HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

5 February 2014

ILARIS 150 mg, powder for solution for injection

B/1 bottle (CIP: 34 009 397 457-6 3)

ILARIS 150 mg, powder and solvent for solution for injection

1 bottle (powder) + 1 bottle (solvent) + 1 injection syringe + 1 needle + 2 adaptors per bottle + 4 cleansing swabs (CIP: 34 009 217 875-9 7)

Applicant: NOVARTIS PHARMA S.A.S.

INN	canakinumab
ATC code (2013)	L04AC08 (interleukin inhibitor)
Reasons for the review	**Extension of the indication CAPS to children aged from 2 years to less than 4 years with body weight of 7.5 kg or above.** **Change in the dose regimen**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"ILARIS is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in [...] children aged 2 years and older with body weight of 7.5 kg or above."**

AB	**Substantial in the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in children aged from 2 years to less than 4 years with body weight of 7.5 kg or above.**
IAB	**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 place 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 suffering from CAPS, including Muckle-Wells syndrome, chronic infantile neurological, cutaneous, articular syndrome (CINCA) or neonatal-onset multisystem inflammatory disease (NOMID), severe forms of familial cold autoinflammatory syndrome (FCAS) or familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.**
Therapeutic use	**First-line medicinal product**
Recommendations	**Exception drug status** **The Committee would like to have, at its next five-yearly assessment, in addition to the data in the β-Confident registry, follow-up data for all CAPS patients treated with ILARIS in France in terms of efficacy, safety and doses used (particularly since high doses maintained long-term increase the risk of infections).**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date (centralised procedure): 23 October 2009 for the treatment of patients from age 4 years suffering from CAPS Extension of indication and change in the dose regimen obtained on 24 January 2013 Marketing Authorisation under exceptional circumstances[1] in patients with CAPS
Prescribing and dispensing conditions/ special status	List I Medicine for hospital prescription only. Initial and repeat prescription reserved for specialists in rheumatology, internal medicine, dermatology or paediatrics. Medicine requiring special monitoring during treatment. Exception drug (Official Gazette of 1 July 2010)

ATC Classification	**2013** L Antineoplastic and immunomodulating agents L04 Immunosuppressants L04A Immunosuppressants L04AC Interleukin inhibitors L04AC08 canakinumab

02 BACKGROUND

The active ingredient of ILARIS is canakinumab, a human monoclonal antibody specifically targeted at interleukin-1β (IL-1β).

Since 1 July 2010, ILARIS (canakinumab) has been included, with exception drug status, for supply to retail pharmacies and to hospitals for use in the treatment, in adults, adolescents and children aged 4 years and older with body weight of more than 15 kg, of cryopyrin-associated periodic syndromes (CAPS) including: Muckle-Wells syndrome (MWS), chronic infantile neurological, cutaneous, articular syndrome (CINCA)/neonatal-onset multisystem inflammatory disease (NOMID), severe forms of familial cold autoinflammatory syndrome (FCAS) or familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash (indication of the Marketing Authorisation).

This inclusion follows the Opinion of 10 February 2010 of the Transparency Committee which assigned to ILARIS a substantial AB and a substantial IAM (IAB II) in the management of patients suffering from CAPS as defined in the indication of the Marketing Authorisation.

Since 24 January 2013, the indication CAPS has been extended to children (aged from 2 years to less than 4 years with body weight of at least 7.5 kg).
In addition, a new dosage regimen allowing the efficacy of ILARIS to be optimised by using higher

[1] This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency will assess any new information that is available every year and, if necessary, the SPC will be updated.

doses in patients who did not achieve complete remission has been validated in the entire population of patients suffering from CAPS.
The new dosage regimen allows the dose to be increased:

- up to 600 mg or 8 mg/kg if the clinical response is not considered satisfactory (resolution of the skin rash and other generalised inflammatory symptoms) after 14 days of treatment in adults and children aged over 4 years with body weight of more than 15 kg,
- up to 8 mg/kg if the clinical response was not considered satisfactory after 7 days of treatment in children aged from 2 to less than 4 years with body weight of between 7.5 and 15 kg.

03 THERAPEUTIC INDICATIONS

"Cryopyrin-Associated Periodic Syndromes
ILARIS is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and **children aged 2 years and older with body weight of 7.5 kg or above**."

- 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.

Systemic Juvenile Idiopathic Arthritis (SJIA)*
ILARIS is indicated for the symptomatic treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.
ILARIS can be given as monotherapy or in combination with methotrexate.

Gouty arthritis*
ILARIS is indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate (see section 5.1 of the SPC)."

**these two new indications will be covered in another Opinion.*

04 DOSAGE IN CAPS

"Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication.
After proper training in the correct injection technique, patients or their caregivers may inject ILARIS if the physician determines that it is appropriate and with medical follow-up as necessary (see section 6.6).

CAPS: Adults, adolescents and children aged 2 years and older
The recommended starting dose of ILARIS for CAPS patients is:
Adults, adolescents and children ≥ 4 years of age:
- 150 mg for patients with body weight > 40 kg,
- 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg,
- 4 mg/kg for patients with body weight ≥ 7.5 kg and < 15 kg,

Children aged 2 to < 4 years of age:
- **4 mg/kg for patients with body weight ≥ 7.5 kg**

This is administered every eight weeks as a single dose via subcutaneous injection.

For patients with a starting dose of 150 mg or 2 mg/kg, 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 or 4 mg/kg every 8 weeks should be maintained. **If a satisfactory clinical response has not been achieved 7 days after this increased dose, a third dose of ILARIS at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.**

For patients with a starting dose of 4 mg/kg, if a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of ILARIS 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

Clinical experience with dosing at intervals of less than 4 weeks or at doses above 600 mg or 8 mg/kg is limited. […]"

05 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

"Infections
ILARIS is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with ILARIS. Physicians should exercise caution when administering ILARIS to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections.
ILARIS should not be initiated or continued in patients during an active infection requiring medical intervention.
Isolated cases of unusual or opportunistic infections have been reported during ILARIS treatment. The causal relationship of ILARIS to these events is unknown.

In approximately 12% of CAPS patients tested with a PPD (purified protein derivative) skin test in clinical trials, follow-up testing yielded a positive test result while treated with ILARIS without clinical evidence of a latent or active tuberculosis infection.
It is unknown whether the use of interleukin-1 (IL-1) inhibitors such as ILARIS increases the risk of reactivation of tuberculosis or of opportunistic infections. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection.
[…]
Neutropenia and leukopenia
Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including ILARIS. Treatment with ILARIS should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment.

Hypersensitivity reactions
Hypersensitivity reactions with ILARIS therapy have been reported. The majority of these events were mild in severity. During clinical development of ILARIS in over 2,300 patients, no anaphylactoid or anaphylactic reactions were reported. However, the risk of severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded. […]"

06 THERAPEUTIC NEED[2]

Cryopyrin-associated periodic syndromes (CAPS) are hereditary autoinflammatory diseases. They have three phenotypical expressions. 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.
Familial cold urbicaria or familial cold autoinflammatory syndrome (FCAS[3]), the least severe form of CAPS, is a very rare disease characterised by a transient eruption, fever and joint pains, following generalised exposure to cold. Attacks generally occur 1-2 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 associated 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, called NOMID in North America), the most severe form, combines 3 main signs: cutaneous signs with an urticarial maculopapular eruption, very often present from birth and variable over time, a joint disorder of variable expression which can cause limited articular episodes that leave no abnormality between episodes, or in an unforeseeable form with abnormalities of the epiphyseal cartilage resembling hypertrophic joint disease (30% of cases), and a disorder of the central nervous system causing headaches. 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 in a setting of chronic inflammation, with episodes of fever of variable intensity and the occurrence of aseptic meningitis with neutrophils.

The exact mortality is not known but concerns the most severe forms. The recognised causes of mortality are complications 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 suffering from intermediate-severity forms of CAPS such as MWS. The life expectancy of these patients without treatment is not known.

The early diagnosis of CAPS 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 suffering from CAPS starts in childhood and lasts throughout life, and requires multiple specialists in addition to the patient's own doctor (general practitioner, paediatrician and paediatric subspecialities, ophthalmologist, ENT specialist, dermatologist, rheumatologist, internist, neurologist and pain management specialist).
The management of children with CAPS must be done in agreement with or directly at a reference centre for autoimmune diseases and rare systemic diseases.

[2] Protocole National de Diagnostic et de soins (PNDS). Fièvres récurrentes héréditaires. Syndromes périodiques associés à la cryopyrine (CAPS). Centre de référence des maladies auto-inflammatoires rares de l'enfant. (CeRéMAI) - January 2013.
[3] Hoffman HM. Familial Cold Autoinflammatory Syndrome, Orphanet Encyclopedia. February 2005.
[4] Grateau G. Le syndrome de Muckle-Wells. Encyclopédie Orphanet. February 2005.
[5] Neven B. Le syndrome CINCA. Encyclopédie Orphanet. February 2007.

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

- 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; preserve quality of life and social and occupational integration.
  In children and adolescents, there are other objectives in addition to those above: to resume or continue schooling; to preserve psychosocial and emotional development; to monitor growth and pubertal development and to discuss specific treatments in the event of abnormalities.

- in the long term: limit the sequelae of the disease; continue permanent monitoring and keep the patient under treatment; avoid secondary amyloidosis, the main complication of the serious forms of MWS and CINCA, and manage that amyloidosis if necessary.

Since CAPS are chronic diseases, a basic treatment likely to slow down the natural progression of the disease, to effectively prevent episodes when they develop and recur, to significantly improve the quality of life, and to be able to prevent the development of secondary amyloidosis in intermediate and serious forms (MWS and CINCA) of CAPS, is justified.

The therapeutic strategy varies with the seriousness of the disease. It ranges from withholding treatment to anti-IL-1 biotherapies, passing through various symptomatic treatments, particularly for joint pain and arthritis.

At present, the only basic 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). Anti-IL-1 biotherapy must also be offered to patients suffering from severe FCAS, beyond cold-induced urticaria (grade A and C). Improvements in central neurological and neurosensory conditions have been described with IL-1 antagonists in patients suffering from severe forms of CAPS, provided that treatment is started sufficiently early (grade B). IL-1 inhibitors act on the inflammatory component of the disease and not on the sequelae; they have no effect on hypertrophic joint disease, and raise the problem, in CNS disorders, of crossing the blood-brain barrier. Special precautions must be taken concerning children under 4 years of age, in whom the risk of infection with encapsulated microorganisms is particularly large.

The pharmacological agents blocking IL-1 include the following:

► The IL-1R antagonist analogue or anakinra

Anakinra (KINERET) is a 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). Several publications have shown, in non-controlled open studies with prospective and retrospective populations, and thus with a questionable level of evidence, the efficacy of anakinra in FCAS, MWS and CINCA (level of evidence grade B). Cases of improvements in neurosensory lesions (in MWS and CINCA) and central neurological lesions (in CINCA) have been observed with anakinra where the doses were increased, hence the importance of regularly assessing the CNS disorder on the basis of the presence of headaches, papillary oedema on the ocular fundus and of lumbar punctures to monitor meningeal inflammation (grade B). For the moment there is no other publication on the beneficial effect of the other IL-1 antagonists on neurological manifestations in CINCA patients. The joint disorder, in its hypertrophic form, is not changed by anakinra. Stopping anakinra has always been followed by the reappearance of the symptoms (grade B). As regards cutaneous reactions, the frequency of pain and undesirable local reactions to injections of anakinra is up to 90% in the first weeks of treatment.

► The anti-IL-1b monoclonal antibody or canakinumab

Canakinumab (ILARIS) is a completely humanised anti-IL1β monoclonal antibody which has a very long half-life (28-30 days). It obtained Marketing Authorisation for the treatment of CAPS from age 4 years in 2009 following a randomised controlled phase III treatment study versus placebo in MWS patients (level of evidence grade A).
If there is no improvement in the symptoms 7 days after the first injection, it is possible, after agreement with specialists experienced in using this product, to double the recommended doses while maintaining an interval of 8 weeks between two injections.
In the light of current knowledge, it is not possible to state that the early administration of ILARIS has a preventive effect on the development of complications.

The other pharmacological treatments used in the past are no longer recommended.[6]
Management also combines treatments of the clinical manifestations (ocular, cutaneous, articular, muscular, neurosensory and neurological, systemic amyloidosis, etc.) and non-pharmacological treatments (hearing aids in Muckle-Wells, etc.).

The main objectives of following up cryopyrin-associated periodic syndromes (CAPS) are: to diagnose and treat early and late complications linked to the disease or to treatments; to diagnose and give appropriate early management of treatment failures and/or any relapses; to limit and then, as appropriate, to diagnose and start early management of the sequelae linked to the disease (or to the treatments); to assess the psychological, familial, social and occupational impact of the disease, and to limit its negative consequences.

Laboratory follow-up on biotherapy should be performed every 3 months, consisting CBC, CRP, ASAT, ALAT, gGT, total bilirubin; the lipid test of total LDL and HDL cholesterol will be carried out every 6 months; optimum SAA and the sample-based proteinuria/creatininuria ratio should be determined twice a year.
This follow-up allows accurate monitoring of the course of the disease (remission or, conversely, aggravation/progression and maintenance of remission); diagnosis and early initiation of the management of failures and/or any side effects of treatment and possible relapses, and limitation and early initiation of the management of sequelae and complications (early and late) linked to the disease or to treatments.

[6] These are: colchicine, DMARDs (Disease-modifying AntiRheumatic Drugs) and anti-TNFα biotherapies which have little or no effect in the treatment of the various clinical manifestations of CAPS; these medicines are therefore not recommended in the treatment of CAPS (grade B). The prescription of H1 antihistamines in the cutaneous manifestations of CAPS is not recommended on account of reduced efficacy. The prescription of high-dose corticosteroids is sometimes necessary in the neurological or neurosensory manifestations of severe forms of CAPS (grade B) but there are major adverse effects, particularly in children. IV immunoglobulins must be avoided in the severe forms of CAPS, since they may cause a major meningeal reaction.

07 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of the medicinal product assessed are medicinal products available at the same stage of therapeutic use and intended for the same population, on the date of the assessment.

07.1 Medicinal products

Another proprietary medicinal product is authorised in this indication.
This is KINERET 100 mg, solution for injection (anakinra, IL-1 receptor antagonist) which obtained European Marketing Authorisation in a centralised procedure on 20 November 2013 in the treatment of CAPS in adults, adolescents, children and babies from age 8 months, weighing at least 10 kg. This indication has not until now been assessed by the TC.

N.B.: The proprietary medicinal product ARCALYST 80 mg/ml, powder and solvent for solution for injection (rilonacept, soluble IL1 receptor) which had obtained Marketing Authorisation in a centralised procedure on 23 October 2009, "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", was never marketed in France. Since it was never marketed in Europe, this proprietary medicinal product had its Marketing Authorisation withdrawn by decision of the European Commission on 24 October 2012.

07.2 Other healthcare technologies

Not applicable

Conclusion
There are no clinically relevant comparators refunded by National Health Insurance.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

ILARIS obtained a Marketing Authorisation in the extension of indication that is the subject of the present assessment in all countries of the European Union.[7] At present, the product is refundable for children aged 2 to less than 4 years in the United Kingdom, Spain, Italy and in Germany.

[7] In the USA and Japan, ILARIS is currently indicated in the treatment of CAPS in children over 4 years of age.

09 ANALYSIS OF AVAILABLE DATA

In support of its application, the company submitted the results of the pooled analysis of two studies:

- Study 2306, an open study the objective of which was to evaluate the safety and long-term efficacy (over at least six months) (the primary efficacy endpoint was complete response[8]) of canakinumab administered SC in a dose of 150 mg (or 2 mg/kg SC in patients with a weight of ≥ 15 kg and ≤ 40kg) in patients with cryopyrinopathy (CAPS). The results available are those of the final analysis.

On the application for inclusion, the TC had, for this study, the results of an interim analysis. This study was not intended to evaluate efficacy and safety in children, given the inclusion criteria and the previous indication. It included 166 patients with CAPS, of which 119 adults, 47 patients aged less than 18 years and 5 aged less than 4 years.

- Study 2308, an open study that followed up 19 Japanese patients with CAPS (4 adults, 15 children aged less than 18 years, 2 aged less than 4 years), the available results of which for efficacy (the primary efficacy endpoint was the number of patients without relapse[9]) and safety are those of an interim analysis at 48 weeks.

The results of these two studies were pooled so as to analyse efficacy and safety as a function of dose, age and patients' phenotypes.

09.1 Efficacy

The pooled analysis of studies 2306 and 2308 included a total of 185 patients with CAPS.
Post-hoc analyses as a function of the dose administered and of the age were carried out.
In the two studies, the dose of canakinumab, which was initially 150 mg (or 2 mg/kg in subjects weighing ≤ 40 kg) was progressively increased up to 600 mg (or 8mg/kg) if there was an incomplete response.
A total of seven patients aged 2 years to less than 4 years corresponding to the population for the extension of indication were included in this pooled analysis.

An analysis of the complete responses was carried out on all patients naive to treatment with canakinumab included its clinical development programme (n=128). Of these patients, 16 received the maximum dose of 600 mg or 8 mg/kg.
A complete response was observed in 7/16 patients.

As regards data in children aged 2 to less than 4 years and weighing < 15 kg, the analysis covered seven children, of whom six with NOMID.
6/7 patients needed an increase in dose of > 2 mg/kg, in most cases up to 8 mg/kg and more (four patients received a dose of 8 mg/kg for 8 weeks).

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[8] A complete response was defined (according to the investigator's evaluation) by an overall evaluation of the intensity of the autoinflammatory disease ≤ classed as "minimal" combined with an evaluation of the skin manifestations ≤ classed as "minimal" and the achievement of a normal concentration of the CRP and/or SAA levels.

[9] In patients with a complete response, a relapse was defined as:
- a CRP and/or SAA level of > 30 mg/l **and**
  - either an overall evaluation of the intensity of the autoinflammatory disease greater than the grade "minimal"
  - or an overall evaluation of the intensity of the autoinflammatory disease rated as "minimal", combined with an evaluation of the intensity of the skin manifestations greater than the grade "minimal"
- stopping treatment, whatever the reason.

A complete response was observed in 4/7 patients.
Two of the four patients with a complete response did not have any relapses.
In patients who needed an increase in dose (to 600 mg), just one patient had a complete response.

09.2 Safety/Adverse effects

9.2.1 Data from studies

9.2.1.1. Results for the maximum dose

The results are from the pooled analysis of five studies performed in the treatment of CAPS and included a total of 194 patients, of whom 28 were treated with the maximum dose of 600 mg or 8 mg/kg.
All had an adverse event. Those most commonly observed were infections of the upper airways (nine patients), nasopharyngitis (eight patients), joint pain (six patients) and gastroenteritis (six patients).
The adverse events involving infections (mainly infections of the upper airways) and gastrointestinal disorders were more common with a dose of 600 mg (8 mg/kg) than with doses of 150 mg (2 mg/kg) and 300 mg (4 mg/kg).
There were no discontinuations of treatment on account of adverse events.

9.2.1.2. Results for children aged 2 to < 4 years of age

All had adverse events: three had gastrointestinal disorders (mainly abdominal pain), the seven children followed up had infections (four had nasopharyngitis, three rhinitis, two gastroenteritis and two had ear infections). Four patients had infections (one case of chickenpox, one viral infection, one patient with influenza, one case of molluscum). These patients all had NOMID and three had doses of 8 mg/kg. No infections associated with opportunistic microorganisms were reported.
There was no discontinuation of treatment on account of adverse events. No event was regarded as being connected with the treatment.

9.2.2 SPC data

“During clinical trials with ILARIS in CAPS patients mean values for haemoglobin increased and those for white blood cell, neutrophils and platelets decreased.
[…]
Antibodies against ILARIS were observed in approximately 1.5% of the patients treated with ILARIS for CAPS. No neutralising antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.”

9.2.3 The risk management plan (RMP)

The RMP provides for the follow-up of risks linked to treatment, particularly:
- risk of infections in patients treated with ILARIS, particularly opportunistic bacterial, viral or fungal infections;
- risk of acute reaction linked to the injection;
- potential risk of immunogenicity likely to cause immune-mediated symptoms.

The following measures are also included:
- for long-term treatments in CAPS: the need for healthcare professionals to perform an annual clinical assessment of patients regarding the potential increased risk of the development of malignancies;
- as treatment with ILARIS should not be initiated in patients with neutropenia, the need to assess the neutrophil count prior to initiating treatment and again after 1-2 months. For long-term treatments in patients with CAPS, a regular assessment of neutrophil counts is recommended during treatment.
- the need to train the patient in the self-injection technique if the patient is willing and able to do so, and to remind healthcare professionals of how to report administration errors.

010 SUMMARY & DISCUSSION

The pooled analysis of studies 2306 and 2308 made it possible to assess the efficacy and safety of the new dosage regimen with the option of increasing doses up to 600 mg or 8 mg/kg and analysing the effect of canakinumab in seven children aged 2 to less than 4 years with CAPS (mainly the NOMID/CINCA phenotype).
These descriptive efficacy and safety data analysed post hoc by dose, age and phenotype are exploratory in nature.

Efficacy
Among the 128 patients naive to canakinumab who were included in the canakinumab development programme, 16 used the maximum dose of 600 mg (or 8 mg/kg); of these, 7 achieved a complete response.
Six of the seven patients aged 2 to less than 4 years needed high doses (8 mg/kg) because of the severity of NOMID/CINCA, but the response rate was low.
According to the EPAR, the data, despite their limitations, suggest that in patients aged 2 to 4 years, particularly those with NOMID/CINCA (no data for the other phenotypes), an increase in the initial dose up to 8 mg/kg produced an improvement in symptoms.

Adverse effects
In open long-term dose-escalation studies, the occurrence of infections (gastroenteritis, respiratory tract infection, including of the upper respiratory tract), vomiting and dizziness were more commonly reported in the group treated with the dose of 600 mg or 8 mg/kg than in the groups with other doses.
The adverse events most commonly observed in children aged 2 to less than 4 years were infections (nasopharyngitis, rhinitis) of mild to moderate intensity. The adverse effect profile was comparable with those observed in children over 4 years of age.
Local tolerability is good.
There was no discontinuation of treatment on account of adverse events.

The analysis of the most recent PSUR (covering the period from 1 July 2012 to 31 December 2012) did not reveal any new signal different from the identified and potential risks seen during monitoring as part of the RMP.
The risks identified in the RMP are infections, neutropenia and thrombocytopenia.
The potential risks are in particular opportunistic infections, immunogenicity reactions, autoimmune reactions, toxicity of the lymphoid organs, severe reactions at the injection site and lipoprotein metabolism disorders.

Comments
It would seem that, in some cases, the current doses cannot achieve a sufficient clinical response, hence the increase in doses.
Since the metabolism of canakinumab is faster in children under 4 years of age, the doses used had to be increased in order to obtain complete responses. Given the over-representation of NOMID/CINCA, which is extremely serious, in these children, the complete response rate was low.
The adverse effect and safety data in children aged 2 to 4 years and data on the dosage regimen with dose titration up to 600 mg (or 8 mg/kg) are limited.
The small number of patients assessed aged 2 to less than 4 years does not allow any formal conclusion to be drawn as to the higher incidence of infectious events in this population than in the overall population, all ages combined. This slight excess risk of infection may be linked to age (immaturity of the immune system in young children) and to the doses used.
The safety profile in children seems to be similar to that observed in older children and adults. In patients who received high doses, no new signal was revealed.
Real-life registry data will support the use and long-term safety of canakinumab in children aged 2 to 4 years (reflection of clinical practice), since there are still doubts about its long-term safety.

High doses maintained long-term increase the risk of infections. In practice it will therefore be necessary to ensure that the long-term prescription of high doses is justified. There seems to be no need to increase the dose in patients with a good prognosis.

011 PLANNED STUDIES

Among the studies currently under way in CAPS:

- an open study of one year's duration and its extension phase will evaluate the efficacy and safety of vaccination in children aged 4 years and less and treated with canakinumab,
- an open follow-up study will evaluate the efficacy and the safety of canakinumab in Japan up to its marketing,
- an open study will evaluate the efficacy and safety of canakinumab in children over 4 years of age and adults in Canada.

Each year, during the annual reassessment of the Marketing Authorisation under exceptional circumstances, the holder of the Marketing Authorisation is asked to supply reports on the ß-Confident Registry, which is designed to provide data on the efficacy and safety of ILARIS in long-term use in children and adult patients with CAPS, treated with ILARIS in current clinical practice.
In these reports, the holder of the Marketing Authorisation is asked to assess precisely the cases for which there is a loss of efficacy (patients reporting discontinuing treatment with ILARIS because of a lack of therapeutic response) in order to determine if this is due to changes during the period of the PK/PD report or the appearance of antibodies (if data are available), or in which a dose adjustment led to an improvement in therapeutic response (patients with an increase in dose with no break in treatment due to lack of therapeutic response).

012 ROLE OF THE MEDICINE IN THE THERAPEUTIC STRATEGY

Since CAPS are genetically determined diseases of early onset, on diagnosis it is necessary to start effective treatment to avoid intestinal and articular involvement and growth disorders.
All children aged 2 years to less than 4 years with CAPS are likely to benefit from treatment with canakinumab (ILARIS), all the more so since in this age group the frequency of severe forms (NOMID/CINCA with risk of neurological and articular involvement) is greater.
ILARIS is therefore a first-line treatment for CAPS. It will however require long-term assessment.
The dosage regimen is selected individually and depends mainly on the phenotype of the CAPS, the seriousness of the symptoms, the patients' age, the time of diagnosis and the account taken of all these associated factors.
If there is no satisfactory clinical response, as assessed by the doctor, the SPC permits one-off dose increases which must be considered only on the basis of the individual prescriber's clinical judgement. Any dose increase must be duly justified.

013 TRANSPARENCY COMMITTEE CONCLUSIONS

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

013.1 Actual benefit

Cryptopyrin-associated periodic syndromes (CAPS) or cryopyrinopathies are a continuum of three "autoinflammatory" diseases of increasing severity, familial cold urticaria, Muckle-Wells syndrome and CINCA/NOMID syndrome. They are characterised by a combination of cutaneous, articular, neurosensory and neurological signs in a biological setting of severe inflammation. These three syndromes cover a spectrum of increasing severity of the same disease: familial cold urticaria is the most benign form, CINCA the most severe form and Muckle-Wells is a phenotype of intermediate severity. These are disabling diseases due to the recurrence of symptoms and the associated complications.
The objectives of managing cryopyrinopathies are to control the symptoms, prevent the recurrence of inflammatory episodes, limit the impact of the disease on the patient's lifestyle and prevent the most serious complications of the inflammatory disease, particularly deafness and amyloidosis.
ILARIS is intended as symptomatic therapy.
The efficacy/adverse effects ratio for this proprietary medicinal product is high. Nevertheless, doubts remain about its long-term safety.
It is a first-line therapy. There is a validated alternative medication (anakinra) which is not currently reimbursed.

Public health benefit:
CAPS are disabling diseases (recurrence of symptoms and complications, particularly renal failure due to amyloidosis), but are a low public health burden because of their rarity. The burden of the extension of indication of ILARIS in children aged from 2 years to less than 4 years is at best low.
Since improving the management of orphan diseases is an identified priority (National Rare Disease Plan 2011-2014), the treatment of this condition is a public health need.
In view of the available data, the impact of ILARIS in the population of very young children is not quantifiable, due to the very small number of children aged from 2 years to 4 years included in these studies. In the absence of any data, the impact on quality of life that could be expected has not been determined. The transferability of the data to current clinical practice is not guaranteed. ILARIS therefore provides a partial response to the identified public health need.

Consequently, in the current state of knowledge, it is not expected that this proprietary medicinal product will benefit public health in this extension of indication.

Consequently, the Committee believes that the actual benefit of ILARIS is substantial in the treatment of cryopyrin-associated periodic syndromes (CAPS) in children aged from 2 years to less than 4 years with body weight of 7.5 kg or above.

013.2 Improvement in actual benefit (IAB)

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 canakinumab's place in the management of these patients in the absence of any available alternative treatment and 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 suffering from CAPS, including Muckle-Wells syndrome, chronic infantile neurological, cutaneous, articular syndrome (CINCA) or neonatal-onset multisystem inflammatory disease (NOMID), severe forms of familial cold autoinflammatory syndrome (FCAS) or familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

014 TARGET POPULATION

The number of patients with CAPS is difficult to estimate because of the lack of epidemiological studies.
The extension of the target population of ILARIS concerns children with CAPS who are 2 to 3 years of age.

These diseases supposedly affect one to two persons in 1,000,000 in the United States and in Western Europe. There would thus be between 60 and 120 cases in France.
CAPS are rare diseases, the prevalence of which is estimated to be 1/360,000 inhabitants in France.
The incidence of cold urticaria (FCAS) is said to be less than 1/1,000,000. Muckle-Wells syndrome is said to occur mainly in Europe, the FCAS form in the United States.
The Committee considered in 2010 that the target population for ILARIS would be of the order of 50 to 100 adult, adolescent and child patients aged more than 4 years, since:
- the distribution of patients across the different syndromes is about 2/3 for Muckle-Wells syndrome (i.e. between 45 and 65 patients), about 1/3 for FCAS familial cold syndrome (i.e. between 15 and 50 patients) and a few patients for chronic infantile, neurological, cutaneous articular syndrome (CINCA) or NOMID (less than 5 patients),
- the FCAS forms are divided into 2 types: severe and non-severe (i.e. 7 to 25 patients with severe forms).

According to data from INED [National Institute of Demographic Studies], on 1 January 2014, the number of children who are, 2 or 3 years of age in the French population is 788,919.

In total, the target population for ILARIS in the extension of indication in children aged from 2 to under 4 years would be of the order of one to three additional patients.

015 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of proprietary medicinal products refundable by National Health Insurance and on the list of medicines approved for hospital use in the extension of indication "treatment of CAPS in children aged from 2 years to less than 4 years with body weight of 7.5 kg or above" and at the dosage in the Marketing Authorisation.

Proposed reimbursement rate: 65%

Packaging
Not appropriate for the prescribing conditions in the population of children aged from 2 years to less than 4 years.

Specific requests inherent to reimbursement
Exception drug status

◗ Request for data

The Committee would like to have, at its next five-yearly assessment, in addition to the data in the β-Confident registry, follow-up data for all CAPS patients treated with ILARIS in France in terms of efficacy, safety and doses used (particularly since high doses maintained long-term increase the risk of infections).