# Health Technology Briefing
# December 2021

## Canakinumab for Schnitzler syndrome

| Company/Developer | Novartis Pharmaceuticals UK Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 33346 | NICE ID: 10700 | UKPS ID: 662114 |
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## Licensing and Market Availability Plans

Currently in phase II/III clinical development.

## Summary

Canakinumab is in clinical development for the treatment of adults with Schnitzler syndrome. Schnitzler syndrome is a rare inflammatory condition. The exact underlying cause is currently unknown, however certain proteins of the immune system (including cytokines) play a role in the development of the inflammation in Schnitzler syndrome. The first clinical sign of this condition is usually a mildly or non-itchy skin rash; other symptoms include fevers, joint pain and inflammation, enlarged internal organs, bone pain and muscle aches. There are currently no approved treatments for Schnitzler syndrome.

Canakinumab is monoclonal antibody (a type of protein) that has been designed to recognise and attach to a cytokine in the body called interleukin-1 beta. This cytokine is involved in causing inflammation and is overproduced in patients with Schnitzler syndrome. By attaching to interleukin-1 beta, canakinumab blocks its activity, helping to reduce inflammation. Canakinumab is given through subcutaneous injection, and if licensed, may be a potential therapeutic option for adults with Schnitzler syndrome.

## Proposed Indication

Adult patients with Schnitzler syndrome.[1]

# Technology

## Description

Canakinumab (Ilaris) is a human anti-interleukin 1 beta (IL-1β) monoclonal antibody which neutralises IL-1β signalling. IL-1β is a pro-inflammatory cytokine that acts as mediator of the peripheral immune response during infection and inflammation, but is also implicated in acute and chronic autoimmune diseases.[2] By attaching to IL-1β, canakinumab blocks its activity, helping to reduce inflammation thereby relieving the symptoms of the disease.[3]

Canakinumab is in clinical development for the treatment of adults with Schnitzler syndrome. In the phase II clinical trial (NCT01390350), canakinumab 150mg or placebo was administered as a single subcutaneous (SC) injection on day 0, with response assessment on day 7 and additional open-label canakinumab treatment upon relapse for patients in both study arms.[1]

## Key Innovation

Approved treatment options are completely lacking in Schnitzler syndrome. The use of systemic corticosteroids, other immunosuppressives, and nonsteroidal antiphlogistics has demonstrated poor efficacy.[4]

In a previous clinical trial (NCT01245127), canakinumab induced a swift and sustained clinical response in the treatment of Schnitzler syndrome, with disappearance of fever and arthralgias, near abolishment of fatigue and rash, and substantial reduction of C-reactive protein levels.[5]

Canakinumab has proved to be an effective, safe and longer-acting alternative to other IL-1 receptor antagonists which require painful daily injections for the treatment of Schnitzler syndrome.[6]

## Regulatory & Development Status

Canakinumab is currently indicated in the UK for the following indications:[7]

- Periodic fever syndromes
  - Cryoprin-associated periodic syndromes (CAPS)
  - Tumour necrosis factor receptor-associated periodic syndrome
  - Hyperimmunoglobulin D syndrome/mevalonate kinase deficiency
  - Familial Mediterranean fever
- Gouty arthritis
- Still's disease

Canakinumab is currently in Phase II and III clinical development for various indications, some of which include:[8]

- Alzheimer's
- Knee osteoarthritis
- Non-Small Cell Lung Cancer (NSCLC)
- Duchenne muscular dystrophy
- Adult-Onset Still's Disease

Canakinumab was granted orphan drug designation in the USA in 2007 for the treatment of cryopyrin-associated periodic syndromes.[9]

# Patient Group

## Disease Area and Clinical Need

Schnitzler syndrome is a rare autoinflammatory condition. The exact underlying cause of Schnitzler syndrome is currently unknown. People affected by this condition often have a blood abnormality called monoclonal gammopathy, a condition in which the body over-produces certain immunoglobulins (typically immunoglobulin M). Immunoglobulins are proteins that are made by certain white blood cells. They play a role in the immune response by helping destroy bacteria, viruses, and other substances that appear foreign and harmful. It is believed that the abnormal accumulation of immunoglobulins in the skin and other parts of the body may play a role in the development of the signs and symptoms of Schnitzler syndrome. Alterations in cytokines may also play a role in the development of this disease. Cytokines are specialized proteins that play an important role in the immune response. Abnormal findings involving a specific cytokine called IL-1 have been found in some people with Schnitzler syndrome.[10]

Symptoms of Schnitzler syndrome include: urticaria (hives) which is a rash that consists of raised, reddish bumps (papules) and flatter, wider lesions (plaques), and is normally the first symptom to appear in individuals with Schnitzler syndrome; fever which may be accompanied by chills and night sweating; bone pain most often affecting the lower legs and hips, and arthritis most often affecting the large joints such as the hips, knees, wrists and ankles; and abnormal enlargement of the lymph nodes (lymphadenopathy), the liver (hepatomegaly) and the spleen (splenomegaly) may also occur in some cases.[11,12]

The exact prevalence of Schnitzler syndrome is unknown and about 150 cases have been reported, primarily in Europe. There is a slight male predominance and the mean age of disease onset is 51 years. Time to diagnosis often exceeds 5 years.[13] The prevalence of Schnitzler syndrome is fewer than 50 patients in England.[14]

## Recommended Treatment Options

There are currently no NICE recommended pharmacological treatment options for this indication/patient population.

NHS reports that therapies such as antihistamines, NSAIDs, steroids, colchicine, hydroxychloroquine and pefloxacin are used as first line treatments for patients with Schnitzler's syndrome. These treatments usually provide only partial or temporary improvement of the symptoms.[14]

## Clinical Trial Information

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| Trial | **ILESCH; NCT01390350, EudraCT- 2010-024156-28;** A Multi-center, Double-blind, Placebo-controlled Phase II Study of the Efficacy and Safety of Canakinumab in Subjects With Schnitzler Syndrome<br>**Phase II –** completed<br>**Location(s):** Germany<br>**Actual study completion date:** May 2018 |
| Trial Design | Randomised, placebo-controlled, parallel assignment, double-blind |
| Population | N=20; Adult patients with symptomatic Schnitzler syndrome; aged 18 years and older |
| Intervention(s) | Canakinumab 150mg subcutaneous (SC) injection on day 0, with response assessment on day 7 and additional open-label canakinumab treatment upon relapse for patients in both study arms |

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| Comparator(s) | Matched placebo |
| Outcome(s) | Primary outcome:<br>The effect of canakinumab on the clinical signs and symptoms of symptomatic Schnitzler syndrome measured by physician's global assessment [Time frame: 16 months]<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | The proportion of patients with complete clinical response at day 7 was significantly higher (P = .001) in the canakinumab-treated group (n = 5 of 7) than in the placebo group (n = 0 of 13). Levels of inflammation markers C-reactive protein and serum amyloid A and quality-of-life scores were significantly improved in canakinumab-treated but not in placebo-treated individuals. Positive effects continued up to 16 weeks.[4] |
| Results (safety) | Adverse events were manageable and included respiratory tract infections, gastrointestinal symptoms, and hypertension.[4] |

## Estimated Cost

Canakinumab is already marketed in the UK; the list price of a 150mg/ml vial is £9,927.80.[15]

## Relevant Guidance

### NICE Guidance

No relevant NICE guidance identified.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Canakinumab for treating periodic fever syndrome TRAPS, HIDS/MKD and FMF (ages 2 years and older). 200209P. February 2020.
- NHS England. Clinical Commissioning Policy: Anakinra to treat periodic fevers and autoinflammatory diseases (all ages). 170062P. June 2018.
- NHS England. 2013/14 NHS Standard Contract for Cryopyrin Associated Periodic Syndrome (all ages). E13/S(HSS)/b.

### Other Guidance

No relevant guidance identified.

## Additional Information

## References

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