MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
4th November 2019

Agenda Item No	
National Programme	Blood and Infection
Clinical Reference Group	Immunology and Allergy
URN	1813

Title
Canakinumab for treating periodic fever syndromes (tumour necrosis factor receptor associated periodic syndrome [TRAPS], hyperimmunoglobulin D syndrome/mevalonate kinase deficiency [HIDS/MKD] and familial Mediterranean fever [FMF])

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
For routine commissioning. Periodic fever and autoinflammatory diseases are a group of very rare genetic conditions that occur in children and adults. In this policy proposition, the diseases included are: a) Familial Mediterranean Fever (FMF) b) Hyperimmunoglobulin D syndrome (HIDS) also known as Mevalonate Kinase Deficiency (MKD) c) Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) Periodic fevers often begin in childhood, sometimes as early as infancy. Each episode lasts for several days to weeks and patients have very high temperatures, extreme fatigue and severe rash. Between attacks, patients can still have extreme tiredness and flu-like symptoms and for some patients there is no break in the illness. This very debilitating condition severely impacts on daily activities such as school attendance, family life and the ability to remain in employment. Long term consequences of these diseases include damage to the kidney and liver and can lead to amyloidosis, a condition in which an abnormal protein called amyloid builds up in tissues and organs and which can also lead to liver and kidney failure.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes / Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	

7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	This outcome looked at how many adverse events or serious adverse events (such as hospitalisation) occurred with canakinumab. In the main study by De Benedetti et al. 2018, the number of adverse events and serious adverse events were higher in participants taking canakinumab compared with placebo (497 versus 136 and 21 versus 8 respectively), however the canakinumab treatment group had longer exposure to treatment compared with the placebo group (more than 12 patient-years compared with 8 patient-years, respectively). The most frequent reported adverse events were infections (particularly respiratory infections), abdominal pain, headaches, and injection-site reactions. The results suggest that people who have treatment with canakinumab are more likely to experience an adverse event or serious adverse event, however most of the adverse events were reported to be mild to moderate in severity. Additionally, the European Public Assessment Report (EPAR) states that "the adverse event profile of canakinumab treatment is overall mostly comparable in the new proposed indication with the approved CAPS indication." These results come from a phase 3 double blind placebo controlled randomised controlled trial (RCT) and are therefore reliable. However, there are some limitations to the studies. These include the fact that there are small numbers of people with the conditions which made it challenging to recruit for the study. Another limitation to the study is that no active comparators were used to assess canakinumab's place in therapy. This means that the study was too small to assess the true treatment effect of canakinumab to control the conditions, and also it did not compare the treatment with treatments currently used for these conditions.
11.	Delivery of intervention	

No	Outcome measure	Summary from evidence review
1.	Complete response	A complete response means that the person's flares were resolved and that they were free of symptoms by day 15 of treatment and had no new flares to week 16. For people with these conditions this outcome is extremely important as it means that they are symptom-free while taking the treatment which can be life-changing. Flares cause crippling fatigue, pain and fever, a complete response means that the recurrent flares stop completely meaning a person can carry out usual daily activities like attending school and working. As described during the PWG meeting, people with these conditions who are treated with canakinumab respond in the following manner: "children are ecstatic, adolescents party and adults get better jobs." The main study found that in participants with TRAPS (n=46), HIDS/MKD (n=72) and cr-FMF, (n=63) there was a statistically significant difference (indicated by a p-value of less than 0.05) in the number of participants who had complete response with canakinumab compared with placebo at week 16 (TRAPS, 45% versus 8%, p=0.006; MKD, 35% versus 6%, p=0.003; cr-FMF, 61% versus 6%, p<0.001 respectively). The results suggest that participants with TRAPS, MKD and cr-FMF are more likely to have their flares resolved and be free of symptoms with canakinumab by day 15 of treatment and can also expect to have no new flare during the first 4 months of treatment. The difference between the canakinumab treatment and placebo is due to the true treatment effect of canakinumab. These results come from a phase 3 double blind placebo controlled randomised controlled trial and are therefore reliable. However, there are some limitations to the studies. These include the fact that there are small numbers of people with the conditions which made it challenging to recruit for the study. Another limitation to the study is that no active comparators were used to assess canakinumab's place in therapy. This means that the study was too small to assess the true treatment effect of canakinumab to control the conditions, and also it did not compare the treatment with treatments currently used for these conditions.
2.	Frequency or recurrence of flares	This outcome looked at how well canakinumab stops the flares from occurring. For people with the condition, this outcome is important to find out whether they have less or more flares with canakinumab. Less flares means that patients can be free of symptoms for longer periods and also plan ahead for personal or social activities without being limited by more flares.

		In the main study, participants who did not meet the primary outcome of complete response at week 16 experienced a decrease in the mean number of flares up to week 40 of treatment (normalised to 1 year) when compared with 12 months before treatment (TRAPS [n=16], 1.2 flares versus 10.1 flares per year; MKD [n=21], 2 flares versus 14.7 flares per year; cr-FMF [n=16]: 1.2 flares versus 32.5 flares per year, respectively) The results suggest people with TRAPS, MKD and cr-FMF who take canakinumab are more likely to have fewer flares compared with no treatment. See outcome number 1 for information on the reliability of results. In addition, there was no statistical analyses reported for this outcome to confirm if this difference was because of the true treatment effect of canakinumab.
3.	Attack severity	This outcome looked at how severe the attack was based on the physician's global assessments using a 5-point scale; absent signs/symptoms (score 0) to severe disease activity (score 4). For people with the condition, this outcome is important to find out if treatment with canakinumab can minimise the severity of attacks that can be disabling and impact on how they feel. Arostegui et al. 2017 (n=9 with HIDS), reported 9 attacks at baseline; 5 were mild and 4 were moderate in severity. During the 6-month treatment period, 2 attacks were reported; 1 was mild and 1 was moderate. During the 24-month extension treatment period, 8 attacks were reported; 1 had no signs or symptoms, 2 had minimal signs and symptoms and 5 were mild. These results suggest that people with HIDS who take canakinumab are likely to have less severe attacks These results should be interpreted with caution as they are based on a single arm study. It means that it did not randomise patients or compare canakinumab with any other treatment. Therefore, it does not reduce the risk of other factors influencing the results and it does not provide comparative evidence versus other treatments for this outcome.
4.	Resolution of baseline flare	This outcome looked at how many people had their baseline flare resolved with canakinumab. For people with the condition, this outcome is important to find out if treatment with canakinumab can make them free of the signs and symptoms and improve how they feel.

		The main study found that in people with TRAPS (n=46), MKD (n=72) and cr-FMF (n=63), more participants had a resolution of their baseline flare with canakinumab (64%. 65% and 81% respectively) compared with placebo (21%, 37% and 31% respectively) at day 15 of treatment period. Results suggest that people with TRAPS, MKD and cr-FMF who take canakinumab are more likely to have their flare resolved when they occur. See outcome number 1 for information on the reliability of results. In addition, there was no statistical analyses reported for this outcome to confirm if this difference between treatment and placebo was because of the true treatment effect of canakinumab.
5.	Physician's global assessment (PGA)	This outcome was a physician's reported outcome and it looked at how well the disease was controlled with canakinumab taking into account fever and clinical signs and symptoms associated with each disease using a 5-point scale with scores of 0 (none) to 4 (severe). A score of less than 2 suggests mild to no signs or symptoms. For people with the condition, this outcome is important to find out if with canakinumab treatment, the person can have better control of their condition and also plan ahead for personal or social activities without being limited by the condition. The main study found that in participants with TRAPS (n=46), HIDS/MKD (n=72) and cr-FMF (n=63). There was a statistically significant difference (indicated by a p-value of less than 0.05) in the number of participants who had a PGA score of less than 2 with canakinumab compared with placebo at week 16 (TRAPS: 45.5% vs 4.2%, p=0.0057; MKD: 46% vs 5.7%, p=0.0011; cr-FMF: 64.5% vs 9.4%, p<0.0001 respectively). The results suggest that people with TRAPS, MKD and cr-FMF who take canakinumab are more likely to have no or minimal signs and symptoms associated with the condition than with placebo and that the difference between the canakinumab treatment and placebo is due to the true treatment effect of canakinumab. See outcome number 1 for information on the reliability of results.
6.	Serological response	This outcome looked at how well the inflammatory markers, C-reactive protein (CRP) and serum amyloid A (SAA) levels were controlled with canakinumab treatment (normal range is less than 10 mg/l for both). For people with the condition it is important to have a lower CRP level because it is a good indicator that the treatment is working to control inflammation.

		Also, it is important to people with the condition to have their SAA levels kept to the lowest level possible to avoid complications such as AA amyloidosis that can cause kidney failure and other organ damage. The main study found that in participants with TRAPS (n=46), HIDS/MKD (n=72) and cr-FMF, (n=63), a statistically significant more participants treated with canakinumab had a CRP level of 10 mg/l or less compared with placebo at week 16 (TRAPS: 36.4% vs 4.2%, p=0.0298; MKD: 40.5% vs 5.7%, p=0.0020; cr-FMF: 67.7% vs 6.3%, p<0.0001 respectively). The main study also found that more participants with TRAPS, MKD and cr-FMF had an SAA level of 10 mg/l or less with canakinumab compared with placebo at week 16 (TRAPS: 27.3% vs 0%, p=0.047; MKD: 13.5% vs 2.9%, p=0.1555; cr-FMF: 25.8% vs 0%, p=0.572 respectively), however a statistically significant difference was only found in the TRAPS population. The results suggest that people with TRAPS, MKD or cr-FMF taking canakinumab are more likely to have lower CRP levels than with no treatment and that the difference between the canakinumab treatment and placebo is due to the true treatment effect of canakinumab. The results also suggest that people with TRAPS are more likely to have lower SAA levels with canakinumab than with placebo. Although the treatment with canakinumab reduced SAA levels in more people with MKD and cr-FMF than with placebo, the statistical test suggests that the difference between the 2 treatments could be due to random chance rather than the true effect of the treatment. Low levels of SAA are important to people with the condition because a high SAA level is associated organ damage, therefore lower levels reduces this risk. See outcome number 1 for information on the reliability of results. In addition, this outcome was measured for a short duration at 16 weeks of treatment. Therefore, there is no information on the effect long-term canakinumab treatment has on the CRP or SAA levels.
7.	Canakinumab dose adjustments	This outcome looked at how many participants needed to make dose adjustments with canakinumab if the baseline flare was not stopped with the first dose and how many responded and also if longer intervals between treatment provides adequate control of flares. For people with the condition, this outcome is important because it provides information about whether or not higher doses of canakinumab can treat flares if lower doses do not provide an adequate response and also, for people who cannot access treatment easily every 4 weeks, then longer treatment intervals of 8 weeks may be an option.

		The main study found that 8%, 29% and 10% of participants with TRAPS (n=60), MKD (n=65) and cr-FMF (n=59) respectively, had their canakinumab dose increased to 300 mg to control their flares. The study also found that an extended dosing interval of canakinumab every 8 weeks was sufficient to maintain disease control in 53%, 23% and 46% of participants with TRAPS, MKD and cr-FMF respectively. The results suggest that people with TRAPS, MKD and cr-FMF who take a higher dose of canakinumab are likely to have their fares stopped if the low dose does not provide adequate control. Also, it suggests that canakinumab administered at 8-weekly intervals may be effective for some people. See outcome number 1 for information on the reliability of results. In addition, there was no statistical analyses reported for this outcome to confirm if this difference between treatment and placebo was because of the true treatment effect of canakinumab.
8.	Use of rescue medicines	This outcome looked at how many participants on canakinumab needed to take rescue medicines that included non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids during a flare. For people with the condition, this outcome is important because people may still need to take additional medicines alongside the canakinumab which increases the burden of medicines to take to manage the condition. Arostegui et al. (2017) (n=9 with HIDS) reported that during 6-month treatment period, 1 participant received rescue medicines (NSAIDS and glucocorticoids) during an attack. The results suggest fewer people with HIDS may need to take rescue medicines while on canakinumab to treat their flare. See outcome number 3 for information on the reliability of results.
9.	Quality of life	This outcome looked at the impact of treatment with canakinumab on the person's health and wellbeing. This was measured by the SF-12 health survey (used in people aged 18 years or over) and the child health questionnaire parent form 50 (CHQ-PF50, for people aged 5 years to less than 18 years of age) that was filled in by the parents of children and adolescents. These tools include questions about physical function, pain, general and mental health, vitality, social function, and physical and wellbeing. Higher scores are better. An increase from baseline of 2 (for CHQ-PF50)/3 (for SF-12), 5, and 8 points in the physical and mental/psychological

		component summary scores corresponds to a small, moderate and large treatment effect, respectively. See outcome number 1 for information on the reliability of results. In addition, these results were based on an exploratory analyses (data generated by a study to answer questions which were not the primary focus of the study) with a small number of participants/ parents completing the health questionnaire.
10.	Discontinuations	This outcome considered how many people had to stop taking canakinumab during the study. For people with the condition, the outcome is important to assess whether or not canakinumab is tolerable. The main study found 4 participants stopped treatment with canakinumab. Two participants with MKD stopped canakinumab during the 16-week treatment period because of lack of efficacy with canakinumab. Two participants with TRAPS stopped canakinumab during the open-label phase (part 3), 1 because of grade 2 neutropenia (low white blood cells), which was considered by the investigator to be related to canakinumab that resolved in 5 days, and the other had a mild reduction in their kidney function, which was considered to be unrelated to the canakinumab. Results suggest that people with TRAPS, MKD and cr-FMF taking canakinumab may need to stop treatment which may or may not be due to adverse events caused by canakinumab or worsening of the condition. See outcome number 1 for information on the reliability of results.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
The clinical commissioning policy supports the use of canakinumab for treating periodic fever syndromes (tumour necrosis factor receptor associated periodic syndrome [TRAPS], hyperimmunoglobulin D syndrome/mevalonate kinase

deficiency [HIDS/MKD] and familial Mediterranean fever [FMF]). This is as per its licensed indication. The safety and efficacy of canakinumab in TRAPS, HIDS/MKD and FMF patients under 2 years of age have not been established. It is excluded from tariff.

Considerations from review by National Programme of Care
The proposal received the full support of the Blood and Infection Programme Board on the 12th September 2019.