HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
17 September 2014

KINERET 100 mg/0.67 ml, solution for injection in pre-filled syringe

B/1 (CIP: 3400927731952)
B/7 (CIP: 3400927732034)
B/28 (CIP: 3400927732263)

Applicant: Sobi France

INN	Anakinra
ATC Code (2014)	L04AC03 (immunosuppressant)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123 2)
Indications concerned	**"KINERET 100 mg/0.67 ml is indicted in adults for the treatment of the signs and symptoms of Rheumatoid Arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone.** **KINERET 100 mg/0.67 ml is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including:** - **Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),** - **Muckle-Wells Syndrome (MWS),** - **Familial Cold Autoinflammatory Syndrome (FCAS). "**

Actual Benefit	➢ **<u>In the indication: rheumatoid arthritis in combination with methotrexate</u>** **Low** ➢ **<u>In the indication: Cryopyrin-Associated Periodic Syndromes (CAPS).</u>** **Substantial**
IAB	➢ **<u>In the indication: rheumatoid arthritis in combination with methotrexate</u>** **These proprietary medicinal products are additions to the range that do not provide an improvement in actual benefit (level V) in comparison with the other previously registered presentations.** ➢ **<u>In the indication: Cryopyrin-Associated Periodic Syndromes (CAPS)</u>** **Given its demonstrated efficiency in severe forms of cryopyrinopathies (CINCA syndrome/NOMID) despite the methodological limitations of the studies available, its ability to cross the blood-brain barrier, the absence of any available alternative treatment in patients aged under 2 years and despite the need for daily injections, KINERET, like ILARIS, provides significant improvement in actual benefit (level II) in the treatment of cryopyrin-associated periodic syndromes (CAPS) in adults, adolescents, children and babies aged 8 months or older with a body weight of 10 kg or above.**
Therapeutic use	➢ **<u>In the indication: rheumatoid arthritis in combination with methotrexate</u>** **Anakinra administered daily by subcutaneous injection at approximately the same time every day is a last-resort disease modifying treatment for rheumatoid arthritis, in patients with an inadequate response to methotrexate at the maximum tolerated dose for at least 3 months and with a contraindication or intolerance to other biotherapies.** ➢ **<u>In the indication: Cryopyrin-Associated Periodic Syndromes (CAPS).</u>** **Taking into account the results of a prospective study in patients with the most severe form of CAPS (CINCA syndrome), anakinra, is a first-line therapy for the three clinical entities grouped under CAPS, in adults and children over the age of 2 years, in the same way as canakinumab. Without comparative studies, these products cannot be prioritised within the therapeutic strategy.** **Between the age of 8 months and 2 years, anakinra is the only treatment that has Marketing Authorization and has been proven effective.**
Recommendations	

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorization (procedure)	Date initiated: 20 November 2013 (centralised procedure) Specific follow-up: Risk Management Plan (RMP) with introduction of four registries
Prescribing and dispensing conditions/special status	Exception drug status Medicine for initial annual hospital prescription Prescription drug limited to certain healthcare professionals: specialists in rheumatology, internal medicine, paediatrics, dermatology.

ATC Classification	2014	
	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AC	Interleukin inhibitors
	L04AC03	anakinra

02 BACKGROUND

This is a request for inclusion of KINERET 100 mg/0.67 ml solution for injection in graduated syringe on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in both of the two following indications:

- **Rheumatoid arthritis in combination with methotrexate**

In this indication, it is an addition to the non-graduated syringe range. On 16 October 2013, within the scope of its renewal of inclusion,[1] the actual benefit of KINERET in a non-graduated syringe was the subject of a re-assessment by the Transparency Committee (opinion of 16 October 2013), estimating that the actual benefit is **low** and does not provide any improvement in actual benefit in the strategy for rheumatoid arthritis management. This opinion was examined at a hearing on 11 June 2014, within the scope of Article R 163-13 of the French Social Security Code, which did not alter its conclusions.
However, the company has not provided any new data for this inclusion.

- **Cryopyrin-Associated Periodic Syndromes (CAPS)**

The request for inclusion of KINERET in this indication only applies to the new graduated syringe; therefore this is an initial inclusion.

KINERET contains the active substance anakinra, a recombinant analogue of IL1a (a naturally occurring interleukin-1 receptor antagonist).

Taking account of the recent evaluations of KINERET in the indication of rheumatoid arthritis (Committee opinion of 11 June 2014) and the absence of new data, only the conclusions from the opinion of 16 October 2013[2] will be included in this opinion.

[1] Opinion for first inclusion of KINERET in the indication of rheumatoid arthritis, dated 10 July 2002, and renewal of inclusion dated 6 February 2008 (substantial actual benefit).
[2] Opinion for renewal of inclusion of KINERET in the indication of rheumatoid arthritis, dated October 16, 2013 (presented in a non-graduated syringe).

03 THERAPEUTIC INDICATIONS

"KINERET 100 mg/0.67 ml is indicated in adults for the treatment of the signs and symptoms of Rheumatoid Arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone.

KINERET 100 mg/0.67 ml is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including:

- **Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA)**
- **Muckle-Wells Syndrome (MWS)**
- **Familial Cold Autoinflammatory Syndrome (FCAS)."**

04 DOSAGE

"**Posology**

Treatment with KINERET 100 mg/0.67 ml should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis and CAPS.

RA: Adults
The recommended dose of KINERET is 100 mg administered once a day by subcutaneous injection. The dose should be administered at approximately the same time each day.

CAPS: Adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above.

Starting dose:
The recommended starting dose in all CAPS subtypes is 1-2 mg/kg/day by subcutaneous injection. The therapeutic response is primarily reflected by reduction in clinical symptoms such as fever, rash, joint pain, and headache, but also in inflammatory serum markers (CRP/SAA levels), or occurrence of flares.

Maintenance dose in mild CAPS (FCAS, mild MWS):
Patients are usually well-controlled by maintaining the recommended starting dose (1-2 mg/kg/day).

Maintenance dose in severe CAPS (MWS and NOMID/CINCA):
Dose increases may become necessary within 1-2 months based on therapeutic response. The usual maintenance dose in severe CAPS is 3-4 mg/kg/day, which can be adjusted to a maximum of 8 mg/kg/day.
In addition to the evaluation of clinical symptoms and inflammatory markers in severe CAPS, assessments of inflammation of the CNS, including the inner ear (MRI or CT, lumbar puncture, and audiology) and eyes (ophthalmological assessment) are recommended after an initial 3 months of treatment, and thereafter every 6 months, until effective treatment doses have been identified. When patients are clinically well-controlled, CNS and ophthalmological monitoring may be conducted yearly.

Elderly population (≥ 65 years)
No dose adjustment is required in RA patients. Posology and administration are the same as for adults 18 to 64 years of age.

Data in elderly CAPS patients are limited. No dose adjustments are expected to be required.

Paediatric population (< 18 years)
RA: The efficacy of KINERET in children with RA (JIA) aged 0 to 18 years has not been established.

CAPS: Posology and administration in children and infants aged 8 months and older with a body weight of 10 kg or above are the same as for adult CAPS patients, based on body weight. No data are available in children under the age of 8 months.

Hepatic impairment
No dose adjustment is required for patients with moderate hepatic impairment (Child-Pugh Class B). KINERET should be used with caution in patients with severe hepatic impairment.

Renal impairment
KINERET must not be used in patients with severe renal impairment (CL_{cr} < 30 ml/minute) (see section 4.3 of the SPC). No dose adjustment is needed for patients with mild renal impairment (CL_{cr} 50 to 80 ml/minute). In the absence of adequate data, KINERET should be used with caution in patients with moderate renal impairment (CL_{cr} 30 to 50 ml/minute).

Method of administration

KINERET is administered by subcutaneous injection.

KINERET is supplied ready for use in a graduated pre-filled syringe, allowing for doses between 20 and 100 mg. As the minimum dose is 20 mg the syringe is not suitable for paediatric patients with a body weight below 10 kg. "

05 THERAPEUTIC NEED

Cryopyrin-associated periodic syndromes (CAPS) or cryopyrinopathies, are hereditary autoinflammatory diseases. If there is clinical reason to suspect a diagnosis of CAPS, it can be confirmed by identification of a mutation of the gene NALP3/NLRP3 that codes for cryopyrin. Three phenotypic expressions are described.

Familial cold urticaria or familial cold autoinflammatory syndrome (FCAS[3]) is the least severe form of CAPS. It is a very rare disease characterised by transient rash, a fever, and joint pain, following general exposure to cold. Attacks generally occur one to two hours after exposure and last less than 24 hours.
Muckle-Wells syndrome[4] (MWS) is a febrile urticarial syndrome with arthritis and neural deafness. The first manifestation is non-pruriginous urticaria, accompanied by slight fever, which is sometimes disabling because it is almost permanent. The other inflammatory signs are mainly joint disorders (joint pain or arthritis) and eye problems (conjunctivitis). These signs are combined with neurosensory deafness starting in adolescence. The seriousness of the condition lies in the unpredictable occurrence of generalised AA-type amyloidosis.

CINCA syndrome[5] (chronic, infantile, neurological, cutaneous articular syndrome, known as NOMID in North America), the most severe form, 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; in severe forms, mental retardation is possible. The neurosensory disorder includes an inflammatory eye disorder (uveitis, papillary disorder, optic neuritis that can cause blindness) and often progressive perceptive hearing loss. This syndrome develops against a background of chronic inflammation, with episodes of fever of varying intensity and aseptic meningitis associated with polymorphonuclear neutrophils.

Mortality is high, as a result of AA amyloidosis (renal failure at the outset, but potentially affecting other organs such as the liver, spleen, heart, digestive tract or the peripheral nervous system) which affects about 25% of untreated patients with intermediate-severity forms of CAPS such as MWS. The average life expectancy of these patients without treatment is not known. Roughly 20% of patients with CINCA die before the age of 20.

Management of cryopyrinopathies
The early diagnosis of cryopyrinopathy guarantees appropriate therapeutic management and a radical change in the quality of life of these patients. The early initiation of specific treatments could prevent the development of potentially irreversible neurosensory and neurological lesions, and probably also amyloidosis lesions.

The management of a patient with CAPS starts in childhood and requires multiple specialists. This management must be done in agreement with or directly at a reference centre for autoimmune diseases and rare systemic diseases.

[3] Hoffman HM. Familial Cold Autoinflammatory Syndrome, Orphanet Encyclopedia. February 2005.
[4] Grateau G. Le syndrome de Muckle-Wells. Orphanet encyclopaedia. February 2005.
[5] Neven B. Le syndrome CINCA. Orphanet encyclopaedia. February 2007.

Since there is no curative treatment, management involves setting several objectives, notably:

- in the short and medium term: restore comfort to everyday life (in particular reduce fatigue and chronic pain), treat any crises, at least partially prevent episodes, and monitor the physical, mental and social development of children and adolescents;
- in the long term: limit the effects of the disease, prevent or treat secondary amyloidosis.

The therapeutic strategy varies with the seriousness of the disease. It ranges from withholding treatment to anti-IL1 biotherapies, passing through various symptomatic treatments, particularly for joint pain and arthritis.

A disease-modifying treatment likely to slow down the natural progression of the disease, to effectively prevent episodes, to significantly improve the quality of life, and to prevent the development of secondary amyloidosis in intermediate and serious forms (MWS and CINCA) of CAPS, is justified.

At present, the only disease-modifying treatments with demonstrated efficacy in CAPS are inhibitors of interleukin-1 (or anti-IL-1 biotherapies). Long-term treatment with IL-1 antagonists must be offered to patients with MWS (grade A) and CINCA (grade B) to avoid episodes of the disease and to try and prevent the appearance of secondary amyloidosis (grade D). This must also be offered to patients with severe FCAS, beyond cold-induced urticaria (grade A and C).

The pharmacological agents blocking IL-1 include the following:

- The IL1R antagonist analogue or anakinra: non-glycosylated human recombinant substance, an analogue of the natural antagonist of the IL-1a and b receptor (IL1-Ra); it has a short half-life (4-6 hours).
- The monoclonal anti-IL1b antibody or canakinumab: fully human monoclonal anti-IL1β antibody with a very long half-life (28-30 days).

The other pharmacological treatments used in the past (colchicine, DMARDs (Disease-Modifying AntiRheumatic Drugs) and anti-TNF biotherapies, IV immunoglobulins) are no longer recommended.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Only one medicinal product has Marketing Authorization and is used for CAPS treatment in patients over the age of 2 years: ILARIS (canakinumab). ILARIS is in the same therapeutic class (interleukin-1 inhibitors) as anakinra.

NAME (INN) *Company*	Indication	Date of opinion	AB	IAB (Wording)
ILARIS (canakinumab) *Novartis*	ILARIS is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents, children and infants aged 2 years and older with a body weight of 7.5 kg or above, 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.	10 February 2010 Inclusion in CAPS from the age of 4 years	Substantial	ILARIS provides a substantial 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.
		5 February 2014 Extension of indication in CAPS children aged 2 to 4 years		Despite the methodological limitations of the available studies, which are due to the small number of children aged from 2 years to less than 4 years that have Cryopyrin-Associated Periodic Syndromes (CAPS), but due to the undeniable value of the role of canakinumab in the management of these patients for whom there is no available alternative treatment or management to date, the Transparency Committee believes that the proprietary medicinal product ILARIS provides a substantial improvement in actual benefit (IAB II) in the management of patients aged from 2 years to less than 4 years with body weight of 7.5 kg or above with CAPS [...]

06.2 Other health technologies

Not applicable.

◗ Conclusion

ILARIS is the clinically relevant comparator of KINERET.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The KINERET proprietary medicinal products obtained Marketing Authorization for CAPS in Europe (centralised procedure in November 2013) and the US (December 2012).

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population
United Kingdom	Pending evaluation by clinical reference groups	-
Spain	Pending evaluation by AEMED [European Association of Aesthetic and Dietary Medicine]	-
Italy	Pending evaluation by AIFA [Italian Medicines Agency]	-
Germany	Pending evaluation	-
United States	Management by the health plans following authorisation	KINERET is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), particularly Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA)/Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

08 ANALYSIS OF AVAILABLE DATA

For the request for inclusion of KINERET in the indication of Cryopyrin-Associated Periodic Syndromes (CAPS), the company provided data:

- from a phase III study, study 03-AR-0298, in patients with CINCA syndrome;
- from six additional published studies, five of which are prospective studies.

08.1 Efficacy

8.1.1 Study 03-AR-0298

Methods

Study 03-AR-0298 is a prospective open-label, single-centre study carried out in the United States between September 2003 and April 2010.

The main objective of this study was to evaluate the efficacy and safety of anakinra in patients with CINCA syndrome after 3-4 months of treatment.

Selection criteria

The main inclusion criteria were:

- CINCA syndrome with at least two of the following criteria:
  - Typical NOMID/CINCA rash
  - CNS involvement (papilloedema, cerebrospinal fluid (CSF) pleiocytosis, sensorineural hearing loss)
  - Typical arthropathic changes on radiographs (epiphyseal and/or patellar overgrowth)
- Onset of symptoms prior to 6 months of age,
- Stable dose of NSAIDs, anti-rheumatic medicinal products or corticosteroids for at least 4 weeks prior to inclusion,
- Washout period for previous biotherapies (anakinra, TNF inhibitors, thalidomide) with six half-lives prior to inclusion.

The main exclusion criteria were:

- Having received the live virus vaccine during 3 months prior to inclusion,
- Tuberculosis (TB), history of tuberculosis or recent close exposure to an individual with TB, positive testing for HIV, Hepatitis B or C,
- A history of congestive heart failure,
- A history of malignancy,
- Any other rheumatic disease or major chronic infectious/inflammatory/immunologic disease,
- The use of other interleukin-1 antagonists.

Treatment administered

All patients received an initial dose of anakinra of 1-2 mg/kg body weight per day. The dose was increased in increments between 0.5 and 1 mg/kg/day, up to a maximum dose of 10 mg/kg/day, depending on the clinical response.[6] A treatment withdrawal phase of 7 days at the end of the first 3 months, initially included in the protocol, was discontinued via an amendment due to the severity of the flares in the first patients in patients that tried this. The patients were followed-up at 1, 3 and 6 months and then every 6 months until 60 months of treatment.

[6] An inadequate clinical response was defined by a change in the Daily Symptom Severity Score of less than 20%, a SAA level > 10 mg/ml, the need to add an anti-rheumatic treatment, a persistent elevated CRP level (> 0.5 mg/dl), active inflammatory disease.

Endpoints

There were multiple primary efficacy endpoints:

- a change in the DSSS (Diary Symptom Sum Score or Daily Symptom Severity Score) from baseline to the next evaluation (performed between 3 and 6 months after baseline); the severity score was estimated by the patient or their entourage according to the following scale for each symptom: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = moderate/severe, 4 = severe. The five symptoms taken into account were: fever, skin rash, joint pain, vomiting, and headache.
- a change in the SAA levels from baseline to the next evaluation (performed between 3 and 6 months after baseline).

The secondary endpoints included:

- Change from baseline to Month 60 in the disease activity assessed by the practitioner using a visual analogue scale (score from 0 "asymptomatic" to 100 "very severe").
- Progression of organ involvement – change from baseline to Month 60 in:
    - The central nervous system: change in intracranial pressure, CSF cell count, seizure, size of the cerebral brain ventricles on the MRI,
    - Hearing loss,
    - The eye: uveitis, papilleodema,
    - The joints: number of painful joints and synovitis,
    - Skin rash,
    - Bone density,
- Change in the combined use of anti-rheumatic medicinal products or corticosteroids,
- Change in the biological inflammation markers (ESR, CRP, SAA) from baseline to Month 60,

Statistical analysis

The number of subjects needed to detect a mean difference between the DSSS at baseline and after treatment, which is equal to the standard deviation of this difference, was estimated to be 10 patients, with an alpha risk $\alpha = 0.05$.

Changes in the endpoint values between baseline and the next evaluation were determined using a Repeated Measures Analysis of Covariance (RMANCOVA) adjusted to the baseline value. Sensitivity analyses were performed, with the missing data management method LOCF (last observation carried forward) and in particular, an analysis of covariance for each measure.

Results

Treatment exposure

A total of 43 patients with CINCA syndrome were enrolled and received anakinra, 9 of whom were excluded from the analysis because treatment was started before the baseline visit, i.e. a modified ITT (mITT) population of 34 patients. It should be noted that 29 patients had complete DSSS score data at baseline.

The mean start dose of anakinra was 1.4 mg/kg/d and 3.2 mg/kg/d at Month 60.

The median duration of exposure was 4.5 patient-years and 22 patients were followed up to 60 months.

Patient characteristics

In the intention-to-treat population, patients were aged from 0.7 to 46.3 years with a median age of 8.4 years, and 72.1% of patients were younger than 12 years (n = 31). More than half of the patients were female (58%).

Among the patient included, seven had a mixed CINCA/MWS (Muckle-Wells Syndrome) phenotype. The median duration of the disease was 0.3 years ranging from 0 to 20.9 years, with a median diagnosis age of 7.7 years.

At baseline, the proportion of days within the last 30 days with at least mild symptom severity was 78.9% for skin rash, 51.3% for joint pain, and 37.3% for headache. This proportion of days for a high level of severity was below 15% for all symptoms except skin rash, for which it was 16.9%.

Forty-seven point one percent (47.1%) of patients were treated with corticosteroids and 26.5% with anti-rheumatic medicinal products. The mean daily dose of corticosteroids was 0.35 mg/kg.
At baseline, the SAA level was 149 mg/l, the CRP level was 51 mg/l and the erythrocyte sedimentation rate (ESR) was 52 mm/h.

Efficacy with respect to the primary efficacy endpoints
The DSSS, daily symptom severity score, dropped 3.5 points (95% CI: [-3.7; -3.3]; $p < 0.0001$) going from 4.5 (± 0.6) at baseline to 0.9 (± 0.3) during the next evaluation (performed between 3 and 6 months after baseline) (n = 29). Improvement was observed from the third day. It should be noted that in Month 60, this score was 0.7 points.
The median SAA level decreased from 149 mg/l at baseline to 6 mg/l during the next evaluation (performed between 3 and 6 months after baseline). For the mean SAA level, [7]a decrease of 206 mg/l ($p < 0.0001$; n = 31) was observed from baseline to the next evaluation (performed between 3 and 6 months after baseline).
The sensitivity analyses confirmed these results.

Efficacy with respect to the secondary endpoints
Progression of disease activity by the practitioner
The VAS score, evaluating disease activity, decreased from 19.1 at baseline to 2.1/100 at Month 60 (n = 28).

Progression of organ damage:
The mean intracranial pressure was 239 mm at baseline and decreased by 52 mm (95% CI [-76; -28], $p < 0.001$) at the next evaluation (performed between 3 and 6 months after baseline) and 83 mm (95% CI [-123; -43], $p < 0.001$) at Month 60 (n = 19). The presence of a ventriculomegaly on the brain MRI barely changed: involving 43.5% of patients at baseline and 41.2% at Month 60 (n = 23).
No change in hearing was observed after treatment, despite an improvement in cochlear damage in the MRI in 15 out of 20 patients with increased contrast uptake.
Visual acuity did not change and the papilleodema intensity score (0 to 4 points) improved from 1.53/4 (95% CI [-1.1; -0.7]) at baseline to 0.46 (95% CI [-1.2, -0.9]) in Month 60 in the worst eye ($p < 0.001$; n = 17).
The surface area of the rash was 10.5% at baseline and decreased by 6.7% at Months 3/6 and 8.3% at Month 60 ($p < 0.001$).
At Month 60, the number of painful joints decreased from 5.2 at baseline to zero (n = 27) and the number of stiff joints stiff decreased from 8.6 to 0.6.
The Z-score for the bone density test was close to -2 at baseline and decreased by 1 point at Month 60.

Combined drug treatment
At Month 60, the number of patients using glucocorticoids decreased from 13 to 8, and from 9 to 7 for the use of anti-rheumatic medicinal products.

Change in the biological inflammation markers
Between baseline and Month 60, the estimated decrease in the average SAA level was 217 mg/l, 57 mg/l for the CRP level and 49 mm/h for the ESR ($p < 0.0001$; n = 31).

Quality of life was evaluated by the CHAQ questionnaire (Childhood Health Assessment Questionnaire), a global childhood health scale with a score between 0 and 3 (increasing disability). The median value of this score at baseline was 0.88 (±0.18) in 28 patients and zero at Month 60 for 13 patients.

[7] Outliers for the SAA level were found ranging up to 1400 mg/l on inclusion.

8.1.2 Additional studies

A prospective,[8] open-label, multicentre study was performed on 20 patients with CAPS, with the main objective being to evaluate the quality of life and long-term efficacy of KINERET over a period of 12 to 54 months. Among the included patients, 15 were diagnosed with CINCA syndrome and 5 with MWS (Muckle-Wells syndrome). The mean age was 12.4 years (±10.9). It was possible to treat 14 of these patient with 1 mg/kg/d of KINERET (maximum dose of 100 mg). The median duration of follow-up was 37.5 months (2-54 months).
Quality of life was studied using the Child Health Questionnaire, evaluating the physical, psychological and social components of the child's health status (score out of 100). This study showed an improvement in the physical score at the last visit, with a score of 38 (±11.8) before treatment and 52.2 (±4.5) ($p < 0.001$) after treatment and the psychosocial score (43.8 ±8.2 and 47.8 ±8.4, before and after treatment, $p < 0.05$).
It should be noted that the number of patients with skin rash decreased from 14 to 4, with arthritis decreased from 13 to 4, with headache decreased from 11 to 4, with papilloedema decreased from 7 to 3, and with hearing loss decreased from 6 to 4.

The objective of a single-centre,[9] prospective, open-label study was to evaluate the efficacy and safety of anakinra in the short and longterm in children and adults with severe MWS. The primary efficacy endpoint was the response in MWS-disease activity score (DAS) after 2 weeks of treatment: this score included an evaluation of fever, headache, eye involvement, hearing impairment, musculoskeletal disease, abdominal pain, renal disease, and skin rash, as well as an overall evaluation of the patient. This study included 12 patients with MWS including 9 women and 7 adults; the mean age of the 5 children was 6.4 years. Musculoskeletal, ocular, auditory or arthralgia manifestations were consistently found for at least 10 of the 12 patients. The median duration of follow-up was 11 months.
All patients had an activity score < 10/20, the threshold defining the control of disease activity, decreasing from 12.8 to 3.2 at 2 weeks ($p = 0.001$).
At 2 weeks, musculoskeletal manifestations had disappeared in all patients, and then reappeared in 3 patients at the end of follow-up. Ocular symptoms were present in 1 patient out of the 12 affected at the end of the 12 weeks, and in 4 patients at the end of follow-up. Of the 8 patients with skin rash at baseline, only 1 still had a rash at 2 weeks and 2 at the end of follow-up.

Four studies that included 10 patients or less found similar results:

- a retrospective study[10] evaluating the change in neurological involvement, carried out on 10 patients with CINCA syndrome, followed for 26 to 42 months;
- a prospective study[11] carried out in 3 patients with MWS evaluating the change in skin rash and biological markers in particular. A resolution was observed in 3 patients;
- two prospective studies[12,13] carried out in 4 and 8 patients with Familial Cold Autoinflammatory Syndrome (FCAS), showed the absence of appearance of skin symptoms after exposure to cold.

[8] Lepore L, Palon G et al. Follow-Up and Quality of Life of patients with Cryopyrin-Associated Periodic Syndromes Treated with Anakinra. J Pediatrics 2010; 157: 310-5.
[9] Kuemmerle-Deschner J, Tyrrell P, Koetter I et al. Efficacy and Safety of Anakinra Therapy in Pediatric and Adult Patients With the Autoinflammatory Muckle-Wells Syndrome. Arthritis Rheum 2011; 63: 840-9.
[10] Neven B, Marvillet I, Terrada, C et al. Long-Term Efficacy of the Interleukin-1 Receptor Antagonist Anakinra in Ten Patients With Neonatal-Onset Multisystem Inflammatory Disease/Chronic Infantile Neurologic, Cutaneous, Articular Syndrome. Arthritis Rheum 2010; 62: 258-67.
[11] Hawkins PN, Lachmann HJ, Aganna E et al.Spectrum of Clinical Features in Muckle-Wells Syndrome and Response to Anakinra. Arthritis and Rheum 2004; 50: 607-12.
[12] Hoffman HM, Rosengren S, Boyle L et al. Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. Lancet 2004; 364: 1779-85.
[13] Ross JB, Finlayson LA, Kloptz PJ et al. Use of anakinra (Kineret) in the treatment of familial cold autoinflammatory syndrome with a 16-month follow-up. J Cutan Med Surg 2008; 12: 8-16.

08.2 Safety/Adverse effects

8.2.1 Data from the clinical study

In study 03-AR-0298, 43 patients received at least one dose of anakinra, 41 of whom had an adverse event (95.6%). The most commonly reported adverse events were headache (48.8%), arthralgia (41.9%), fever (39.5%), upper respiratory tract infections (39.5%), nasopharyngitis (34.9%) and skin rash (32.6%). Ten patients presented with an injection site reaction (18.6%). Fourteen patients presented with serious adverse events during the course of the study (pneumonia: n = 3 and gastroenteritis: n = 2).
For 15 patients (34.9%), the adverse event was treatment-related; for 7 patients, it was a serious adverse event.
Six hepatic adverse events (hepatic cytolysis) occurred in 5 patients, one of which was considered to be of moderate severity. All events were resolved without stopping the treatment.
No deaths were reported.

8.2.2 SPC data

Changes were made to the SPC dated 20 November 2013 under the heading "4.8 Adverse effects" with the addition of hepatic adverse effects.
As a reminder, the adverse events identified, according to their frequency, were the following:

- Very common (≥ 1/100 and < 1/10): headaches, injection site reaction;
- Common (≥ 1%, < 10%): severe infections, neutropenia;
- Uncommon: (≥ 1/1 000, < 1%): allergic reactions including anaphylaxis, angioedema, urticaria and pruritus, increased liver enzymes, rash;
- Not known: non-infectious hepatitis.

8.2.3 PSUR data

According to the last PSUR covering the period from May 2010 to May 2013, the known safety profile of anakinra has not changed.

08.3 Usage/prescription data

According to IMS (winter moving annual total 2014), the prescription of KINERET in non-graduated syringe is not enough in retail pharmacies to be included in the panel. According to the GERS [an economic interest group of pharmaceutical companies which produces market statistics] moving annual total in June 2014, 27,829 packs with 7 vials of KINERET 100 mg were sold.
As a reminder, these numbers correspond to the prescription of KINERET in the indication of rheumatoid arthritis and in two indications: CAPS, without Marketing Authorization until now, and juvenile idiopathic arthritis, still without Marketing Authorization, recommended by the national healthcare protocols.

08.4 Summary & discussion

The company is asking for inclusion of KINERET in graduated syringe form in two indications.

Rheumatoid arthritis in combination with methotrexate

This is an addition to the range. The company has not provided any new efficacy data.
The graduated syringe presentation does not change the therapeutic value of KINERET in the treatment of rheumatoid arthritis in combination with methotrexate.
With regards to safety, some cases of non-infectious hepatitis have been reported resulting in changes to the SPC.

Cryopyrin-Associated Periodic Syndromes (CAPS)

The request for inclusion of KINERET in this indication is based on study 03-AR-0298, a prospective, open-label, single-centre study, the main objective of which was to evaluate the efficacy and safety of anakinra in patients with CINCA syndrome after 3 to 4 months of treatment.
There were multiple primary efficacy endpoints, including:

- the variation in DSSS, the daily symptom severity score assessed by the patient or his entourage, between baseline and the evaluation carried out between 3 and 6 months, and according to a severity scale that increases from 0 to 4 for each symptom (fever, skin rash, joint pain, vomiting, headache).
- the change in SAA levels between baseline and the evaluation carried out between 3 and 6 months.

A total of 43 patients with CINCA syndrome were included, including 35 patients newly treated with anakinra (mITT population), and 29 with complete DSSS score data at baseline. The mean age of patients included was 8.4 and 72.1% of patients were below the age of 12 (n = 31). Among the patient included, seven had a mixed CINCA/MWS phenotype. It should be noted that the severity of the disease in the patients enrolled in this study is greater than in the studies carried out with canakinumab.

The average start dose of anakinra was 1.4 mg/kg/d and 3.2 mg/kg/d at Month 60. The median duration of exposure was 4.5 patient-years and 22 patients were followed up to 60 months. Forty-seven point one percent (47.1%) of patients were treated with corticosteroids and 26.5% with anti-rheumatic medicinal products.
At baseline, the proportion of days within the last 30 days with at least one symptom with a low level of severity was 78.9% for skin rash, 51.3% for joint pain, and 37.3% for headache. This proportion of days for a high level of severity was below 15% for all key symptoms except rash, which had a score of 16.9%. The SAA level was 149 mg/l, the CRP level was 51 mg/l and the erythrocyte sedimentation rate (ESR) was 52 mm/h.

The DSSS, primary efficacy endpoint, dropped 3.5 points (95% CI: [-3.7; -3.3]; $p < 0.0001$) going from 4.5 (±0.6) at baseline to 0.9 (±0.3) during the next evaluation (performed between 3 and 6 months after baseline) (n = 29). The median SAA level decreased from 149 mg/l at baseline to 6 mg/l during the next evaluation performed between 3 and 6 months after baseline. Between baseline and the next evaluation (performed between 3 and 6 months after baseline), the mean SAA level[14] decreased by 206 mg/l ($p < 0.0001$; n = 31).

Among the secondary endpoints, the VAS (visual analogue scale) score used by the practitioner to evaluate the disease activity and the change in organ system involvement were evaluated at Month 60. The VAS score decreased from 19.1 at baseline to 2.1/100. With regards to organ involvement, a significant decrease by 83 mm was observed in intracranial pressure, 8.3% in the surface area of skin rash (baseline value: 10.5%), in the number of painful and stiff joints (decreasing from 5.2 and 8.6 respectively to a value close to zero) and in the papilloedema

[14] Outliers for the SAA level were found ranging up to 1400 mg/l on inclusion.

intensity score (from 1.53/4 to 0.46/4). Visual acuity and hearing did not change. Moreover, at Month 60, the number of patients using glucocorticoids decreased from 13 to 8, and from 9 to 7 for the use of anti-rheumatic medicinal products.
At Month 60, the estimated decrease in the mean SAA level was 217 mg/l, 57 mg/l in the CRP level and 49 mm/h in the ESR ($p < 0.0001$; $n = 31$). These high values should be interpreted within the context of the outliers included in the analysis, which could result in an overestimation of the decrease.
It should be noted that these analyses were carried out in patients who completed the 60-month follow-up, i.e. 22 patients (or less depending on the variables, due to missing data).

Results similar to those from study 03-AR-0298 were found in two studies, one prospective and one retrospective, performed on smaller sample sizes (enrolment of 20 and 10 patients with CINCA syndrome, respectively).
Two prospective studies specifically included 12 and 3 patients with MWS, finding a similar improvement in symptoms.
Familial Cold Autoinflammatory Syndrome (FCAS) was the subject of cold exposure studies, including 8 and 4 patients respectively. Under treatment with anakinra, no skin rash was found after exposure.

In terms of safety, the profile of KINERET is barely changed in relation to the adverse events reported in patients treated for rheumatoid arthritis. The observed adverse events were consistent with the SPC. The most frequently reported events were headaches, infections and injection site reactions. Hepatic events (increase in liver enzymes and non-infectious hepatitis) were the subject of a recent addition in the SPC.

08.5 Planned studies

The Marketing Authorization of KINERET is dependent on a Risk Management Plan (RMP). The risks under consideration in this RMP (version of 13 September 2013) are:

- Significant risks: injection site reactions, immunogenicity, serious infections, neutropenia, allergies, liver disorders, interactions with TNF antagonists;
- Potential risks: neoplasia, macrophage activation syndrome, medication errors, off-label use;
- Important missing information: use in pregnant or lactating women, patients with heart failure, use during chronic infections or cancer, interactions with live vaccines.

The proprietary medicinal product KINERET 100 mg/0.67 ml was the subject of a paediatric investigation plan validated on 28 March 2012.

09 THERAPEUTIC USE

Rheumatoid arthritis in combination with methotrexate

The usual management of rheumatoid arthritis involves the systematic prescription of an immediate action anti-inflammatory (NSAID, low-dose corticosteroid) and a disease-modifying treatment (methotrexate, synthetic antimalarials, salazopyrin, gold salts, etc.) in order to induce clinical remission and limit the progression of joint damage and subsequent disability. Methotrexate is considered as the most effective disease-modifying treatment. Given the phenomena of treatment failure or intolerance to various disease-modifying treatments, one disease-modifying treatment can be replaced by another.

TNF inhibitors such as etanercept (ENBREL) and adalimumab (HUMIRA) are used alone or in combination with methotrexate, in the event of inadequate response or intolerance to disease-modifying treatments, including methotrexate (unless contraindicated). Infliximab (REMICADE) is to be used in combination with a disease-modifying drug, particularly methotrexate. TNF inhibitors may also be used as first-line therapy in some active and severe forms of rheumatoid arthritis.

Furthermore, in February 2013 the French Society of Rheumatology stated that "Although this medicinal product is not currently considered to be as effective as other available biotherapies in the indication of rheumatoid arthritis at the group level, it seems that KINERET is still useful in certain patients with rheumatoid arthritis."

In light of the current data, anakinra administered daily by subcutaneous injection at approximately the same time every day is a last-resort treatment in the disease-modifying treatment of rheumatoid arthritis, in patients with an inadequate response to methotrexate at the maximum tolerated dose for at least 3 months and with a contraindication or intolerance to other biotherapies. The combination of KINERET with etanercept or other TNF inhibitors is not recommended due to increased risk of serious infections without improved clinical benefit (see "Special warnings, Precautions for use" and "Interactions" in the SPC).

Cryopyrin-Associated Periodic Syndromes (CAPS)

Given that cryopyrinopathies are genetically determined and have an early onset, particularly the most severe form (CINCA/NOMID), it is necessary to start an effective disease-modifying treatment as soon as the diagnosis is made so as to prevent visceral and joint damage, and stunted growth.

At present, the only disease-modifying treatments with demonstrated efficacy in CAPS are interleukin-1 inhibitors. Long-term treatment with IL-1 antagonists must be offered to patients with MWS and CINCA to avoid episodes of the disease and to try and prevent the appearance of secondary amyloidosis. This must also be offered to patients with severe FCAS, beyond cold-induced urticaria.

Two anti-interleukin-1 substances currently have Marketing Authorization in France:

- anakinra (an analogue of the natural antagonist of the IL-1a and b receptor), with a short half-life (4-6 hours), and which can cross the blood-brain barrier, needs to be injected daily and is authorised in adults and children from the age of 8 months or with a body weight of 10 kg or above;
- canakinumab (fully human monoclonal anti-IL1β antibody), with a very long half-life (28-30 days), needs to be injected twice a month and is authorised in adults and children from the age of 2 years; it has not been proven that canakinumab can cross the blood-brain barrier.

The fact that anakinra crosses the blood-brain barrier means that it might have an effect on the neurological symptoms of the disease.

Taking into account the results of a prospective study in patients with the most severe form of CAPS (CINCA syndrome), anakinra, is a first-line treatment for the three clinical entities grouped under CAPS, in adults and children over the age of 2 years, in the same way as canakinumab. Without comparative studies, these products cannot be prioritised within the therapeutic strategy.
Between the age of 8 months and 2 years, anakinra is the only treatment that has Marketing Authorization and has been proven effective.

The other pharmacological treatments used in the past (colchicine, DMARDs (Disease-Modifying Antirheumatic Drugs) and anti-TNF biotherapies, IV immunoglobulins) are no longer recommended.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

➢ **In the indication: rheumatoid arthritis in combination with methotrexate**

◗ Rheumatoid arthritis is a chronic, inflammatory rheumatic condition involving progressive joint destruction, and with functional, psychological, social and occupational repercussions, which are sometimes serious. Early signs are pain in the joints, particularly in the wrists and hands, combined with morning stiffness, and joint swelling (synovitis). A typical patient would present with an inflammatory syndrome, joint involvement (erosions, in rare cases joint destruction), and maybe non-articular involvement (e.g. rheumatoid nodules). The disease progresses by episodes (flare-up) and results in handicap if not treated.

◗ KINERET is intended as symptomatic treatment.

◗ The efficacy/adverse effects ratio for KINERET is modest.

◗ Alternative medicinal products exist.

◗ Public health benefit:
The addition of a presentation in graduated syringe to the existing presentations is not likely to have an impact on public health.

◗ In light of the current data, anakinra is a last-resort treatment in the therapeutic strategy of rheumatoid arthritis in patients with an inadequate response to methotrexate at the maximum tolerated dose for at least 3 months and with a contraindication or intolerance to other biotherapies.

Taking account of these points, the Committee considers that the actual benefit of KINERET is low in the indication of rheumatoid arthritis in combination with methotrexate.

➢ **<u>In the indication: Cryopyrin-Associated Periodic Syndromes (CAPS).</u>**

◗ Cryopyrin-associated periodic syndromes (CAPS) or cryopyrinopathies are a continuum of three "autoinflammatory" diseases of increasing severity, familial cold urticaria, Muckle-Wells syndrome and CINCA syndrome /NOMID. These are disabling diseases due to the recurrence of symptoms (cutaneous, joint, neurosensory and neurological) and the associated complications.
◗ KINERET is intended as symptomatic therapy.
◗ The efficacy/adverse effects ratio for this medicinal product is high.
◗ Canakinumab is a therapeutic alternative.
◗ It is a first-line therapy.

◗ Public health benefit:

Cryopyrin-Associated Periodic Syndromes (CAPS) are rare autoinflammatory diseases of varying severity which, at best, has a low impact on public health.

Improvement in the management of orphan diseases is part of the Plan National Maladies Rares [National Rare Diseases Plan] 2011-2014, so the treatment of this disorder is a public health need.

In view of the available data (prospective, single-centre, open-label study in North American patients) and in the absence of comparative data versus interleukin inhibitors in particular, the impact that can be expected for KINERET on patient morbidity and mortality is not quantifiable. The role of KINERET in the improvement of functional, biological and quality-of-life parameters cannot be defined.

It is not expected that KINERET will have an impact on the organisation of care compared with the usual treatment of these diseases.

The presented data were collected from very small cohorts (due to the rarity of this syndrome) of North American patients, who were treated in a single centre; therefore the transferability of the data to current clinical practice in France cannot be guaranteed.

KINERET appears to provide a partial response to an identified public health need.

As a result, particularly given the rarity of this syndrome, it is not expected that this proprietary medicinal product will have an impact on public health in this indication.

Consequently, the Committee believes that the actual benefit of KINERET is substantial in the treatment of cryopyrin-associated periodic syndromes (CAPS) in adults, adolescents, children and babies aged 8 months or older with a body weight of 10 kg or above.

010.2 Improvement in actual benefit (IAB)

➢ **<u>In the indication: rheumatoid arthritis in combination with methotrexate</u>**

These proprietary medicinal products are additions to the range that do not provide an improvement in actual benefit (level V) in comparison with the other previously registered presentations.

➢ **<u>In the indication: Cryopyrin-Associated Periodic Syndromes (CAPS).</u>**

Given its demonstrated efficiency in severe forms of cryopyrinopathies (CINCA syndrome /NOMID) despite the methodological limitations of the studies available, its ability to cross the blood-brain barrier, the absence of any available alternative treatment in patients aged under 2 years and despite the need for daily injections, KINERET, like ILARIS, provides significant improvement in actual benefit (level II) in the treatment of cryopyrin-associated periodic syndromes (CAPS) in adults, adolescents, children and babies from the age of 8 months with body weight of 10 kg or above.

010.3 Target population

Cryopyrin-Associated Periodic Syndromes (CAPS)

The number of patients with CAPS is difficult to estimate because of the lack of epidemiological studies or registries.

The estimated prevalence of this disease in France is 1/360,000 according to a recent epidemiological study,[15] i.e. 200 patients. According to expert opinion, this disease affects 150 to 200 patients in France.

The maximum target population is therefore 200 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use as a last-resort treatment in the therapeutic strategy for rheumatoid arthritis in patients with an inadequate response to methotrexate at the maximum tolerated dose for at least 3 months and with a contraindication or intolerance to other biotherapies.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the treatment of cryopyrin-associated periodic syndromes in adults, adolescents, children and babies aged 8 months or older with a body weight of 10 kg or above.

◗ Proposed reimbursement rate: 65%

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

[15] Cuisset L, Jeru I, Dumont B et al. Mutations in the autoinflammatory cryopyrin-associated periodic syndrome gene: epidemiological study and lessons from eight years of genetic analysis in France. Ann Rheum Dis 2011; 70: 495-9.