different relativity and a higher price for canakinumab. However, the ESC advised that neither approach was well supported by the trial data. The PBAC ultimately recommended that the equi-effective doses be determined from the products' respective Product Information, with any further proportional weighting that accounts for the use of tocilizumab in patients under or above 30 kg to be determined by the Department.

7.7 The PBAC noted that the financial estimates were based on the current tocilizumab market, which includes patients with polyarticular disease. This disease course had been excluded from the requested listing for canakinumab. Consequently, the evaluation advised that the estimated number of treated patients was not likely to be accurate. The submission also did not include an estimate of the number of patients aged greater than 18 years likely to be treated. For greater financial certainty with listing canakinumab, the PBAC recommended that the canakinumab restriction target the same patient population (as well as the same prescriber types) as tocilizumab's restriction.

7.8 <u>Advice to the Minister under subsection 101(3BA) of the Act</u>
In accordance with subsection 101(3BA) of the Act the PBAC advised that it is of the opinion that, on the basis if the material available to it at its March 2015 meeting,

canakinumab should not be treated as interchangeable on an individual patient basis with any other drugs.

7.9 The PBAC advised that canakinumab is not suitable for prescribing by nurse practitioners.

7.10 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
CANAKINUMAB				
Initial 1 Treatment Powder for injection, 150 mg /1 mL	TBA	TBA	Ilaris®	NV
Continuing Treatment Powder for injection, 150 mg/1 mL	TBA	TBA	Ilaris®	NV
Initial 2 Treatment Powder for injection, 150 mg /1 mL	TBA	TBA	Ilaris®	NV

TBA – to be announced

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	To be finalised
Severity:	To be finalised
Condition:	Juvenile idiopathic arthritis
PBS Indication:	To be finalised
Treatment phase:	To be finalised
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment criteria:	To be finalised

Clinical criteria:	To be finalised
Population criteria:	To be finalised
Prescriber Instructions	To be finalised
Administrative Advice	To be finalised NOTE: Special pricing arrangements apply
Cautions	To be finalised

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.