5.1 ANAKINRA 100 mg/0.67 mL, 28 x 0.67 mL syringes; Kineret®; A.Menarini Australia Pty Ltd.

1 Purpose of Application

1.1 The major submission sought a Section 100 (Highly Specialised Drugs Program), Authority Required listing for anakinra for the treatment of cryopyrin-associated periodic syndromes (CAPS).

2 Requested listing

2.1 The submission proposed the following listing:

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (Units)	No. of Rpts.	Proprietary Name and Manufacturer	
ANAKINRA anakinra 100 mg/0.67 mL, injection, 28 x 0.67 mL syringes	1	28	5	Kineret	A.Menarini

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	-
Condition:	Cryopyrin associated periodic syndromes
PBS Indication:	Cryopyrin associated periodic syndromes
Treatment phase:	-
Restriction Level / Method:	*Public Hospital: Authority required (STREAMLINED)* *Private Hospital: Authority required*
Treatment criteria:	-
Clinical criteria:	-
Population criteria:	-
Foreword	-
Definitions	-
Prescriber Instructions	-
Administrative Advice	-
Cautions	-

2.2 It was noted that TGA Delegate proposed to limit treatment to adult and paediatric patients aged 8 months and older with a body weight of 10 kg or above.

2.3 The sole availability of the 100 mg pre-filled syringes raised a quality use of medicines issue regarding wastage and possible multiple use of the product. As anakinra needs to be injected on a daily basis and therefore likely to be administered by the patient, a quality use of medicine issue may arise if the patient does not self-administer anakinra correctly. The ESC noted that the pre-sub-committee response (PSCR) acknowledged this issue and stated that the sponsor is not able to provide any alternate dose forms but that the sponsor is in the process of introducing a graduated syringe, which will facilitate accurate administration of doses between 20 and 100 mg.

2.4 To minimise the risk of leakage beyond the restriction (e.g. use in rheumatoid arthritis), the option of stipulating that a clinical diagnosis of CAPS must be confirmed by genetic analysis/skin biopsy was considered. However, it was noted that there is currently no MBS listing for genetic testing to determine CAPS. The PSCR considered this is likely to be both clinically and technically challenging as a significant proportion (30-50%) of patients who present clinically with CINCA/NOMID and respond favourably to therapy with IL-1 blocking agents are negative for mutations in the relevant gene. The ESC considered that it would be preferable for some mechanism to exist to limit use beyond the PBS restriction and noted the PSCR's proposal of a risk sharing arrangement to mitigate this risk.

2.5 The ESC noted that there is limited evidence available on the use of anakinra in patients with less severe types of CAPS – stable familial cold autoinflammatory syndrome (FCAS) or mild-moderate Muckle-Wells syndrome (MWS). Therefore, the ESC advised that limiting PBS subsidy to those patients with active moderate-to-severe CAPS whose symptoms cannot be controlled by best supportive care, would best reflect the evidence presented. In the PSCR, the sponsor indicated that it was not opposed to a restriction explicitly limiting treatment to patients with active moderate-to-severe disease.

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

3 Background

3.1 The submission was made under TGA/PBAC parallel process provisions. The TGA Clinical Evaluator's Report and Delegate's Overview were available at the time of PBAC consideration in November 2014. The TGA Delegate proposed to register anakinra for the following indication without the need to seek advice from the Australian Committee on Prescription Medicines:

> *'Kineret (anakinra) is indicated in adult and paediatric patients aged 8 months and older with a body weight of 10 kg or above for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) including Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA), Muckle-Wells Syndrome (MWS), and Familial Cold Autoinflammatory Syndrome (FCAS).'*

3.2 Anakinra was previously listed on the PBS for treatment of severe active rheumatoid arthritis. However, following a review of the biological DMARDs in 2010, it was removed from the schedule due to a disagreement about the proposed new price.

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

4 Clinical place for the proposed therapy

4.1 CAPS are a group of rare autoinflammatory diseases (prevalence reported to be between 1 and 3 per million) including three phenotypes: chronic infantile neurological, cutaneous, articular syndrome (CINCA) (also called neonatal-onset multisystem inflammatory disease (NOMID)), Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS).

4.2 Diagnosis of CAPS is primarily based on clinical manifestations and disease history. All three phenotypes of CAPS are caused by mutations in NLRP3. Genetic testing for the NLRP3 mutations is available in Australia but not reimbursed via the MBS. There is clinical evidence that not all cases of clinically typical CAPS have an NLRP3 gene mutation identified[1]. Somatic mutations occurring during foetal development (somatic mosaicism) have been found to explain a number of apparently mutation-negative cases[1]. Skin biopsy is also helpful in the diagnosis of CAPS, as the urticaria-like skin rash in CAPS is histologically different from normal urticaria. Overall, diagnosis of CAPS is complex and difficult due to the rarity of the disease and the overlap of symptoms with other diseases.

4.3 The submission claimed that the current therapies for patients with CAPS are interleukin-1 (IL-1) blockade ± best supportive care. As stated in the submission, clinician opinion indicates that off-label anakinra (supplied privately or provided via hospital formulary arrangements) is the most prescribed chronic therapy for CAPS. The source of the clinical opinion was not provided by the submission. It is expected that the TGA registration and PBS listing of anakinra would result in minimal change to CAPS treatment in Australian clinical practice. It was noted that canakinumab is TGA approved for the treatment of CAPS in patients aged 2 years and older and is dosed less frequently than anakinra. The submission claimed that canakinumab is not however actively marketed in Australia. The source of this claim was not provided in the submission.

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

5 Comparator

5.1 The submission nominated best supportive care as the main comparator.

5.2 The ESC questioned whether canakinumab is an appropriate comparator but noted the submission's claim that off-label anakinra use (supplied privately or provided via hospital formulary arrangements) is the most prescribed therapy for CAPS. In the

context of no existing therapies being PBS-listed for CAPS, the ESC advised that best supportive care was an 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 and welcomed the input from individuals (9), a health care professional (1) and organisations (2) via the Consumer Comments facility on the PBS website. The individual comments described some of the benefits of treatment with anakinra including improvement in symptoms and quality of life, and the need for treatment options in a rare disease such as CAPS.

6.3 Rare Voices of Australia outlined the supportive evidence and experience with anakinra for CAPS in Europe and the United States of America (USA). This organisation further commented that PBS listing would achieve greater equity in access for Australian patients and noted the difficulty in the current consumer comments process reaching audiences with a rare disease.

6.4 Comments received from the Autoinflammatory Alliance, an organisation based in the USA, outlined the positive benefits of anakinra in terms of resolving debilitating symptoms such as fevers, rash, headache, pain and preventing further hearing and vision loss in an individual patient. The comments further outlined the benefits of early access to treatment in a patient's life and the translation of these benefits into quality of life improvements.

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

Clinical trials

6.5 The submission was based on two prospective, non-randomised comparative studies and two non-comparative studies:

- Study 03-AR-0298 (Intention-to-treat (ITT) diary population, N=29): a long-term (5 years) study investigating the use of anakinra in children and adults with CINCA, which included a withdrawal period from anakinra (maximum 7 days, occurring after 3 months of anakinra treatment). This allowed a between-group comparison of anakinra ± best supportive care versus best supportive care in the so-called "withdrawal population" – 11 patients who completed the period of anakinra withdrawal (and then reinstituted anakinra treatment) and 11 patients who were enrolled after the withdrawal period being removed from the protocol and received continuous anakinra treatment (withdrawal group versus treatment group);

- Study by Lepore (2010) (N=19): a registry-based study including a cohort of patients with CINCA or MWS who received anakinra ± best supportive care (n=14) and a control cohort treated with best supportive care (n=5);
- Study by Kuemmerle-Deschner (2011) (N=12): a single-centre, before-and-after study of MWS patients who were treated with anakinra ± best supportive care; and
- Study by Ross (2008) (N=8): a single-centre, single-arm study of subjects with longstanding FCAS receiving anakinra treatment.

6.6 Details of the studies presented in the submission are provided in the table below.

Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
Nonrandomised studies		
Study 03-AR-0298	Clinical study report: A long-term outcome study with the IL-1 receptor antagonist anakinra/kineret® in patients with neonatal onset multisystem inflammatory disease (NOMID/CINCA syndrome)	May 2012
	Goldbach-Mansky R, Dailey NJ, Canna SW, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1 beta inhibition.	The New England Journal of Medicine 2006; 355(6): 581-92.
	Sibley CH, Plass N, Snow J, et al. 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): 2375-86.
	Leinonen M, Hallen B, Olivecrona H. A2: rapid and sustained response in patients suffering from severe cryopyrin-associated periodic syndromes treated with anakinra (kineret®).	Arthritis & Rheumatology 2014; 66 (Suppl 11): S3.
Lepore 2010	Lepore L, Paloni G, Caorsi R, 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): 310-5.
	Caroli F, Pontillo A, D'Osualdo A, et al. Clinical and genetic characterization of Italian patients affected by CINCA syndrome.	Rheumatology 2007; 46(3): 473-8.
	Gattorno M, Tassi S, Carta S, et al. Pattern of interleukin-1beta secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with CIAS1 mutations.	Arthritis & Rheumatism 2007; 56(9): 3138-48.
	Lasiglie D, Traggiai E, Federici S, et al. Role of IL-1 beta in the development of human T(H)17 cells: lesson from NLPR3 mutated patients.	PloS ONE 2011; 6(5): e20014.
Kuemmerle-Deschner 2011	Kuemmerle-Deschner JB, Tyrrell PN, Koetter I, et al. Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome.	Arthritis & Rheumatism 2011; 63(3): 840-9.
	Kuemmerle-Deschner JB, Wittkowski H, Tyrrell PN, et al. Treatment of Muckle-Wells syndrome: analysis of two IL-1-blocking regimens.	Arthritis Research & Therapy 2013; 15(3): R64.
	Wittkowski H, Kuemmerle-Deschner JB, Austermann J, 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): 2075-81.
Ross 2008	Ross JB, Finlayson LA, Klotz PJ, 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.

Source: Table 6, pp25-26 of the main submission.

6.7 The key features of the studies are summarised in the table below.

Key features of the included evidence

Studies	N	Design/ duration	Risk of bias	Patient population	Key outcome	Use in modelled evaluation
Anakinra versus best supportive care or anakinra single arm						
Study 03-AR-0298	29 (ITT diary population) 22 (withdrawal population)[a]	P, NR, WD, OL 60 mths	High	CAPS – CINCA/MWS	• Change in DSSS from baseline	Not used
Lepore 2010	19	P, NR, OL 38 mths (treatment group) 45mth (control group)[b]	High	CAPS – CINCA/MWS	• Change in the number of patients with CAPS symptoms before and after treatment	Used
Kuemmerle-Deschner 2011	12	P, BA, OL 11 mths	High	CAPS - MWS	• Change in MWS DAS from baseline • Change in the number of patients with CAPS symptoms before and after treatment	Used
Ross 2008	8	P, WD, OL 18 mths	High	CAPS - FCAS	• Change in scores on the FCAS symptom scale from baseline • Change in the number of patients with CAPS symptoms before and after treatment	Used
Proportion meta-analysis	60	Included Studies 03-AR-0298, Lepore 2010 and Kuemmerle-Deschner 2011; Outcome: percentages of patients with CAPS symptoms before and after treatment[c]				Not used

P = prospective; NR = not randomised; WD = withdrawal study; OL=open label; CAPS = cryopyrin-associated periodic syndrome; CINCA = chronic infantile neurological, cutaneous, articular syndrome; MWS = Muckle-Wells syndrome; DSSS = diary symptom sum score; BA = before after study design; DAS = disease activity score; FCAS = familial cold autoinflammatory syndrome.

[a] Between group comparison (anakinra withdrawal group versus anakinra continuous treatment group)

[b] Duration of follow-up for 4 (out of 5) patients in the untreated cohort

[c] Data on the number of patients with CAPS symptoms in Study 03-AR-0298 were not provided in the clinical study report, but extracted by the sponsor for the purpose of the proportion meta-analysis.

Source: compiled during the evaluation

- Subjects in all studies received open-label treatment with daily subcutaneous doses of anakinra. The primary outcome of change in CAPS symptoms in these studies is largely subjective and relies on patient or parent reports of the frequency and severity of symptoms. This may have been influenced by the lack of concealment of allocation to the new therapy. The true benefit of anakinra may have been overestimated. Overall, the ESC advised that there is a high risk of bias in the included non-randomised studies.

6.8 The ESC also advised of the applicability limitations of the quasi-experimental studies given that the populations in the studies were not entirely consistent with the PBS population which, according to the claims made in the submission, is treatment-

experienced patients who are currently using off-label anakinra. These limitations were:

- Study 03-AR-0298: exclusion criteria included the use of other anti-IL-1 inhibiting agents or the initiation of a longer acting IL-1 inhibiting agent;
- Ross 2008: exclusion criteria included subjects having previous received with anakinra or another IL-1 blockade therapy;
- Kuemmerle-Deschner 2011: exclusion criteria included those concurrently treated with immunomodulatory agents such as methotrexate;
- Lepore 2010: exclusion criteria were not reported

Comparative effectiveness

Study 03-AR-0298

6.9 Results of changes in diary symptom sum score (DSSS) – the primary outcome – during the study period of 03-AR-0298 are presented in the table below. There was a high attrition rate (14/29 (48.3%)) in terms of the available diary data. If patients with DSSS data systematically differed from those with missing data, there is a potential for attrition bias.

Change from baseline DSSS[a] (key symptoms) in Study 03-AR-0298 (ITT diary population)

Time point	N	Absolute value Mean ± SD	Change from baseline[b] Mean (SE)	Change from baseline[b] 95% CI
Baseline	29	4.5 ± 3.2	—	—
Month 3	26	0.5 ± 0.7	-3.4 (0.1)	[-3.7, -3.2]
Month 6	25	0.4 ± 0.6	-3.5 (0.1)	[-3.7, -3.3]
Month 3-6	—	—	-3.5 (0.1)	[-3.7, -3.3]
Month 12	24	0.3 ± 0.6	-3.6 (0.1)	[-3.9, -3.3]
Month 36	18	0.5 ± 0.8	-3.5 (0.2)	[-3.8, -3.2]
Month 60	15	0.5 ± 0.9	-3.5 (0.2)	[-3.8, -3.1]

DSSS = diary symptom sum score (key symptoms including fever, rash, joint pain, vomiting and headache); ITT = intention-to-treat; SD = standard deviation; SE = standard error; CI = confidence interval

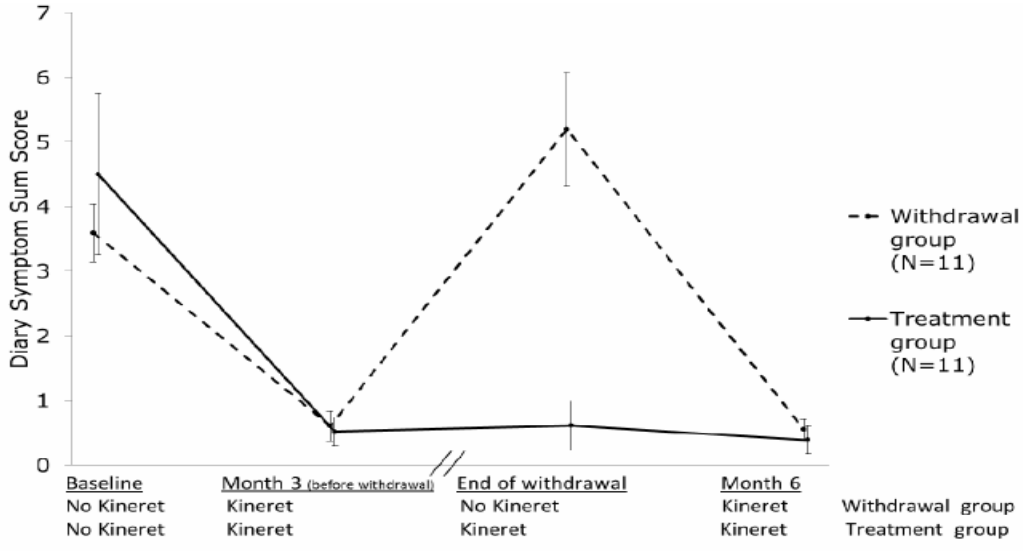
[a] DSSS ranges from 0 to 20. A decrease in the score indicates an improvement of disease symptoms

[b] Estimated changes based on the repeated measures analysis of covariance model including visit (month) as a fixed factor and baseline as a covariate.

Source: Table 13, p50 of the main submission; Table 14.2.1.1.1, p183 of the clinical study report

6.10 Changes in DSSS for the withdrawal group and the treatment group (i.e. withdrawal population) in Study 03-AR-0298 are presented in the figure below.

Comparative DSSS (key symptoms)[a] over time in Study 03-AR-0298 (withdrawal population)



DSSS = diary symptom sum score
[a] DSSS ranges from 0 to 20. A decrease in the score indicates an improvement of disease symptoms
Source: Figure 6, p52 of the main submission.

Lepore 2010 Study

6.11 The table below summarises the change in symptoms in the anakinra group and the control group in the Lepore 2010 Study.

Comparative change in the number of patients with clinical manifestations in Study Lepore 2010

	Anakinra group n (N=14)			Control group n (N=5)		
	Before treatment	Last follow-up	Change	Before treatment	Last follow-up	Change
Fever	9	0	-9	3	0	-3
Rash	14	0	-14	5	4	-1
Arthritis	13	0	-13	4	4	0
Headache	11	0	-11	3	4	1
Papilledema	7	4	-3	2	3	1
Hearing loss	6	6	0	3	4	1
Bone dysplasia	5	5	0	1	2	1
Acute phase reactants[a]	14	0	-14	5	4	-1

[a] Including serum amyloid A, C-reactive protein, erythrocyte sedimentation rate, immunoglobulin G and immunoglobulin A.
Source: Constructed during the evaluation based on Figure 9, p63 of the main submission

Kuemmerle-Deschner 2011 Study

6.12 All 12 patients in the single-arm Kuemmerle-Deschner study responded to anakinra as measured by the disease activity score (DAS) (MWS DAS of <10) at 2 weeks. The mean DAS at Week 2 was 3.2, representing a statistically significant improvement

compared to baseline (p<0.001). This study excluded patients concurrently treated with immunomodulatory agents (such as methotrexate) at patient enrolment. A before-and-after comparison from this study may overestimate the benefit of anakinra over best supportive care in clinical practice. In addition, the study did not find compelling evidence of a beneficial treatment effect from anakinra on some important CAPS complications, including renal failure, papilloedema and sensorineural hearing loss. It was acknowledged that the median follow-up of 11 months in this study may not be sufficient to examine the impact of anakinra on these CAPS complications.

Ross 2008 Study

6.13 All eight patients in this single-arm study had their FCAS-associated clinical manifestations resolve within 1 day after the initiation of anakinra therapy and remained symptom-free during the 4-week treatment period. Following withdrawal of anakinra treatment, the symptoms relapsed completely in all but one (the patient with moderate FCAS) within 36 hours. Patients enrolled in the Ross study were not allowed to receive best supportive care 2 weeks before the baseline visit.

Proportion meta-analysis

6.14 Overall, from the proportion meta-analysis of the 03-AR-0298, Lepore and Kuemmerle-Deschner studies, patients receiving anakinra had statistically significantly improvements in all symptoms/inflammatory markers from baseline to the last follow-up. This supported the conclusions from the individual studies. As expected, results showed a high degree of heterogeneity in results across the studies. The ESC advised that the meta-analysis' validity is severely limited by:
1) the extremely small control group (n=5, solely from the Lepore study); and
2) the incomparability of some important prognostic factors between treated and untreated arms (confounding) and across treated cohorts (heterogeneity).
Therefore, the meta-analysis is exploratory in nature and should be interpreted with caution.

6.15 The superior treatment effect of anakinra over best supportive care in terms of resolving common CAPS symptoms and inferior safety was supported by the evidence presented in the submission. However, consistent with the Commentary, the ESC advised that the magnitude of the clinical benefits of anakinra cannot be reliably estimated, due to

- the open-label administration of anakinra and the subjective nature of the outcomes,
- the difference in some patient characteristics between the treatment groups and their controls in Studies 03-AR-0298 and Lepore 2010,
- the absence of control groups in the studies by Kuemmerle-Deschner (2011) and Ross (2008), and
- the very small number of patients in the included studies.

6.16 Evidence indicated that anakinra had a limited effect on some important complications of CAPS (e.g. hearing loss, bone dysplasia and mental retardation), especially if treatment with anakinra did not start until the advanced stages of the

disease. The impact of anakinra on the prevention of organ involvement was not well-supported by the clinical evidence provided in the submission.

Comparative harms

6.17 The submission did not present any safety data comparing anakinra ± best supportive care versus best supportive care alone. The absence of this information made it impossible to estimate the proportions of adverse events (AEs) reported in anakinra studies that are likely to be attributable to anakinra therapy, rather than best supportive care and/or CAPS disease.

6.18 The most common AEs associated with anakinra ± best supportive care were infections and injection site reactions. Serious drug-related AEs included infections, (e.g. pneumonia) and gastroenteritis. The table below summarises treatment-emergent AEs (TEAEs) by categories reported in Study 03-AR-0298. All AEs recorded from the first dose of anakinra up to the month 60 visit, the last day of study medication, or the data cut-off date, are presented. TEAE is defined as any AE which did not occur prior to initiation of anakinra treatment. The safety population involved a total of 43 patients who received anakinra, of which 26 subjects (60.5%) had a treatment duration of greater than 4 years. The median duration of anakinra exposure was 4.9 years and total exposure was 159.8 patient-years. Overall, the AE reporting rate decreased after the first year of anakinra treatment.

Overview of adverse events in Study 03-AR-0298 (safety population)

Event category	Patient count (N=43)		Event count	
	No. patients	%	No. events	%
Any treatment-emergent adverse event	41	95.3	1,233	100%
Severe treatment-emergent adverse event	7	16.3	14	1.1
Serious treatment-emergent adverse event	14	32.6	24	1.9
Significant treatment-emergent adverse event	15	34.9	32	2.6
Death	0	0.0	0	0.0
AE leading to permanent discontinuation	0	0.0	0	0.0
AE leading to temporary discontinuation	1	2.3	3	0.2
AE leading to dose adjustment	5	11.6	11	0.9

Source: Table 18, p60 of the main submission

6.19 Given the small numbers of treated patients in all anakinra studies (34 in Study 03-AR-0298, 14 in Lepore 2010, 12 in Kuemmerle-Deschner 2011 and 8 in Ross 2008), some important AEs might not be captured in these studies.

Benefits/harms

6.20 On the basis of the four quasi-experimental studies presented in the submission, anakinra appeared to have superior effectiveness, in terms of resolving common CAPS symptoms, and an inferior safety profile, compared with best supportive care. However, anakinra's relative benefits and harms compared with best supportive care could not be accurately quantified due to the observational design of the studies and the very small sample sizes.

Clinical claim

6.21 The submission described anakinra ± best supportive care as superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care.

6.22 The Commentary and ESC observed that the superior treatment effect of anakinra over best supportive care in terms of resolving common CAPS symptoms and inferior safety is supported by the evidence presented in the submission. The Commentary and ESC further observed that the evidence indicated that anakinra had a limited effect on some important complications of CAPS (e.g. hearing loss, bone dysplasia and mental retardation), especially if treatment with anakinra had not started until the advanced stages of the disease. The impact of anakinra on the prevention of organ involvement was not well-supported by the clinical evidence provided in the submission.

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

Economic analysis

6.23 The submission presented one cost-effectiveness analysis (short-term) and two cost-utility analyses (one short-term and one long-term). This was consistent with the clinical claim that anakinra is superior in terms of effectiveness but inferior in terms of safety to best supportive care. The submission described the approach as a stepped economic evaluation. However, this description was not consistent with the 2013 PBAC Guidelines as the final step (Step 3) was not an adaptation of previous steps, but an entirely new analysis incorporating a completely different population and data sources (with the exception of the response rate and incidence of adverse events). Therefore, the Commentary presented the short term (Steps 1 and 2) and long term (Step 3) analyses separately, and retained the submission's terminology of Steps 1, 2 & 3. The steps of the economic evaluation and model structures are summarised below.

Steps in the economic evaluation

Step	Description
Step 1	Study based cost-effectiveness analysis, stratified by CAPS phenotype
Step 2	Short-term cost-utility analysis, stratified by CAPS phenotype, which draws on health related quality of life data from the anakinra studies "mapped" to a utility instrument using information available from the published literature
Step 3	A long term modelled cost-utility analysis which considers the long term costs and consequences of initiating anakinra treatment in a cohort of newly diagnosed CINCA/NOMID patients aged <1 year.

CAPS= cryopyrin-associated periodic syndromes; CINCA = chronic infantile neurological, cutaneous, articular syndrome; NOMID = neonatal-onset multisystem inflammatory disease
Source: p95, Section D of the submission

Summary of model structure and rationale – Short-term model

Model Structure	Decision analytic model
Time horizon	1 month in the model base case versus up to 60 months in the studies
Outcomes	Response (Step 1) QALY (Step 2)
Methods used to generate results	For each phenotype: Step 1: Study based results for cost per month / response Step 2: Study based results for cost per month / QALY with translation of study-based HRQoL measures to utilities as described in Section C.2 of the submission.
Transition probabilities	Response rates from the anakinra studies.
Discount rate	N/A
Software package	Excel 2010

QALY=quality adjusted life year; HRQoL = health related quality of life
Source: constructed during the evaluation

Summary of model structure and rationale – long-term model

Time horizon	30 years in the model base case versus median follow up of 37.5 months in the study (Lepore)
Outcomes	QALYs
Methods used to generate results	Monte Carlo simulation with 1,000 iterations
Cycle length	1 year
Transition probabilities	Anakinra arm: • Response rate: 100% • Death: age-specific all-cause mortality • CINCA Complications: 0% Best supportive care arm: • Response rate: 0% • Death: annual probability of death for non-responders = 0.01224; • CINCA Complications: based on transformation of epidemiological studies to annual probabilities. Assumes incidence of complications constant across life time (most epidemiological studies related to mean age of 11-12 years).
Discount rate	5% for costs and outcomes
Software package	Treeage 2014

QALY=quality adjusted life year; HRQoL = health related quality of life; CINCA = chronic infantile neurological, cutaneous, articular syndrome
Source: constructed during the evaluation

6.24 The key drivers of the model are summarised below.

Key drivers of the model

Description	Method/Value	Impact
Short-term model		
Response rates	Based on the response rates observed in three of the anakinra studies. Response rates remain uncertain due to the small sample sizes and open-label nature of the studies.	High, favours anakinra
Dose of anakinra	Assumed one syringe / patient / day (≤100/mg/day) for all CAPS phenotypes. This may be an underestimate based on recommended dosing, particularly for patients with CINCA.	High, favours anakinra
QALYs	Transformation of DLQI scores to utility weights based on 'mapping' algorithms (e.g. regression analysis) obtained from the literature. Mapping algorithms were based on an observed relationship between DLQI and EQ-5D utilities in a predominately adult psoriasis population. Treatment with anakinra results in a utility increment of 0.34 in the base case.	Moderate, favours anakinra
Long-term model		
Time horizon	Base case of 30 years. 5, 10, 15 and 20 years are examined in sensitivity analyses.	High, favours anakinra
Response rates	Based on the response rate observed in Lepore (patients with CINCA only, anakinra arm n=10, control n=4). Response rates remain uncertain due to the small sample size and open-label design of the study.	High, favours anakinra
Complication rates	Patients who respond (e.g. 100% of the anakinra arm and 0% of the best supportive care arm) are assumed to be at no risk of developing CINCA-related complications (e.g. hearing / vision loss etc.) and have the same mortality as the general population. This assumption has not been adequately justified and is not supported by the evidence presented in Section B.	High, favours anakinra
	Complication rates, their costs and utilities have been gathered from the literature. They are based on heterogeneous populations and small epidemiological studies.	Moderate, favours anakinra
Dose of anakinra	The submission has assumed that all patients will receive ≤100 mg/day (1 syringe). This may not be sufficient for CINCA patients with a weight more than 25-33 kg, based on the recommended dose of 3-4 mg/kg/day.	High, favours anakinra
QALYs	Utility values for other complications sourced from the literature and largely not comparable. Utility values applied in the economic model remain uncertain, like in the short term model.	Moderate, favours anakinra

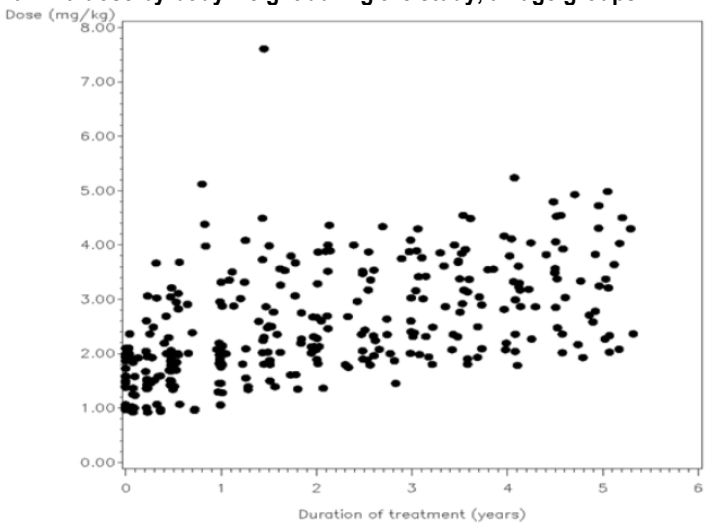
DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol five dimension scale; QALY = quality-adjusted life year; CINCA = chronic infantile neurological, cutaneous, articular syndrome.
Source: Compiled during the evaluation

6.25 The ESC advised that the transformation of DLQI scores to utility weights based on 'mapping' algorithms from literature was highly likely to be invalid given the low goodness of fit (in two of the mapping algorithms, the range of the R^2 value was 0.27 and 0.242). Only the Ross 2008 study used the DLQI which has not been validated in CAPS and given its focus on dermatological symptoms, may not reflect the whole spectrum of symptoms associated with CAPS. The model also used the pre-value for non-responders and the treatment value for responders. All of these limitations in the mapping process resulted in a likely invalid transformation to utilities. For model 3, the submission also sourced utilities for various health states associated with the

sequelae of the disease (such as mental retardation and renal transplants) from the published literature. Many of these utilities were not comparable because the patient populations differed and different instruments were used in different studies. Furthermore the model assumed an unsubstantiated disutility of 0.1 associated with injection site reaction.

6.26 The submission assumed that all patients will receive ≤100 mg/day of anakinra (one syringe). While this may be sufficient for patients with less severe disease (FCAS or MWS), it may not be sufficient for patients with chronic infantile neurological, cutaneous, articular syndrome (CINCA) weighing more than 25-33 kg, based on the recommended dose of 3-4 mg/kg/day. This would underestimate anakinra treatment costs. The ESC further advised that the dosing patterns in Study 03-AR-0298 suggest increased dosing over time (and therefore increasing treatment costs) that may potentially not be explained by patients' age-related weight increases. In the figure shown below, although a 'line of best fit' is not drawn, there appeared to be a trend towards increasing dosing on a per mg/kg basis over time.

Anakinra dose by body weight during the study, all age groups



Source: Figure 8, November 2014 Kineret PBS submission, pp.59

6.27 The ESC advised that a time horizon of 6 years as opposed to 30 years for the long-term model would be more appropriate because this shorter timeframe more closely reflected the evidence base (i.e. 03-AR-0298 had 5 year follow-up data and Lepore 2010 had 4 year follow-up data).

6.28 Results of the short-term economic analyses (Steps 1 and 2) and long term model (Step 3) are provided in the tables below.

Results of the short term economic evaluation

Analysis	Costs*					Outcomes**			ICER
	ANA		BSC		INC	ANA	BSC	INC	
	Drug	Other	Drug	Other					
Step 1 - Cost effectiveness (monthly cost per responder*)**									
FCAS	[redacted]								
MWS	[redacted]								
CINCA/ NOMID	[redacted]								
Step 2 - Cost utility (cost/QALY)									
FCAS	[redacted]								
MWS	[redacted]								
CINCA/ NOMID	[redacted]								

NAA = anakinra; BSC = best supportive care; INC = increment; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; FCAS = familial cold autoinflammatory syndrome; MWS = Muckle-Wells syndrome; CINCA = chronic infantile neurological, cutaneous, articular syndrome; NOMID = neonatal-onset multisystem inflammatory disease.
*Cost/month
** Response rate/month or quality-adjusted life years
*** Response was defined as "symptom free" (e.g. no CAPS-related symptoms: fever, headache, rash or joint pain) in the Lepore study (CINCA patients) and in the Ross study (FCAS patients); but defined as MWS disease activity score of <10 in the Kuemmerle-Deschner study (MWS patients).
Source: Table 43, p108 Section D of the submission

Results of the long term economic evaluation

Group	Costs	QALYs	ICER ($/QALY)
ANA	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	
Incremental	[redacted]	[redacted]	

ANA = anakinra; BSC = best supportive care; QALY = quality-adjusted life year; ICER = incremental cost-effectiveness ratio.
Source: Table 51, p115 Section D of the submission

6.29 Sensitivity analyses were presented in the submission and further analyses were performed during the evaluation. As noted earlier, both the short term and the long term evaluations were most sensitive to the dosage of anakinra, the response rate and the utility estimates for responder and non-responders, all of which were subject to limitations in derivation. The ESC noted that the long term model was also particularly sensitive to the assumptions associated with the probabilities of developing CINCA-related long term complications among responders and non-responders. When assuming anakinra has no effect in reducing CINCA-related long term complications, the incremental cost per QALY increased to $75,000/QALY - $105,000/QALY from a base case of less than $15,000/QALY.

6.30 Overall, the ESC advised that the Step 3 model is highly likely to be unreliable due to concerns with the transformation of DLQI scores to utility weights, the incomparability of the utility weights of the other health states, the length of the model duration, potential underestimates of the dose of anakinra used in practice and therefore the estimated treatment costs, the probability of developing complications and the costs of managing these complications.

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

Drug cost/patient/year: $[redacted]

6.31 Based on the submission's assumption of 100 mg/day (one syringe) of anakinra, distributions of FCAS, MWS and CINCA of [redacted]%, [redacted]% and [redacted]% respectively, compliance rates of [redacted]% for FCAS, [redacted]% for MWS and [redacted]% for CINCA, and a public/private hospital usage split of [redacted]%/[redacted]%, the estimated cost of anakinra is $[redacted] per patient per year. As noted earlier, CINCA patients that weigh more than 25-33 kg may need 2 syringes per day, based on the recommended dose of 3-4 mg/kg/day. The PSCR indicated that the sponsor is willing to consider the possibility of a risk share arrangement, but the ESC noted that no specific details were proposed.

Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC.

6.33 The estimated usage and costs of anakinra are presented below.

Estimated use and costs of anakinra

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated					
FCAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MWS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CINCA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of anakinra prescriptions / packs					
FCAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MWS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CINCA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS (less patient co-payments)					
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FCAS = familial cold autoinflammatory syndrome; MWS = Muckle-Wells syndrome; CINCA = chronic infantile neurological, cutaneous, articular syndrome

No additional cost to the MBS and other government health budget is estimated in the submission.

Source: Table 55, p123 of the main submission.

The redacted table above shows that at Year 5, the estimated total number of patients treated with anakinra would be less than 10,000 and the total net cost to the PBS would be less than $10 million.

6.34 The estimated financial cost to the PBS was uncertain primarily due to the paucity of reliable data on the prevalence of CAPS in the Australian population. Sensitivity analyses indicated that the prevalence of CAPS in Australia appeared to have the most impact on the financial estimates. The PSCR provided results of an Australian registry of CAPS published in abstract form (Mehr et al., 2014) which indicated that the local prevalence of CAPS is likely to be at least [redacted] per million. The ESC noted that this estimate is slightly lower than the submission's estimated disease prevalence of between 1 and 3 per million. Accepting the sponsors claim that off-label anakinra use (supplied privately or provided via hospital formulary

arrangements) is the most prescribed therapy for CAPS, given the uncertainty that surrounds the incidence and prevalence of CAPS in Australia, and the sensitivity of the financial estimates to CAPS prevalence, the ESC queried whether the sponsor could provide current utilisation data of anakinra for use in CAPS in Australia, to inform the estimated financial cost to the PBS. In the Pre-PBAC Response, the sponsor advised that it currently supplies approximately ■ packs of anakinra per month to Australian (mainly hospital) pharmacies.

6.35 The submission indicated that the sponsor would be willing to enter into a risk sharing agreement to address any uncertainty regarding the size and composition of the eligible population.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of anakinra for the treatment of moderate to severe cryopyrin-associated periodic syndromes (CAPS) under the Section 100 Highly Specialised Drugs Program (HSDP) on the basis of acceptable cost-effectiveness compared to best supportive care.

7.2 The PBAC noted that CAPS is a rare condition for which anakinra had been designated by the TGA as an orphan drug for the CAPS indication and that there are currently no drugs listed on the PBS for the specific treatment of CAPS. The consumer comments received in support of anakinra reflected this gap in treatment and the PBAC acknowledged these comments.

7.3 Despite noting that the drug canakinumab is TGA approved for the treatment of CAPS in patients aged 2 years and older and is dosed less frequently than anakinra, the PBAC accepted that off-label anakinra (supplied privately or provided via hospital formulary arrangements) is currently the most prescribed chronic therapy for CAPS. The PBAC therefore accepted that best supportive care was the appropriate comparator.

7.4 The PBAC agreed with the ESC advice and Commentary that the clinical evidence presented in the submission from four quasi-experimental studies made it difficult to reliably estimate the magnitude of the clinical benefit of anakinra in CAPS due to the open-label administration, subjective nature of the outcomes, differences in some patient characteristic between treatment and control groups, absence of control groups, very small sample numbers and very limited long term data. However, the PBAC considered that the evidence presented consistently showed that anakinra had a superior treatment effect over best supportive care in terms of resolving symptoms common in cryopyrin-associated periodic syndromes (CAPS). The PBAC was satisfied that anakinra provides, for some patients, a significant improvement in efficacy over best supportive care.

7.5 The PBAC noted that the submission did not present any safety data comparing anakinra ± best supportive care versus best supportive care alone. The absence of this information did not make it possible to estimate the proportions of adverse

events reported in anakinra studies that are likely to be attributable to anakinra therapy, rather than best supportive care and/or CAPS disease. The PBAC noted that the total exposure to anakinra in patient years in Study 03-AR-298 was 159.8 patient years and considered the submission's clinical claim of inferior safety compared to best supportive care likely to be true on the basis of the reported adverse events in Study 03-AR-0298 (safety population).

7.6 The PBAC acknowledged the difficulties associated with obtaining clinical data in rare conditions such as CAPS but recognised that it was unlikely that better data would become available. Noting the limitations with the clinical evidence presented, the PBAC accepted the submission's clinical claim that anakinra ± best supportive care is superior in terms of comparative effectiveness and inferior in terms of comparative safety over best supportive care alone.

7.7 The PBAC considered the submission's approach to the economic analysis (cost-effectiveness/cost-utility analyses) to be consistent with the clinical claim but accepted the ESC advice that the results of the economic models (both short and long term models), particularly when expressed as cost/QALYs, were likely to be invalid for reasons relating to the reliability of transforming Dermatology Life Quality Index (DLQI) scores to utility weights, model duration, potential underestimation of anakinra dosing (and therefore drug costs) and an underestimation of the potential risk of CINCA complications developing. When the results of the economic analysis were expressed as an ICER for the monthly cost/responder for each CAPS variant, the PBAC considered the results (ICER of less than $15,000/responder) to be relatively more robust and sufficiently acceptable in the context of CAPS being a rare disease with debilitating clinical symptoms.

7.8 The PBAC expected that a modest financial impact to the PBS would occur due to the small number of patients expected to require treatment. The PBAC noted further noted that the proposed annual drug cost per patient was considered to be relatively high ($[redacted]). Together with this high drug cost, the PBAC considered that it would be appropriate that a risk sharing arrangement between the sponsor and the Commonwealth is implemented to manage any risk of leakage into rheumatoid arthritis and mild forms of FCAS. The risk sharing arrangement should be a strict cap ([redacted]) on Commonwealth expenditure above a calculated level that is based on the expected patient numbers as estimated in the submission and the submission's assumption that all patients will receive ≤100 mg/day of anakinra (one syringe).

7.9 The PBAC noted that prior to delisting on 1 December 2010, the dispensed price as per the November 2010 PBS Schedule for the maximum quantity (28 syringes) of anakinra was $[redacted]. The new ex-manufacturer price proposed by the submission for CAPS is higher.

7.10 In terms of implementing a PBS restriction, the PBAC recommended that anakinra be subsidised for patients with moderate to severe CAPS, which is the patient population that best reflects the clinical evidence provided. To minimise the risk of leakage beyond the restriction (e.g. use in rheumatoid arthritis), the PBAC considered whether the listing should stipulate that a clinical diagnosis of CAPS must be confirmed by genetic analysis/skin biopsy but noted advice that there is currently

no MBS listing for genetic testing to determine CAPS and that a significant proportion (30-50%) of patients who present clinically with CINCA/NOMID and respond favourably to therapy with IL-1 blocking agents are negative for mutations in the relevant gene. Therefore, the PBAC did not recommend that a PBS restriction should stipulate that a clinical diagnosis of CAPS must be confirmed by genetic analysis/skin biopsy. In view of the complexity and rarity of CAPS as a medical condition, the PBAC noted that CAPS would be mainly managed in tertiary health settings and therefore further recommended that anakinra be prescribed by or in consultation with a rheumatologist.

7.11 The PBAC advised that anakinra is not suitable for prescribing by nurse practitioners.

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

7.13 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (Packs)	Max. Qty (Units)	No. of Rpts	Proprietary Name and Manufacturer	
ANAKINRA anakinra 100 mg/0.67 mL, injection, 28 x 0.67 mL syringes	1	28	5	Kineret	A.Menarini

Category / Program	Section 100 – Highly Specialised Drugs Program (Private Hospital) Section 100 – Highly Specialised Drugs Program (Public Hospital)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Moderate to severe
Condition:	Cryopyrin associated periodic syndromes
PBS Indication:	Moderate to severe cryopyrin associated periodic syndromes
Treatment phase:	-
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined

Treatment criteria:	Must be treated by a rheumatologist or in consultation with a rheumatologist.

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

Menarini welcomes the PBAC recommendation to reimburse anakinra for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS).