

Clinical Commissioning Policy: Canakinumab for treating periodic fever syndromes: TRAPS, HIDS/MKD and FMF (ages 2 years and older)

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Policy Statement

NHS England will commission canakinumab for treating periodic fever syndromes: TRAPS HIDS/MKD and FMF in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About periodic fever syndromes; tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) and familial Mediterranean fever (FMF)

Tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) and familial Mediterranean fever (FMF) may be caused by a variety of different genetic defects. The underlying gene defects can cause abnormal activation of the immune system leading to excessive inflammation throughout the body ([European public assessment report \[EPAR\] for canakinumab](#)).

The onset of periodic fevers often begins at childhood, sometimes as early as infancy. Diagnosis of the TRAPS, HIDS/MKD and FMF can be challenging. Family history, clinical evaluation and genetic testing can be helpful, but as yet there is no standardised test available.

Each episode (or flare) lasts for several days to weeks and can cause the person to have a very high temperature, along with symptoms that include extreme fatigue and severe rash. The period between episodes varies depending on the periodic fever, but flares can occur every few weeks spontaneously or be triggered in certain situations. Between flares, patients can still have extreme tiredness and flu-like symptoms and for some patients, there is no gap between flares. As a result of ongoing symptoms, plus uncertainty and concern about when the next flare may happen, daily activities such as school attendance, family life and the ability to remain in employment can be severely impacted by these periodic fever syndromes.

People with these periodic fever syndromes have high levels of certain proteins which cause inflammation which in turn can cause damage to organs including the kidneys and liver over time. Amyloidosis (a condition in which an abnormal protein called amyloid

builds up in tissues and organs) is a complication in people with these conditions and can lead to kidney or liver failure, which can require transplantation.

About current treatments

Current clinical treatments for TRAPS, HIDS/MKD and FMF include symptom treatment for fever, inflammation and pain associated with these conditions. Those treatments include non-steroidal anti-inflammatory drugs (NSAIDs) and short-term high doses of glucocorticoids. Continued NSAIDs use is associated with an increased risk of gastrointestinal and cardiovascular events and continued glucocorticoids use can cause osteoporosis. Glucocorticoids can also suppress growth and may affect the development of puberty in children. Colchicine is also used in people with FMF to control fever attacks and to prevent secondary amyloidosis. However, some people with FMF cannot tolerate or do not respond to colchicine treatment.

[Anakinra](#) is used outside of its marketing authorisation for treating people with TRAPS, HIDS/MKD and FMF who have had a poor response to first line treatments or in whom standard treatments are poorly tolerated and/or for whom long-term high dose glucocorticoid treatment would be the only other treatment option.

About the new treatment

Canakinumab, is a monoclonal antibody (a type of protein that has been designed to recognise and attach to a messenger molecule or 'cytokine' in the body called interleukin-1 beta). This messenger is involved in causing inflammation and is found in high levels in people with periodic fever syndromes. By attaching to interleukin-1 beta, canakinumab blocks its activity, helping to reduce inflammation thereby relieving the symptoms of the diseases. At the time of developing this policy, canakinumab is the only treatment that has a UK marketing authorisation "for the treatment of adults and children aged 2 years or more with TRAPS, MKD/HIDS and FMF."

What we have decided

NHS England has carefully reviewed the evidence to treat TRAPS, HIDS/MKD and FMF with canakinumab. We have concluded that there is enough evidence to make the treatment available in line with the criteria for commissioning set forth below.

1 Introduction

Tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome /mevalonate kinase deficiency (HIDS/MKD) and familial Mediterranean fever (FMF) are inherited auto-inflammatory conditions classified under a single term of periodic fever syndromes. Periodic fever syndromes may be caused by different genetic defects. The underlying gene defects lead to abnormal activation of the innate immune system, leading to dysregulation of cytokines (such as interleukin-1 beta) and excessive inflammation ([European public assessment report \[EPAR\] for canakinumab](#)).

There is overlap in the clinical features across the periodic fever syndromes. These include recurrent episodes of systemic inflammation accompanied by fever (called 'flares' or 'attacks') and characteristic symptoms and signs in target organs and body systems. Between flares, patients can still have extreme tiredness and flu-like symptoms and for some patients, there is no gap between flares. As a result, of ongoing symptoms, plus uncertainty and concern about when the next flare may happen, daily activities such as school attendance, family life and the ability to hold down a job can be severely impacted by these periodic fever syndromes. People with these conditions may develop amyloidosis (a condition in which an abnormal protein called amyloid builds up in tissues and organs), which can lead to kidney or liver failure.

TRAPS, HIDS/MKD and FMF are rare conditions with limited treatment options. Current clinical treatment includes the use of NSAIDs (for all conditions) and glucocorticoids (for TRAPS and HIDS/MKD only) to manage fever, inflammation and pain associated with the conditions. However, these treatments do not control the underlying cause of the symptoms or reduce the frequency of attacks. Continued use of glucocorticoids and NSAIDs are associated with adverse effects such as osteoporosis and increased risk of gastrointestinal and cardiovascular events, respectively. Colchicine is also used in people with FMF to control fever attacks and to prevent secondary amyloidosis. However, colchicine is associated with adverse effects of diarrhoea and transient elevation of transaminases (liver enzymes), and

the rare adverse effects of liver dysfunction, leukopenia (low white blood cells), and neuromyopathy (disease affecting nerves and muscles). People with FMF who do not respond to or are intolerant to colchicine have very few treatment options ([EPAR: canakinumab](#)).

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1 kappa isotype. It binds specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators ([summary of product characteristics: canakinumab](#)).

Canakinumab has a UK marketing authorisation for the treatment of TRAPS, HIDS/MKD and FMF in adults and children aged 2 years and older. It is available as a solution for subcutaneous injection and is administered every 4 weeks as a single dose. The recommended starting dose of canakinumab is:

- 150 mg for people with body weight 40 kg or more
- 2 mg/kg for people with body weight between 7.5 kg and 40 kg

Although not specified in the SPC, canakinumab administered every 8 weeks has been studied and may be an option for a sub-group of patients.

2 Definitions

Term	Definition
Amyloidosis	A condition in which an abnormal protein called amyloid builds up in tissues and organs
Autosomal dominant inheritance	1 gene that is mutated and is inherited from either parent causing a genetic disorder
Autosomal recessive inheritance	2 genes that have mutated are inherited, with 1 coming from each parent, causing a genetic disorder
Biologics	Medicines that are monoclonal antibodies for example canakinumab
Colchicine	Colchicine is a medicine that modulates white cell function and is used as preventative treatment in most people with FMF and sometimes in other periodic fever conditions. Its effectiveness may reduce over time and it may cause intolerable adverse effects such as diarrhoea
Colchicine resistant- familial Mediterranean fever	People with FMF who have an incomplete response to adequate colchicine doses
Corticosteroids	Also known as steroids and are anti-inflammatory medicines used to treat a range of conditions. There are 2 main classes, glucocorticoids (see below) and mineralocorticoids.
C-reactive protein	A type of protein that is raised in response to inflammation
Cytokines	A type of protein produced by cells that have a part to play in the immune system. There are different cytokines based on either the type of cell that makes them or the action they have in the body (for example interleukin 1 is made by leukocytes [type of white blood cell] that acts on other leukocytes). Excess amounts of cytokines can cause inflammation and tissue destruction
Erythrocyte sedimentation rate	Sedimentation rate measures how long it takes red blood cells (erythrocytes) to settle in a test tube over a given period. People with FMF have an elevated

	sedimentation rate, which is an indication of inflammation
Exploratory analyses	Analyses which are performed on the data generated by a study to answer questions which were not the primary focus of the study but which are of interest to the researchers; these analyses may help the researchers to answer new questions which have arisen based on the results of the study or to decide on new questions to investigate in future studies
Febrile	Feverish
Familial Mediterranean fever	Usually, an autosomal recessive syndrome and is caused by mutations of the MEFV gene: occasionally cases of heterozygous FMF (people with only a single copy of a MEFV mutation) are observed suggesting that the disease may be more accurately referred to as variably penetrant autosomal dominant but with gene dosage effect
Hyperimmunoglobulin D syndrome/ mevalonate kinase deficiency	An autosomal recessive syndrome caused by mutations in the mevalonate kinase gene
Glucocorticoids	A class of corticosteroids that has anti-inflammatory and immune system suppressing actions
NSAIDs	Non-steroidal anti-inflammatory drugs
Periodic fever syndrome	Several different auto-inflammatory diseases that have similar symptoms. The primary symptom being a recurrent fever for which no infectious cause can be found
Serum amyloid A	A type of protein produced by the body in response to infection, tissue injury and malignancy. See amyloidosis
Tumour necrosis factor receptor associated periodic syndrome	An autosomal dominant syndrome caused by a mutation of the TNFRSF1A gene

3 Aims and Objectives

This policy considered canakinumab for treating the following periodic fever syndromes in adults, adolescents and children aged 2 years and older:

- tumour necrosis factor receptor associated periodic syndrome (TRAPS),
- hyperimmunoglobulin D syndrome /mevalonate kinase deficiency (HIDS/MKD)
- familial Mediterranean fever (FMF) in combination with colchicine, if appropriate.

The objectives were to:

- Define the eligibility criteria for canakinumab.
- Define the commissioning arrangements required for canakinumab.

4 Epidemiology and Needs Assessment

In England, the estimated prevalence in children and adults that are treated with these conditions (based on expert clinical advice) is 90 people with TRAPS, 38 people with HIDS/MKD and 40 people with cr-FMF.

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indications.

The evidence review primarily considers the results of 1 randomised controlled trial (RCT) (De Benedetti et al. 2018) that was the pivotal study that compared canakinumab with placebo in people with TRAPS (n=46), MKD (n=72) and colchicine-resistant FMF (cr-FMF, n=63) in separate cohorts. It also includes 4 phase 2 open-label single-arm studies, Arostegui et al. 2017 (n=9 with HIDS), Brik et al. 2014 (n=7 with cr-FMF), Gattorno et al. 2017 (n=20 with TRAPS) and Gul et al. 2015 (n=9 with cr-FMF) that all measured efficacy relative to baseline values.

Evidence from the pivotal study suggests that significantly more people with TRAPS, MKD and cr-FMF reported complete response with canakinumab compared with

placebo (45% versus 8%, odds ratio [OR] 9.17 [95% confidence interval [CI] 1.51 to 94.6] p=0.006, 35% versus 6%. OR 8.94 [95% CI 1.72 to 86.4] p=0.003 and 61% versus 6%, OR 23.8 [95% CI 4.38 to 227.5] p<0.001, respectively) at week 16 of the randomised treatment period. The pivotal study also found that in participants with TRAPS, MKD and cr-FMF who did not have a complete response at week 16, the mean number of flares decreased from baseline (10.2, 14.7 and 32.5 per year respectively) to week 40 (normalised to 1 year, 1.2, 2 and 1.2 per year respectively).

In the pivotal study, more participants with TRAPS, MKD and cr-FMF were found to have better control of their condition (measured by the physician's global assessment score [PGA]) and a reduction in inflammation (measured using C-reactive protein [CRP] and serum amyloid A [SAA]) with canakinumab compared with placebo. By reducing the SAA level, the risk of developing kidney failure is reduced which is an important finding for people with the condition

In summary, the studies suggest that canakinumab may resolve flares (or 'attacks'), reduce the number and intensity of flares, reduce inflammation and improve disease control and health-related quality of life in people with TRAPS, HIDS/MKD and cr-FMF. When interpreting these results, the evidence gaps and limitations (see below) should also be taken in to account.

No deaths, opportunistic infections (infections due to changes in the patient's immune system) or cancers were reported in any of the included studies.

Adverse events and serious adverse events were higher with canakinumab compared with placebo (497 versus 136 and 21 versus 8, respectively) during the randomised treatment period of 16 weeks, although people in the canakinumab group had a longer exposure to treatment (12.1, 19.1 and 16.4 patient-years, respectively) compared with the combined placebo group (8 patient-years). The most frequently reported adverse events were infections (particularly respiratory infections), abdominal pain, headaches, and injection-site reactions with 12 being considered serious and had resolved.

A similar adverse event profile was reported in the supporting open-label studies. The pivotal study reported 4 participants discontinued treatment with canakinumab because of adverse events, 1 of which was thought to be unrelated to the

canakinumab. Additionally, the EPAR states that “the adverse event profile of canakinumab treatment is overall mostly comparable in the new proposed indication with the approved CAPS indication.”

The summary of product characteristics for canakinumab states that more than 2,600 people have been treated with canakinumab, including children, healthy volunteers and people in interventional studies with cryopyrin-associated periodic syndromes (CAPS), TRAPS, HIDS/MKD, FMF, systemic juvenile idiopathic arthritis, gouty arthritis or other interleukin-1 beta mediated diseases. The summary of product characteristics (SPC) states that canakinumab is associated with an increased incidence of serious infections and that people receiving treatment should be monitored carefully for signs and symptoms of infections during and after treatment. Caution should be exercised when treating people with infections, a history of recurring infections or underlying conditions that may predispose them to infections.

Canakinumab treatment was commonly studied in children aged 2 years and older and adults only. No data are available for people with renal or hepatic impairment and there is limited data on using canakinumab in pregnant women. Only a sub-population of FMF, cr-FMF, was included in the studies, therefore there is limited data for people with FMF who have no prior use of colchicine.

Main limitations of the studies included the number of participants with TRAPS, HIDS/MKD and cr-FMF in the studies was small because of the conditions being rare. Most of the participants with cr-FMF in the studies took colchicine alongside canakinumab which may confound the results in this population. Most of the studies were of a short duration and so long-term efficacy and safety data are limited in people with TRAPS, HIDS/MKD and FMF. There were no other active comparators to assess place in therapy.

The supporting 4 phase 2 open-label studies’ design and conduct mean they are subject to bias and confounding, are difficult to interpret, and cannot support firm conclusions, although it is important to note that placebo arms are limited for ethical reasons when conducting clinical trials in severe diseases such as these.

6 Criteria for Commissioning

Patient eligibility criteria

Canakinumab may be used in people who have:

TRAPS

- A confirmed diagnosis of TRAPS:
 - Based on family history (first degree relative¹) and history of episodes and associated symptoms, genetic testing, clinical phenotype, evaluation and identification of characteristic symptoms (for example long or life-long lasting fever episodes, skin rash, musculoskeletal pain (tissue pain), abdominal pain, eye manifestations) or
 - Documented evidence of at least 6 episodes a year (based on the inclusion criteria for De Benedetti [2018] and Gattorno [2017]) or
 - Documented evidence of chronic or recurrent disease activity supported by substantially elevated acute phase markers (that include CRP and SAA)

AND whose disease is poorly managed by first line treatments such as NSAIDs or glucocorticoids or with documented significant adverse effects associated with first line treatments.

HIDS/MKD

- A confirmed diagnosis of HIDS/MKD:
 - Based on family history (first degree relative¹) and history of episodes and associated symptoms, genetic testing, clinical phenotype, evaluation and identification of characteristic symptoms (for example long or life-long lasting fever episodes, lymphadenopathy (swollen lymph glands), aphthous ulcers (mouth ulcers), abdominal pain or
 - Documented evidence of at least 6 episodes a year (based on the inclusion criteria for De Benedetti [2018] and Gattorno [2017]) or

¹ This may be supportive but non-mandatory since people with the condition may present with “de novo” such as “first in family” mutations.

- Documented evidence of chronic or recurrent disease activity supported by substantially elevated acute phase markers (that include CRP and SAA) or
- Other supportive tests may include urine tests to detect the presence of mevalonate kinase.

AND whose disease is poorly managed by first line treatments such as NSAIDs or glucocorticoids or with documented significant adverse effects associated with first line treatments.

FMF

- A confirmed diagnosis of FMF:
 - Based on family history (first degree relative¹) and history of episodes and associated symptoms, genetic testing, clinical phenotype, [Tel-Hashomer diagnostic criteria](#), evaluation and identification of characteristic symptoms (chest pain, abdominal pain, arthralgia/arthritis [aching joints/swollen joints], skin rash) or
 - Documented evidence of 1 or more episodes per month despite colchicine (1.5 to 3 mg/day or equivalent paediatric adjusted regimen), or with unacceptable side-effects to colchicine or
 - Documented evidence of chronic or recurrent disease activity supported by substantially elevated acute phase markers (that include CRP and SAA).

AND whose disease is poorly managed by first line treatments such as NSAIDs and where colchicine has not proved effective or where there are documented significant adverse effects associated with first line treatments.

Treatment initiation

Treatment should begin during active flare. The recommended starting dose for the treatment of TRAPS, HIDS/MKD and FMF is 150 mg for people with a body weight greater than 40 kg and 2 mg/kg for people with body weight between 7.5 kg and 40 kg. If the flare is not resolved after 7 days of first dose then another dose of 150 mg (2 mg/kg for body weight between 7.5 kg and 40 kg) is given, with subsequent maintenance dose being equal to the initial loading dose 4-weekly. Canakinumab should not be injected earlier than 4 weeks after the last dose.

Continuation criteria

- Blood tests: measures of systemic inflammation (CRP and SAA levels less than 10 mg/l, when not experiencing a flare)
- Physician's global assessment (PGA): scores of less than 2²
- At least a 50% reduction in baseline number of annual flares or significant subjective decrease in the intensity of flares

People with TRAPS, MKD/HIDS or cr-FMF who have a partial response (less than defined above) should continue for 6 months. If, at the end of that period the disease response achieved is below the threshold of moderate response (defined as a PGA (defined in the pivotal study [De Benedetti et al. 2018](#)) score of less than 2 plus CRP level of 10 mg/l or less when not flaring or a reduction by 50% or more from baseline, and no reduction in flare intensity) the treatment should be stopped.

Stopping criteria for TRAPS, HIDS/MKD and FMF/cr-FMF

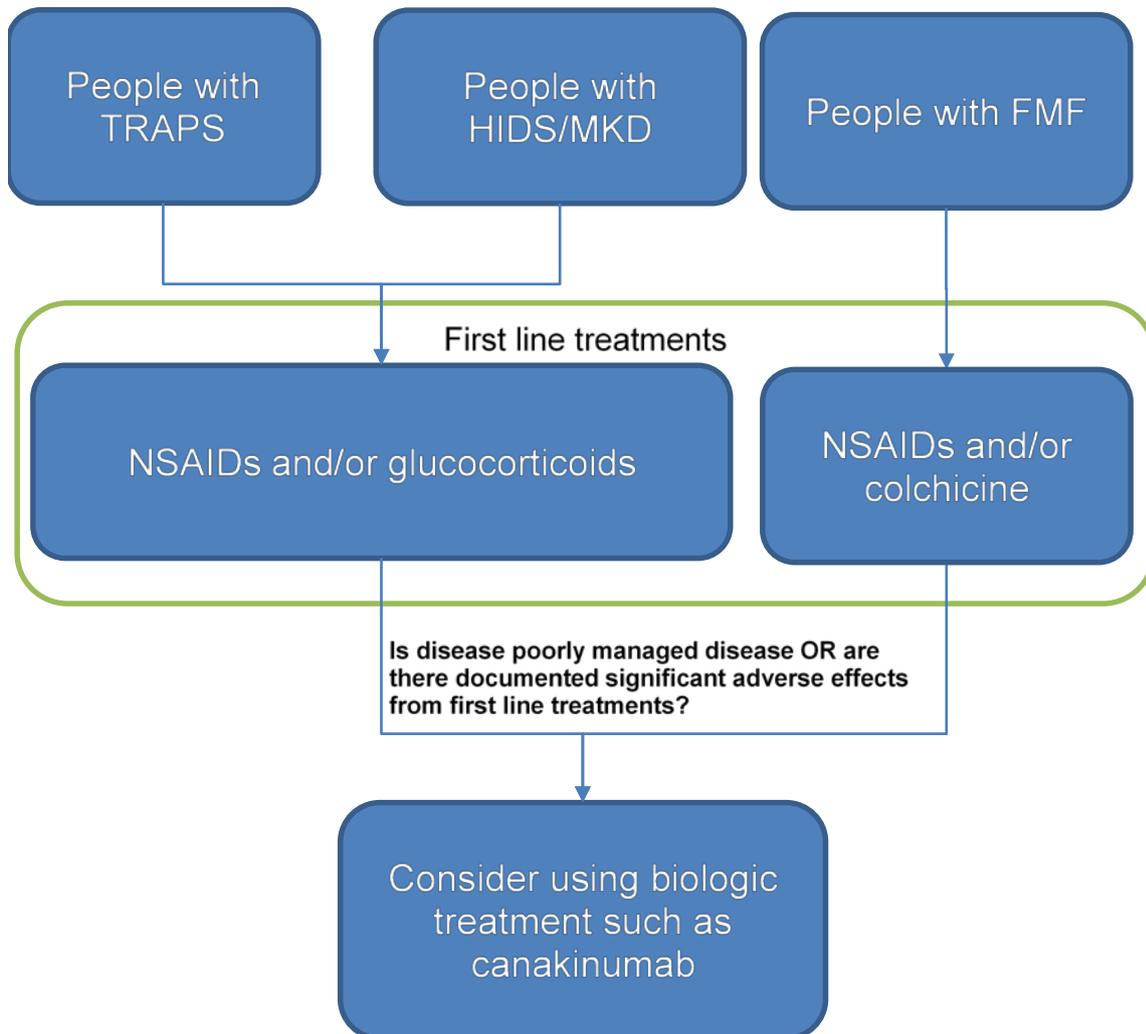
The stopping criteria for all three diseases are:

- Inadequate clinical response to treatment (defined above)
- Emergence of adverse effects, including neutropenia; these may be managed by varying the dose or occasionally temporarily discontinuing the drug
- Active infection requiring medical intervention (see [SPC](#))
- Unusual or opportunistic infections including aspergillosis, atypical mycobacterial infections, herpes zoster (see [SPC](#))
- Unusual laboratory tests such as raised LFTs, platelets, neutrophils
- If canakinumab is poorly tolerated
- If there is evidence of non-compliance

Approval for use of canakinumab requires a multidisciplinary Team (MDT) discussion between the referring centre and the European Reference Network (ERN) centre.

² The PGA score is the score used in the CLUSTER study (NEJM 2018 378:1908-19) which classed disease activity by physician's global assessment from: absent (0), minimal (1), mild (2), moderate (3) to severe (4) in relation to the severity of the patient's symptoms.

7 Patient Pathway



Canakinumab treatment should be managed within specialist centres that have the expertise to manage these complex conditions. Typically, such centres are member of the Rare Immunodeficiency, Autoinflammatory and Autoimmune Disease Network (RITA) ERN. Centres with expertise in adult rheumatology, paediatric rheumatology and adult or paediatric immunology (as appropriate) may prescribe this treatment after discussion with an English NHS Trust that is a member of the RITA ERN.

Canakinumab should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication (SPC: canakinumab).

8 Governance Arrangements

Canakinumab can only be prescribed for people with TRAPS, HIDS/MKD and cr-FMF by providers who centres are member of the Rare Immunodeficiency, Autoinflammatory and Autoimmune Disease Network (RITA) ERN. Centres with expertise in adult rheumatology, paediatric rheumatology and adult or paediatric immunology (as appropriate) may prescribe this treatment after discussion with an English NHS Trust that is a member of the RITA ERN.

Provider organisations must register all people with TRAPS, HIDS/MKD and cr-FMF using prior approval system software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined

9 Mechanism for Funding

The proposed mechanism for funding is via established mechanisms for high-cost tariff-exempt drugs to NHS England Specialised Commissioning teams.

10 Audit Requirements

The services will develop a standard data set of biochemical markers and attack frequency and use a standard monitoring system to collate this for standard clinical audit processes. Services will meet annually to share and review outcomes based on the agreed data collection. Patient representatives and commissioners will be invited to this audit day.

11 Documents which have informed this Policy

The documents that have informed this policy include a review of the clinical evidence available for canakinumab, the [European public assessment report](#) (EPAR), [Summary of product characteristics](#) (SPC) [NHS England's specialised](#)

[clinical commissioning policy for anakinra](#), as well as the publications listed in the reference section below.

12 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or not for routine commissioning.

13 References

Arostegui JI, Anton J, Calvo I et al (2017) Open-Label, Phase II Study to Assess the Efficacy and Safety of Canakinumab Treatment in Active Hyperimmunoglobulinemia D with Periodic Fever Syndrome. *Arthritis & Rheumatology* 69(8): 1679–1688

Bashardoust B (2015) Familial Mediterranean fever; diagnosis, treatment, and complications. *Journal of Nephro pharmacology* 4(1): 5–8

Brik R, Butbul-Aviel Y, Lubin S et al (2014) Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study. *Arthritis & Rheumatology* 66 (11): 3241–3

De Benedetti, Gattorno M, Anton J et al (2018) Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. *The New England Journal of Medicine* 378(20): 1908–1919

Gattorno M, Obici L, Cattalini M et al (2017) Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. *Annals of the Rheumatic Diseases* 76(1): 173–178

Genetic and Rare Diseases Information Centre: hyperimmunoglobulin D syndrome. <https://ghr.nlm.nih.gov/condition/mevalonate-kinase-deficiency> (accessed Nov. 2018).

Genetic and Rare Diseases Information Centre: familial Mediterranean fever. <https://ghr.nlm.nih.gov/condition/familial-mediterranean-fever> (accessed Nov 2018).

Genetic and Rare Diseases Information Centre: tumour necrosis factor receptor associated periodic syndrome. <https://ghr.nlm.nih.gov/condition/tumor-necrosis-factor-receptor-associated-periodic-syndrome> (accessed Nov 2018).

Gul A, Ozdogan H, Erer B et al (2015) Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. *Arthritis Research & Therapy* 17: 243

National Organisation for Rare Disorders: [Report on mevalonate kinase deficiency](#). (accessed Nov 2018).

NHS England, Clinical Commissioning Policy: Anakinra to treat periodic fevers and autoinflammatory diseases (all ages), July 2018. <https://www.england.nhs.uk/wp-content/uploads/2018/07/1713-anakinra-for-periodic-fever.pdf> (accessed Nov 2018).

Ozen S, Demirkaya E, Erer B, et al (2015) EULAR recommendations for the management of familial Mediterranean fever. *Annals of the rheumatic diseases* 75: 644–651

Ter Haar N, Oswald M, Jeyaratnam J et al (2015) Recommendations for the management of autoinflammatory diseases. *Annals of the Rheumatic Diseases* 74(9): 1636–1644

Nigrovic, MD (2018) [Periodic fever syndromes and other auto-inflammatory diseases: An overview](#). UpToDate (accessed Nov 2018).

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