GIG CYMRU NHS WALES

Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)

Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy Position PP228

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

January 2022

Version 1.0

PARCH - RESPECT

PARTNERIAETH - PARTNERSHIP

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Document information	
Document purpose	Policy Position
Document name	Canakinumab for treating periodic fever syndromes: TRAPS, HIDS/MKD and FMF (ages 2 and older)
Author	Welsh Health Specialised Services Committee
Publication date	25 January 2022
Commissioning Team	Neurosciences and Complex Conditions
Target audience	Chief Executives, Medical Directors, Directors of Finance, Clinical Immunologists, Allergists, Rheumatologists, Paediatrics, Clinical Genetics
Description	NHS Wales routinely commission this specialised service in accordance with the criteria described in this policy
Document No	PP228
Review Date	2025

Contents

Policy Statement

Welsh Health Specialised Services Committee (WHSSC) commission canakinumab for treating periodic fever syndromes in people aged 2 years and over in accordance with the criteria outlined in this document.

In creating this document WHSSC has reviewed the relevant guidance issued by NHS England[1] and has concluded that canakinumab should be made available.

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy position statement.

This policy may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian, or Local Authority.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this policy position statement.

[1] https://www.england.nhs.uk/wp-content/uploads/2020/03/Canakinumab-for-treating-periodic-fever-syndromes-TRAPS-HIDSMKD-and-FMF-ages-2-years-and-older.pdf

1. Introduction

This Policy Position Statement has been developed for the planning and delivery of canakinumab for treating periodic fever syndromes in people aged 2 and over who are resident in Wales. This service will only be commissioned by the Welsh Health Specialised Services Committee (WHSSC) and applies to residents of all seven Health Boards in Wales.

1.1 Plain language summary

Periodic fever syndromes include, 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.

1.2 Aims and Objectives

This Policy Position Statement aims to define the commissioning position of WHSSC on the use of canakinumab for people with periodic fever syndromes.

The objectives of this policy are to:

- ensure commissioning for the use of canakinumab is evidence based
- ensure equitable access to canakinumab
- define criteria for people with periodic fever syndromes to access treatment
- improve outcomes for people with periodic fever syndromes.

1.3 Epidemiology

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 [2].

1.4 Current Treatment

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 can be 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. However, it is currently not commissioned for use in any of these indications in NHS Wales[3].

1.5 Proposed 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

[2] Clinical Commissioning Policy Proposition: canakinumab for treating periodic fever syndromes: TRAPS, HIDS/MKD and FMF (ages 2 and older), 2019
[3] https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/anakinra-kineret1/

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."

1.6 What NHS Wales has decided

WHSSC has carefully reviewed the relevant guidance issued by NHS England. We have concluded that canakinumab should be made available within the criteria set out in section 2.1.

2. Criteria for Commissioning

The Welsh Health Specialised Services Committee approve funding of canakinumab for treating periodic fever syndromes in people aged 2 and over, in-line with the criteria identified in the policy.

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

2.1 Inclusion Criteria

Canakinumab may be used in people who have:

TRAPS

- A confirmed diagnosis of TRAPS:
  - Based on family history (first degree relative[4]) 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 relative[2]) 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), aphtous ulcers (mouth ulcers), abdominal pain.

[4] This may be supportive but non-mandatory since people with the condition may present with "de novo" such as "first in family" mutations.

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).

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 relative[5]) 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.

2.2 Treatment Initiation

Begin treatment 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

[5] This may be supportive but non-mandatory since people with the condition may present with "de novo" such as "first in family" mutations.

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.

2.3 Continuation of Treatment

Continuation of treatment 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: scores of less than 2.
- 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.

2.4 Stopping Criteria for TRAPS, HIDS/MKD and FMF/cr-FMF

The stopping criteria for all 3 diseases are:

- Inadequate clinical response to treatment (see section 2.3 Continuation of Treatment).
- 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.

2.5 Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.6 Patient Pathway (Annex i)

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 a Centrethat is a member of the RITA ERN.

Canakinumab can only be prescribed by Providers who have an NHS Wales contract and are compliant with the service specifications for specialised immunology, paediatric medicine, and paediatric rheumatology (these service specifications are currently in development by WHSSC).

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

2.7 Exceptions

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

2.8 Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to WHSSC. Providers are expected to submit the following information:

- Service activity
- Treatment success rates
- Adverse incidents or SUIs
- Patient Reported Outcome Measures (PROMS).
- Patient Reported Experience Measures (PREMS).

The designated centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should

be made for patients with communication difficulties and for children, teenagers and young adults.

2.9 Responsibilities

Referrers should:

- inform the patient that this treatment is not routinely funded outside the criteria in this policy, and
- refer via the agreed pathway.

Clinician considering treatment should:

- discuss all the alternative treatment with the patient
- advise the patient of any side effects and risks of the potential treatment
- inform the patient that treatment is not routinely funded outside of the criteria in the policy, and
- confirm that there is contractual agreement with WHSSC for the treatment.

In all other circumstances an IPFR must be submitted.

3. Documents which have informed this policy

The following documents have been used to inform this policy:

- **National Institute of Health and Care Excellence (NICE) guidance**
  - NICE Commissioning Support Programme: Scope to inform clinical evidence review of: canakinumab for the treatment of periodic fever syndromes (TRAPS, HIDS/MKD and FMF), NICE ID012, June 2018

- **NHS England policies**
  - Clinical Commissioning Policy Proposition: canakinumab for treating periodic fever syndromes: TRAPS, HIDS/MKD and FMF (ages 2 and older), 2019

This document should be read in conjunction with the following documents:

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

4. Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

5. Putting Things Right

5.1 Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to WHSSC.

5.2 Individual Patient Funding Request (IPFR)

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, an IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

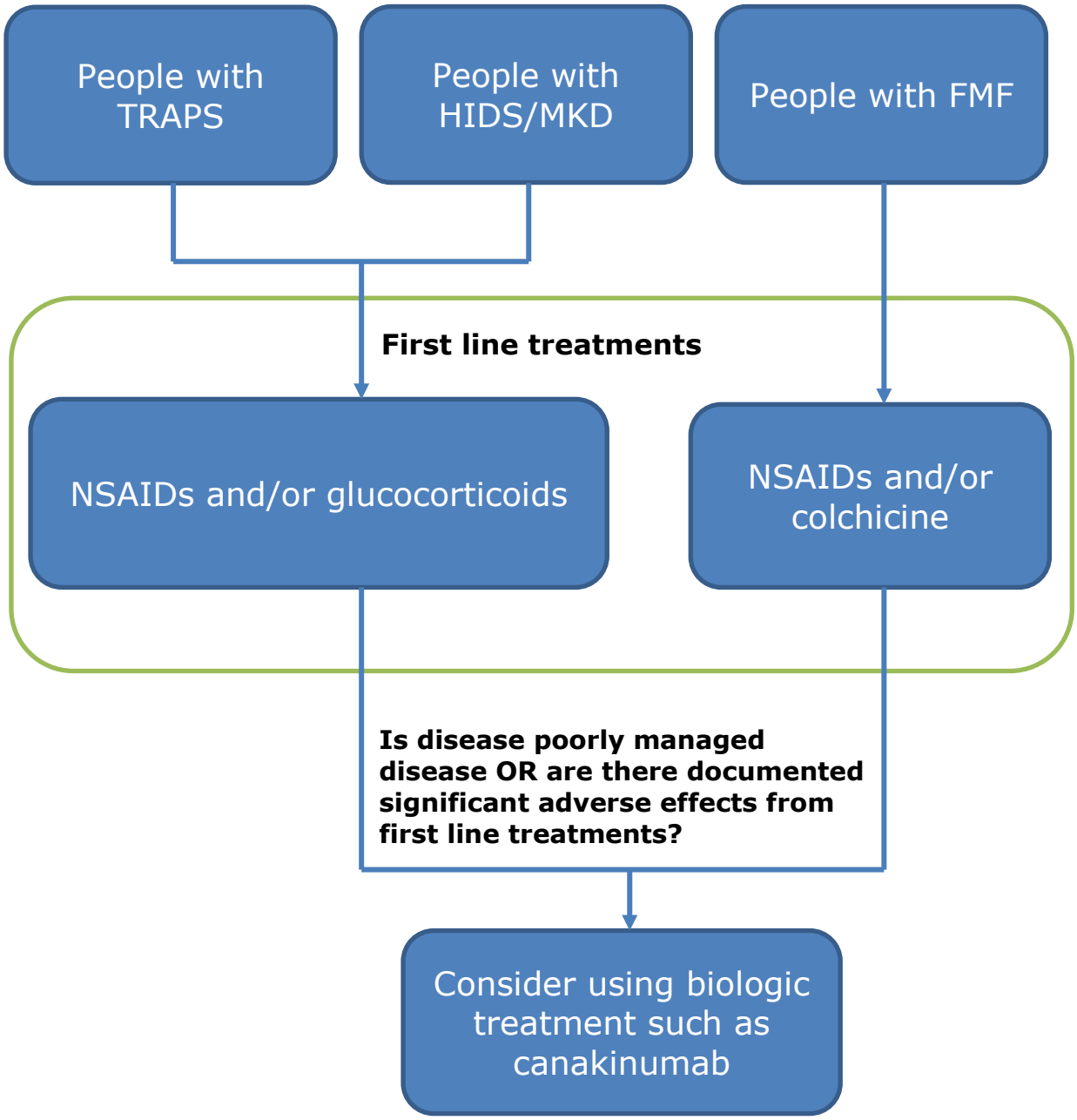
6. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

This policy has been subjected to an Equality Impact Assessment.

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

Annex i Patient Pathway



Annex ii Abbreviations and Glossary

Abbreviations

FMF	Familial Mediterranean Fever
HIDS	Hyperimmunoglobulin D Syndrome
IPFR	Individual Patient Funding Request
MKD	Mevalonate Kinase Deficiency
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
TRAPS	Tumour Necrosis Factor Receptor Associated Periodic Syndrome
WHSSC	Welsh Health Specialised Services Committee

Glossary

Amyloidosis
A condition in which an abnormal protein called amyloid builds up in tissues and organs.

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.

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.

Glucocorticoids
A class of corticosteroids that has anti-inflammatory and immune system suppressing actions.

Individual Patient Funding Request (IPFR)
An IPFR is a request to Welsh Health Specialised Services Committee (WHSSC) to fund an intervention, device or treatment for patients that fall outside the range of services and treatments routinely provided across Wales.

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.

Tumour Necrosis Factor Receptor Associated Periodic Syndrome
An autosomal dominant syndrome caused by a mutation of the TNFRSF1A gene.

Welsh Health Specialised Services Committee (WHSSC)
WHSSC is a joint committee of the seven local health boards in Wales. The purpose of WHSSC is to ensure that the population of Wales has fair and equitable access to the full range of Specialised Services and Tertiary Services. WHSSC ensures that specialised services are commissioned from providers that have the appropriate experience and expertise. They ensure that these providers are able to provide a robust, high quality and sustainable services, which are safe for patients and are cost effective for NHS Wales.