HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

10 February 2010

**ILARIS 150 mg powder for solution for injection**
**B/1 vial (CIP: 397 457-6)**

**Applicant: NOVARTIS PHARMA SAS**

canakinumab

List I
Medicine for hospital prescription only.
Initial prescription and renewal restricted to specialists in rheumatology, internal medicine, dermatology, or paediatrics.
Medicine requiring special monitoring during treatment.

Orphan medicinal product (date of designation: 20 March 2007)

ATC code: L04AC08

Exceptional-prescription drug

Date of Marketing Authorisation (centralised procedure): 23 October 2009

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

*This medicine has been authorised under "Exceptional Circumstances". This means that because of the rarity of the disease it has been impossible to get complete information on the medicine. The EMA will review any new information on the medicine every year, and the SPC will be updated as necessary.*

Medical, Economic, and Public Health Assessment Division

# 1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredient

canakinumab

## 1.2. Indications

"ILARIS is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight above 15 kg, including:

- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash."

## 1.3. Dosage

"Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of CAPS.
After proper training in the correct injection technique, patients may self-inject ILARIS if their physician determines that it is appropriate and with medical follow-up as necessary.

Adults, adolescents and children aged 4 years and older
The recommended dose of ILARIS is 150 mg for CAPS patients with body weight > 40 kg and 2 mg/kg for CAPS patients with body weight ≥ 15 kg and ≤ 40 kg. This is administered every eight weeks as a single dose via subcutaneous injection.
If a satisfactory clinical response (resolution of rash and other generalised inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of ILARIS at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg and 4 mg/kg should be maintained. No experience exists for doses > 600 mg every 8 weeks. Clinical experience with dosing at intervals of less than 4 weeks is limited.

Special populations
*Paediatric population*
ILARIS is not recommended for use in children below 4 years of age or with body weight below 15 kg due to a lack of clinical data.

*Elderly*
Clinical experience in patients above 65 years is limited, therefore caution is recommended.

*Hepatic impairment*
ILARIS has not been studied in patients with hepatic impairment.

*Renal impairment*
No dose adjustment is needed in patients with renal impairment. However, clinical experience in such patients is limited."

## 2. SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2010)

| | |
|---|---|
| L | Antineoplastic and immunomodulating agents |
| L04 | Immunosuppressants |
| L04A | Immunosuppressants |
| L04AC | Interleukin inhibitors |
| L04AC08 | canakinumab |

### 2.2. Medicines in the same therapeutic category

ARCALYST 80 mg/ml, powder and solvent for solution for injection, (rilonacept) from REGENERON company indicated "for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) with severe symptoms, including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children aged 12 years and older."
(Date of Marketing Authorisation by centralised procedure: 23 October 2009, proprietary product not evaluated by the Transparency Committee)

### 2.3. Medicines with a similar therapeutic aim

The treatments used at present are symptomatic and used off-label (see Therapeutic strategy).

## 3. ANALYSIS OF AVAILABLE DATA

The clinical development of canakinumab (ILARIS) in the treatment of cryopyrin-associated periodic syndromes (CAPS) is based on:
- a dose-titration study (study 2102), which will not be described because it evaluated a dosage regimen different from the one accepted in the Marketing Authorisation[1],
- a phase III comparative study versus placebo, carried out in patients with Muckle-Wells syndrome (study 2304),
- an open, long-term follow-up study that is still ongoing (study 2306), for which we have interim results (analysis on 9 January 2009).

### 3.1. Efficacy results

#### 3.1.1. Results of the clinical study versus placebo (study 2304)[2]

Method and aim:
Phase III, randomised, double-blind, comparative study, the main aim of which was to evaluate the efficacy and safety of canakinumab therapy in patients with Muckle-Wells syndrome in comparison with placebo, after 24 weeks of treatment.

This study had 3 phases:

[1] This phase II study had 2 administration phases: an intravenous administration phase (with an initial injection of 10 mg/kg then a 2nd one of 1 mg/kg administered until relapse), then a subcutaneous administration phase using a dose of 150 mg; during the latter phase the efficacy and safety of canakinumab were evaluated.
[2] Lachmann, Koné-Paut et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. NEJM 2009;360(23):2416-2425

- an initial phase lasting 8 weeks during which all patients received a subcutaneous injection of canakinumab on an open basis. Patients responding to canakinumab at the end of this initial phase were included in the 2nd phase of the study.
- This 2nd phase, which lasted 24 weeks, was a randomised, double-blind comparison versus placebo.
- The 3rd phase, an open phase lasting 16 weeks, during which all the patients were treated with canakinumab, included patients who had either completed the 2nd phase or relapsed during the 2nd phase. Patients started the 3rd part of the study in the 32nd week of treatment or earlier in the case of those who relapsed during the 2nd phase. The data from this phase, of an exploratory nature, will not be described; only the comparative results of the 2nd phase will be presented.

Inclusion criteria:
- patients with Muckle-Wells syndrome with a confirmed NLRP3/NALP3 mutation in need of treatment
- patients of 4 to 75 years of age weighing ≥ 15 and < 100 kg
- patients previously treated with an interleukin-1 antagonist (anakinra, IL-1 inhibitors under development, canakinumab), after discontinuation of that treatment and a finding of relapse[3].

Non-inclusion criteria:
- a history of repeated (bacterial, fungal, or viral) infections or signs of infection in progress
- immunocompromised patients and patients positive for HIV or hepatitis B or C
- patients who had been vaccinated with a live vaccine in the last three months or patients with a positive tuberculin test.

Administration regimen:
The patients received canakinumab s.c. at a dose of 150 mg if their body weight was > 40 kg and at a dose of 2 mg/kg if their body weight was ≥ 15 kg and ≤ 40 kg, in accordance with the SPC.
During the 1st phase, a single injection was administered.
During the 2nd phase, the patients received an injection of either canakinumab or placebo every 8 weeks.
During the 3rd phase, the patients received an injection of canakinumab every 8 weeks.

Primary endpoint:
Percentage of patients with relapse after 24 weeks of treatment (during the 2nd phase)

A complete response was defined (depending on the investigator's assessment) as a global assessment of autoinflammatory disease intensity of ≤ "minimal" together with an assessment of skin manifestations of ≤ "minimal" and a normal concentration of CRP and/or SAA.

In the patients who obtained a complete response, a relapse was defined as:
- a CRP and/or SAA value of > 30 mg/l **and**
  **- either** a global assessment of autoinflammatory disease intensity > "minimal"
  **- or** a global assessment of autoinflammatory disease intensity of "minimal" together with an assessment of skin manifestations > "minimal"
- discontinuation of treatment for any reason.

[3] Previously treated patients could only join the study after their treatments had been discontinued for the predetermined specific periods:
- 1 week for corticosteroids ≥ 20 mg/day or > 0.4 mg/kg,
- 3 weeks for colchicine, dapsone, mycophenolate,
- 4 weeks for etanercept, leflunomide, thalidomide, ciclosporin,
- 8 weeks for adalimumab, intravenous immunoglobulin,
- 12 weeks for infliximab, 6-mercaptopurine, azathioprine, cyclophosphamide, chlorambucil.

The protocol specified that, to establish canakinumab's superiority to placebo on the primary endpoint with a power of 90% on the assumption of a frequency of relapse of 15% in the canakinumab group and 90% in the placebo group, 10 patients were to be included in each group.

Main secondary endpoints:
- change in inflammation markers (levels of CRP and SAA)[4]
- investigator's global assessment of autoinflammatory disease activity and symptoms[5]
- patient's assessment of symptom intensity[6]
- quality of life[7] (the analysis of which was exploratory).

Characteristics of the patients at inclusion:
Table 1: Clinical characteristics of the patients

| | **1st phase** | **2nd phase** | |
|---|---|---|---|
| | **canakinumab group N = 35** | **canakinumab group N = 15** | **placebo group N = 16** |
| Age (years) | | | |
| Mean (SD) | 34 (14.9) | 34.3 (14.39) | 33.4 (16.09) |
| Age groups (n) | | | |
| ≥ 4 - < 17 years | 4 | 2 | 2 |
| 17 - < 41 years | 17 | 6 | 9 |
| ≥ 41 - < 75 years | 14 | 7 | 5 |
| | | | |
| Median weight (kg) | 61.0 | 60.0 | 62.5 |
| Previous treatment with anakinra (n) | 17 | 5 | 8 |
| Confirmed NALP3 mutation (n) | 35 | 15 | 16 |
| Audiogram result | | | |
| Normal (n) | 5 | 3 | 1 |
| Non-significant abnormality (n) | 8 | 4 | 3 |
| Significant abnormality (n) | 22 | 8 | 12 |
| CRP level (mg/l) | | | |
| Mean (SD) | 30.7 (27.1) | 29.2 (25.7) | 37.6 (29.0) |
| Median | 20.0 | 19.6 | 26.0 |

[4] C-reactive protein (CRP) and serum amyloid A (SAA) were the two biological inflammation markers investigated. CRP is the standard examination routinely used for the monitoring of autoinflammatory diseases. SAA is not used in everyday practice but is evidently the most sensitive marker of inflammation between clinical attacks and also correlates very well with the risk of amyloidosis. Normal CRP value: 10 mg/l, normal SAA value: 2.5 mg/l

[5] investigator's global assessment of autoinflammatory disease intensity (on a 5-term scale: absent, minimal, mild, moderte, severe).
investigator's assessment of the intensity of the following 8 manifestations: skin involvement (urticarial rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue or malaise, other symptoms connected with the autoinflammatory disease, other symptoms not connected with the disease.

[6] patient's assessment of the following symptoms: fever or cold shivers, skin rash, joint or muscle pain, eye discomfort or redness, fatigue, headaches, and other symptoms. The presence and intensity of the clinical symptoms were measured using a 5-term scale (absent, minimal, mild, moderate, severe).

[7] evaluated using 3 questionnaires:
- FACIT-F (Functional Assessment of Chronic Illness Therapy Fatigue) which takes account of the impact of fatigue on general health; a maximum score of 52 corresponds to good general health.
- SF-36 (Medical Outcome Short Form (36) Health Survey), with evaluation of the physical score and mental score. This scale runs from 0 to 100; a score > 50 indicates a better quality of life.
- CHQ-PF28 (Child Health Questionnaire), scale running from 0 to 100, a score > 50 indicating a better quality of life for the child.

| SAA level (mg/l) | | | |
|---|---|---|---|
| Mean (SD) | 137.3 (165.6) | 141.9 (178.4) | 162.2 (167.6) |
| Median | 48.9 | 48.2 | 111.9 |

Thirty five patients were included in this study. The patients' mean age was 34 years.
At the time of inclusion, the inflammatory disease intensity of the majority of the patients was moderate. Levels of the biological markers testify to the intensity of the inflammatory reaction.
Two of the patients included had amyloidosis. The most commonly observed neurosensory abnormalities were audiogram abnormalities.

At the end of the 1st phase, 31/35 patients showed a complete response and were included in the 2nd phase of the study (15 patients in the canakinumab group and 16 in the placebo group).

Primary endpoint:
After 24 weeks' treatment, a relapse was observed in 13/16 patients in the placebo group. No patients in the canakinumab group had a relapse ($p < 0.001$).

Main secondary endpoints:

- change in inflammation markers (levels of CRP and SAA)
After 24 weeks' treatment, the median CRP value was 2.3 mg/l in the canakinumab group and 24.4 mg/l in the placebo group. The difference between these 2 groups is statistically significant ($p < 0.001$).
The median SAA value was 6.1 mg/l with canakinumab and 43.4 mg/l with placebo. This difference is statistically significant ($p = 0.002$).

- assessment of symptoms
At the end of the 2nd phase, after 24 weeks' treatment, a statistically significant difference ($p < 0.001$) was observed between the canakinumab and the placebo group on the endpoints assessed by the investigator:

- investigator's global assessment of autoinflammatory disease intensity: rated as absent in 8/15 patients in the canakinumab group, rated as minimal in 7/15 patients in the canakinumab group and 4/16 patients in the placebo group, rated as mild in 8 patients in the placebo group
- assessment of skin involvement: rated as absent in 14/15 patients in the canakinumab group and 5/16 patients in the placebo group, rated as minor in 1 patient in the canakinumab group and 3 patients in the placebo group, rated as mild in 5 patients in the placebo group.

There was no difference between the 2 groups in respect of the endpoint "patient's assessment of inflammatory-disease and symptom intensity".

- quality of life
After 24 weeks' treatment, no improvement in fatigue, assessed using the FACIT-F score, was observed in either of the groups. The mean score for this fell from 40.5 to 37.6 (-2.9) in the canakinumab group (n = 11) and from 40.7 to 32.8 (-7.8) in the placebo group (n = 13).

The mean mental score on the SF-36 scale fell from 46.7 to 44.9 (-1.8) in the canakinumab group (n = 11) and from 47.3 to 45.8 (-1.5) in the placebo group (n = 12). The mean physical score fell from 52.1 to 46.9 (-5.2) in the canakinumab group (n = 11) and from 49.8 to 43.2 (-6.6) in the placebo group (note that the initial values are close to normal values).

In children, the physical score on the CHQ-PF28 questionnaire rose from 53.0 to 54.9 (+1.8) in the canakinumab group (n = 3) and fell from 53.8 to 41.8 (-12.0) in the placebo group

(n = 2). The psychosocial score fell from 49.5 to 46.1 (-3.4) in the canakinumab group and rose from 57.2 to 57.3 (+0.1) in the placebo group.

#### 3.1.2. Results of the non-comparative study (study 2306)

The aim of this open study was to evaluate the long-term safety and efficacy (at least six months) of canakinumab administered s.c. at a dose of 150 mg (or 2 mg/kg s.c. in patients weighing ≥ 15 kg and ≤ 40 kg) in patients with a cryopyrin-associated periodic syndrome. The results presented are those of an interim analysis carried out on 9 January 2009.
In total, 98 patients were included; 54 of them had previously been treated with canakinumab and included in studies 2102 (n = 24) and 2304 (n = 30).
The majority of the patients were over 18 years of age; 19.4% of the patients were between 4 and 18 years of age. 70.4% of the patients had Muckle-Wells syndrome and 19.4% of the patients had FCAS.

In 37% of the patients who had previously been treated with canakinumab (20/54), the intensity of the autoinflammatory disease was rated as absent, whereas it was mild to moderate in over 50% of the newly included patients. Most of the patients (87%) from trials 2304 and 2102 did not have any skin manifestations, whereas 63.6% of the *de novo* patients had minimal to moderate skin involvement. The mean CRP value was 12.43 mg/l and the mean SAA value 35.4 mg/l (these values were higher in the *de novo* population).
In total, 90.6% of the patients did not relapse (77/85).
The global intensity of the inflammatory disease was null in 54% of the patients, minimal in 26%, mild in 16.5%, moderate in 3.5%, and severe in none.

### 3.2. Tolerance data

#### 3.2.1 from the 2nd, comparative phase of study 2304

All the patients in the canakinumab group (n=15) and 14/16 patients in the placebo group had at least one adverse event.
The main adverse events were:

- infections, in 12 patients in the canakinumab group and 9 in the placebo group. These infections were principally rhinopharyngitis, flu-like syndromes, gastroenteritis, urinary tract infections, and viral infections,
- gastrointestinal disorders (diarrhoea and nausea), in 6 patients in the canakinumab group and 5 in the placebo group,
- respiratory disorders (cough), in 5 patients given canakinumab and 1 given placebo.

These adverse effects did not lead to any discontinuation of treatment. There were neither severe infections nor any opportunistic infections.
No anti-canakinumab autoantibodies were detected.

### 3.2.1 From the SPC

"Safety data from 104 CAPS patients is available. A total of 10 serious adverse reactions that were considered by the investigator as related to treatment were reported during the clinical programme in CAPS, of which the most frequent events were infections (3) and vertigo (2). The most frequently reported adverse events included upper respiratory tract infections and nasopharyngitis across all CAPS studies. Dose and duration of treatment have no impact on the type or frequency of adverse events.
Cases suggestive of hypersensitivity reactions with ILARIS therapy have been reported in patients treated with canakinumab in clinical trials. The majority of these events were mild in severity. No anaphylactoid or anaphylactic reactions have been reported.
Twenty-three paediatric CAPS patients (4-17 years of age) demonstrated similar efficacy and safety to adult patients. Specifically, the overall frequency and severity of infectious episodes in paediatric patients were comparable to that in the adult population. Infection of the upper respiratory tract was the most frequently reported infection."

The European risk management plan includes more specific monitoring for dizziness, infections, and development of malignant diseases. Prescribers must be informed of the risk of serious infections, including opportunistic bacterial, viral, and fungal infections, in patients treated with ILARIS and of the identified or potential risk of immunogenicity that might lead to immune-mediated symptoms.

A prospective registry (ß-CONFIDENT) which was first set up in 35 countries in November 2009 will provide long-term (5-year) follow-up data from patients treated with ILARIS according to the Marketing Authorisation.
This registry will make it possible to define the global safety profile of canakinumab and to evaluate its use in everyday practice and its long-term impact on disease progression. In addition, the growth of children of 4-18 years of age will be monitored.

## 3.3. Conclusion

The clinical development of canakinumab (ILARIS) in the treatment of cryopyrin-associated periodic syndromes (CAPS) is based chiefly on a phase III, randomised, double-blind, comparative study, the main aim of which was to evaluate the efficacy and safety of canakinumab therapy in patients with Muckle-Wells syndrome in comparison with placebo, after 24 weeks of treatment.
This study had 3 phases: an initial phase lasting 8 weeks during which all patients received a subcutaneous injection of canakinumab on an open basis, a 2nd phase – a randomised double-blind comparison versus placebo – which lasted 24 weeks and included all patients responding to canakinumab at the end of the 1st phase, and a 3rd, open phase, in which all the patients received an injection of canakinumab every 8 weeks for 16 weeks.
At the end of the 1st phase, 31 of the 35 patients included had had a complete response.
During the 2nd phase, a statistically significant difference in favour of canakinumab (n = 15) relative to the placebo group (n = 16) was observed on the primary endpoint - the percentage of patients with relapse after 24 weeks of treatment (0/15 patients versus 13/16, $p < 0.001$). Similarly, there was a statistically significant difference in favour of canakinumab in the following secondary endpoints: change in inflammation markers (CRP and SAA), investigator's global assessment of the intensity of the autoinflammatory disease and the skin involvement. On the other hand, no difference between the 2 groups was observed in respect of the endpoint "patient's assessment of inflammatory-disease and symptom intensity".
No conclusion can be drawn from the quality-of-life results as the analysis performed and measurement tools used were not specific to autoinflammatory diseases.

The treatment’s effects on the neurological disturbances were not evaluated. The meningeal passage of the product is unknown.

The main adverse events were of an infectious, respiratory, and gastrointestinal nature.
The Committee wishes to be provided annually with a progress report and the findings of the ß-CONFIDENT registry.

## 4. TRANSPARENCY COMMITTEE CONCLUSIONS

### 4.1. Actual benefit

Cryopyrin-associated periodic syndrome (CAPS) is a hereditary autoinflammatory disease. It has three phenotypic expressions. A diagnosis of CAPS is suggested by the clinical picture; it can be confirmed by identification of a mutation of the NALP3 gene that codes for cryopyrin.
Muckle-Wells syndrome[8] is febrile urticaria syndrome with arthritis and nerve deafness. The initial manifestations are urticaria accompanied by a mild fever, which is non-pruriginous, and occasionally incapacitating due to its being near-constant. The other inflammatory signs are chiefly articular (arthralgia or arthritis) and ocular (conjunctivitis). In addition to these signs there is nerve deafness which comes on in adolescence. The seriousness of the disorder lies in the fact that it sometimes causes generalised AA amyloidosis.
Familial cold urticaria or familial cold autoinflammatory syndrome (FCAS[9]) is a very rare disease characterised by transient rash, a fever, and joint pain, following general exposure to cold. The attacks generally occur 1-2 hours after the exposure and last less than 24 hours.
CINCA syndrome[10] (known as NOMID In North America) combines 3 main signs: cutaneous signs with an urticaria-type maculopapular rash, which very often is present from birth and varies over time, joint problems, which vary in their expression and which can induce sporadic articular episodes that leave no abnormalities between attacks or, unpredictably, epiphyseal cartilage abnormalities that give the appearance of hypertrophic arthropathy (30% of cases), and disturbances of the central nervous system that cause headache. This syndrome develops against a background of chronic inflammation, with episodes of fever of varying intensity and aseptic meningitis associated with polymorphonuclear neutrophils.
ILARIS falls under the category of symptomatic treatment.
The efficacy/adverse effect ratio is high.
There is a validated alternative medicinal product which is not available at the present time.

Public health benefit:
Cryopyrin-associated periodic syndromes (CAPS syndromes) are incapacitating diseases (recurring symptoms and complications, in particular renal impairment due to amyloidosis and deafness), though, because of their rarity, represent a small public-health burden.
As improving the management of orphan diseases is an identified priority (GTNDO*, Rare Diseases Plan), treatment of this disorder is a public-health need.
On the basis of the available data (comparative study, versus placebo, of patients responding to canakinumab, short duration of follow-up), the expected impact of the proprietary product ILARIS on morbidity/mortality and quality of life is not quantifiable.
The identified public-health need is only partially met by the proprietary product ILARIS.
Consequently, in the current state of knowledge, this proprietary product is not expected to have any public health benefit.

*Groupe Technique National de Définition des Objectifs [National technical group for the setting of public-health objectives] (DGS [Ministry of Health])

The actual benefit of ILARIS is substantial.

[8] Grateau G. Le syndrome de Muckle-Wells. Encyclopédie Orphanet, February 2005
[9] Hoffman HM. FamilialeCold Autoinflammatory Syndrome, Orphanet Encyclopedia. February 2005
[10] Prieur AM. Le syndrome CINCA. Encyclopédie Orphanet. October 2003

### 4.2. Improvement in actual benefit (IAB)

ILARIS brings an important improvement in actual benefit (IAB II) in the management of patients (adults, adolescents, and children over 4 years of age) with cryopyrin-associated periodic syndrome, including Muckle-Wells syndrome, chronic infantile neurological, cutaneous, articular syndrome (CINCA) or neonatal-onset multisystem inflammatory disease (NOMID), and severe forms of familial cold autoinflammatory syndrome (FCAS) or familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

### 4.3. Therapeutic strategy

The therapeutic aims in cryopyrin-associated periodic syndromes are to control the symptoms, to prevent recurrence of the inflammatory episodes that characterise these disorders, to limit the impact of the disease on quality of life, and to prevent the most serious complications of the inflammatory disease, notably deafness and amyloidosis.

Treatment of familial cold urticaria or familial cold autoinflammatory syndrome is based on palliative methods and NSAIDs or anakinra, an interleukin-1 receptor antagonist (KINERET[11]), which do not have specific marketing authorisation for this type of syndrome.
The use of anakinra in these indications has been reported in publications based on isolated cases or case series, but its efficacy has not been backed up by a controlled trial. Efficacy appears satisfactory with a daily injection, its local tolerability is poor, and a substantial rebound effect on discontinuation of treatment limits its use.
In the treatment of Muckle-Wells syndrome, the hearing problem can be dealt with by the use of a hearing aid. Countless antiinflammatory and immunosuppressant drugs have been used without success.
The treatment of CINCA syndrome is disappointing. NSAIDs are used and high-dose corticosteroid therapy can be necessary. The basic therapies, immunosuppressants, have not demonstrated their efficacy. Intravenous immunoglobulins must be avoided as they can provoke a substantial meningeal reaction.

**Therapeutic use of ILARIS (canakinumab)**

The treatment alternatives for the treatment of CAPS are interleukin-1 inhibitors, including:

- anakinra (KINERET), used off-label, for which the efficacy studies are limited and local tolerability poor,
- rilonacept (ARCALYST), which is indicated in the treatment of CAPS (FCAS and MWS in patients over 12 years of age) but which has a safety profile comprising pain at the injection site, infection, and formation of antibodies.

ILARIS is the only effective treatment available at present for the management of CAPS.
In the current state of knowledge, it is not possible to assert that early administration of ILARIS has a preventive effect with regard to the development of complications.

### 4.4. Target population

The number of patients with CAPS is hard to estimate considering the lack of epidemiological study or registry.
These diseases are reported to affect 1-2 persons in every 1,000,000 in the United States and Western Europe. There would thus be between 60 and 120 patients in France.

[11] KINERET 100 mg, solution for injection (anakinra, IL-1 receptor antagonist) indicated in the treatment of signs and symptoms of rheumatoid arthritis in combination with methotrexate, in patients with an inadequate response to methotrexate alone.

The incidence of cold urticaria (FCAS) is reported to be less than 1/1,000,000. Muckle-Wells syndrome is said to be the predominant form in Europe and FCAS the predominant form in the United States.
Bearing in mind that:
- the distribution of patients between the various syndromes is approximately 2/3 with Muckle-Wells syndrome (i.e. 45-65 patients), approximately 1/3 with familial cold syndrome FCAS (i.e. 15-50 patients), and just a few patients with chronic infantile neurological, cutaneous, articular syndrome CINCA or NOMID (less than 5 patients),
- the FCAS forms split into 2 groups: severe and non-severe (i.e. 7-25 patients with severe forms),
the target population for ILARIS would thus be abount 50-100 patients.

### 4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage in the marketing authorisation.

4.5.1. Packaging: Appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65%

4.5.3. Status of exceptional-prescription drug