HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

23 April 2014

ILARIS 150 mg, powder for solution for injection

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

ILARIS 150 mg, powder and solvent for solution for injection

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

Applicant: NOVARTIS PHARMA SAS

INN	Canakinumab
ATC Code (2013)	L04AC08 (interleukin 1 inhibitor)
Reason for the review	**Extension of indication**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123 2)
Indication concerned	**"Gouty arthritis attacks when NSAIDs and colchicine are contraindicated, not tolerated, or do not work adequately, and when use of corticosteroids is not appropriate"**

Actual Benefit	**The actual benefit of ILARIS is substantial.**
Improvement in Actual Benefit	**In view of:** **- the therapeutic need for treatment in patients with gouty arthritis attacks who do not respond adequately to NSAIDs and colchicine and cannot receive corticosteroids;** **- the likely efficacy of canakinumab in these patients but the low level of evidence of available data (*post hoc* sub-group analysis) and possible adverse effects;** **the Transparency Committee considers that ILARIS provides a minor improvement in actual benefit (level IV) in the treatment of gouty arthritis attacks in a population restricted only to those patients who have frequent gouty arthritis attacks who do not respond adequately to NSAIDs, colchicine and corticosteroids or who cannot receive these treatments.**
Therapeutic use	**Given the therapeutic need in the Marketing Authorisation population, canakinumab (ILARIS) is a therapeutic option despite the low efficacy profile in this population and its possible adverse effects. The Committee states that ILARIS is a last-line treatment of gouty attacks and should only be used after considering the real therapeutic need. Once remission is obtained, the urate lowering therapy should be optimised and combined with hygiene and dietary measures.**
Target population	**600 patients**
Recommendations	**The Committee wishes, within 2 years, to have data on the characteristics of patients treated in France with gouty arthritis attacks collected on the basis of a cohort study.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised procedure): 23 October 2009 (in patients with CAPS) Marketing Authorisation under exceptional circumstances[1] only in patients with CAPS Indication extension obtained on 18 February 2013 in gouty arthritis.
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 status

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

02 BACKGROUND

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

Since July, 1st 2010, this proprietary medicinal product has been 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 (CAPS) in adults, adolescents and children aged 4 years and older with a body weight of 15 kg or above (Opinion of 10 February 2010). An opinion favourable to the refundable indication extension in young children (aged 2 to under 4 years old) with CAPS was issued by the Committee on 5 February 2014.

In rheumatology, ILARIS has obtained two indication extensions:
- on 18 February 2013, in hard-to-treat attacks of gouty arthritis, the subject of the present assessment;
- on 26 August 2013, in SJIA, a separate Opinion will be issued by the Committee for this indication.

ILARIS is the 1st biotherapy to obtain a Marketing Authorisation for gout. Anakinra, another IL-1, was used off-label in this indication in situations where no further therapeutic options are available.

[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.

03 THERAPEUTIC INDICATIONS

Indication concerned by the review:
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. "

Other indications not affected by the assessment:

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 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.

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. "
**these indications have been covered in other Opinions*

04 DOSAGE

The treatment should be initiated and supervised by a specialist physician experienced the diagnosis and treatment of gouty arthritis and in the use of biological medicines. ILARIS should be administered by a healthcare professional.
Management of hyperuricaemia with appropriate urate lowering therapy (ULT) should be instituted or optimised. ILARIS should be used as an on-demand therapy to treat gouty arthritis attacks.

The recommended dose of ILARIS for adult patients with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, ILARIS should be administered as soon as possible after the onset of a gouty arthritis attack.
Patients who do not respond to initial treatment should not be re-treated with ILARIS. In patients who respond to the treatment and require re treatment, there should be an interval of at least 12 weeks before a new dose of ILARIS may be administered.

For dosages in the other indications, see SPC.

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.
Treatment of gouty arthritis
ILARIS should not be administered during an active infection.

Neutropenia and leukopenia
Neutropenia (absolute neutrophil count [ANC] < 1.5 x 109/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. If a patient becomes neutropenic or leukopenic, the absolute WBC counts (blood count) should be monitored closely and treatment discontinuation should be considered.

Malignancies
Malignancy events have been reported in patients treated with ILARIS. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown.

Hypersensitivity reactions
Hypersensitivity reactions with ILARIS treatment have been reported. The majority of these events were mild in severity. During clinical development of ILARIS in over 2300 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

The treatment of gout is based on pharmacological and non pharmacological measures. Hygiene and dietary measures should be proposed and followed as first-line treatment: reducing alcohol intake, calorie intake and consumption of purines (delicatessen products, offal, ...). Correction of often associated comorbidities (hyperlipidaemia, hypertension, hyperglycaemia, obesity, use of tobacco) is a significant part of the treatment.
If the hygiene and dietary measures are inadequate in reducing serum uric acid levels below 360 µmol/l (or 60 mg/l), a urate lowering agent, a xanthine oxidase inhibitor (allopurinol, febuxostat), should be initiated, preferably some time after the acute attack. Probenecid is the therapeutic alternative in the event of intolerance or contraindication to at least one of the xanthine oxidase inhibitors, but it is not recommended when the creatinine clearance test is <50 ml/min. Another uricosuric medication, benzbromarone (DESURIC), is only available in the form of temporary authorisation for use by a named patient [ATU nominative in French] in certain specific situations following withdrawal of Marketing Authorisation and discontinuation of marketing in 2003 due to hepatic adverse effects.

Attacks may occur during the first few months of urate lowering therapy. Their prevention is based on NSAIDs or colchicine for 3 to 6 months, even longer in cases of tophus. Corticosteroids may also be used in certain cases.
However, the contraindications and precautions for using NSAIDs and colchicine may restrict their use in certain situations, particularly in elderly subjects with comorbidities.

Consequently, there is an unmet therapeutic need in rare patients with comorbidities, making it impossible to use the usual treatments for gout attacks, particularly NSAIDs, colchicine and corticosteroids.

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

There is no other medication with Marketing Authorisation in the symptomatic treatment of adult patients with frequent gouty arthritis attacks who cannot receive NSAIDs, colchicine or corticosteroids.

07.2 Other health technologies

Not applicable

Conclusion

At the moment, there is no clinically relevant comparator reimbursed by National Health Insurance in this indication.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Marketing Authorisation:
ILARIS has a Marketing Authorisation for gouty arthritis in all the countries in the European Union. However, it does not have a Marketing Authorisation in Canada, Japan or the USA (rejected by the FDA in 2011 with a request for a study of a sub-group likely to derive particular benefit from the treatment).

Reimbursement:
At the time of writing this documentation, ILARIS is reimbursed in Germany.
In the United Kingdom, NICE does not recommend canakinumab for gout[2] due to lack of data submitted by the company.

[2] "NICE is unable to recommend the use in the NHS of canakinumab for treating gouty arthritis attacks and reducing the frequency of subsequent attacks because no evidence submission was received from the manufacturer of the technology." The manufacturer informed NICE that it would not be making an evidence submission for this appraisal. The manufacturer stated that it will not be promoting canakinumab for this specific indication in the UK. NICE TA281 April 2013.

09 ANALYSIS OF AVAILABLE DATA

The efficacy data from two active-controlled clinical studies (H2356 and H2357) and their extension phases (H2356 E1 and H2357 E1) were provided and considered.
To evaluate the safety, two phase II dose-finding studies were provided and considered.

09.1 Efficacy

The efficacy data for canakinumab (ILARIS) in the treatment of gouty arthritis attacks are from two phase III, controlled studies[3] using an identical study design with triamcinolone acetonide (TA).

Study design
12-week active comparator-controlled (TA), randomised, double blind studies, followed by a 12-week double-blind extension (i.e. a total of 24 weeks – 6 months of monitoring).

Objective
The main objective of these two studies was to show the superiority of a single subcutaneous injection of 150 mg of canakinumab over a single intramuscular injection of 40 mg of triamcinolone acetonide.

Treatments
The patients received a double injection on D1: a subcutaneous injection (canakinumab 150 mg or placebo) and an intramuscular injection of TA 40 mg (or its placebo).
In the event of new attacks, the patients were able to be re treated with the same treatment and at the same dose observing a minimum period of 15 days between two injections.
The urate lowering doses (allopurinol, probenecid, for example) or colchicine should remain stable throughout the study.
The patients who did not tolerate pain very well were allowed to take rescue treatment after the 6-hour post-treatment assessment: paracetamol (maximum 3 g/d) and/or codeine (180 mg/d) and oral prednisolone if necessary.

Inclusion criteria
Patients aged 18 to 85 years with:
- an acute attack of gout (defined by the ACR criteria[4] 1977) which started less than 5 days prior to randomisation with a pain intensity of ≥ 50 mm on the VAS (0-100 mm);
- frequent attacks of gout (at least 3 attacks in the 12 month prior to randomisation), where there was a contraindication, intolerance or no efficacy in the case of NSAIDs and/or colchicine.

Endpoints
The study included two co-primary endpoints: pain intensity at 72 hours, measured on the VAS from 0 to 100 mm and the time to onset of a new attack of gout within 12 weeks of the treatment ending.
Among the secondary endpoints, the percentage of patients who had recourse to rescue treatment.

Statistical analysis
The statistical analyses were not carried out in the intention to treat population, that is for all the randomised population, but for all the randomised population who received at least one dose of

[3] Schlesinger N, Alten RE, Bardin T et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomized, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012; 71:1839-1848.
[4] American College of Rheumatology.

treatment defined as "Full analysis set" (FAS). Statistical significance was required for the two co-primary endpoint variables.

Results

- Patient characteristics, see Table 2

Overall, 456 patients were randomised to receive either a single subcutaneous injection of canakinumab or TA on D1: 230 in Study H2356 (115 in each group) and 226 in Study H2357 (112 in the canakinumab group and 114 in the TA group).
No statistically significant difference was shown between the two treatment groups in each of the studies in terms of demographic and medical characteristics.
The patients included in these studies were predominantly men (> 90%), who had an average age of 53, with an average BMI of 32 kg/m² and many comorbidities: 59.5% had hypertension, 15% had diabetes, and 87% grade 2 to 5 renal failure.
The proportion of patients aged 75 years and older was very low - 13 patients, i.e. less than 3% of the patients included.
The average number of attacks of gout was 6.5 in the 12 months prior to randomisation.
Forty to 45% of patients received urate lowering therapy. The presence of tophi was noted in 29% of patients. The proportion of patients in the canakinumab group with a contraindication to NSAIDs was 91%, colchicine 42% and both 34%. In other words, 65% of patients included had no contraindication to NSAIDs and colchicine and consequently were able to receive standard treatment for attacks of gout.

Overall, 78% of patients treated with canakinumab received a single dose of canakinumab.

Table 1. Main demographic and medical characteristics of patients included in Studies H2356 and H2357

	H2356		H2357		Grouped data	
	Canaki	**TA**	**Canaki**	**TA**	**Canaki**	**TA**
	n = 113	**n = 115**	**n = 112**	**n = 114**	**n = 225**	**n = 229**
Sex, n (%)						
Male	101 (89.4)	108 (93.9)	100 (89.3)	105 (92.1)	201 (89.3)	213 (93.0)
Female	12 (10.6)	7 (6.1)	12 (10.7)	9 (7.9)	24 (10.7)	16 (7.0)
Age (year), mean (SD)	54 (11.2)	54.6 (10.7)	51 (12.1)	53 (12.3)	52.3 (11.8)	53.6 (11.5)
BMI (kg/m^2), mean (SD)	31.8 (4.7)	31.6 (4.7)	32 (6.0)	32 (5.5)	32 (5.4)	31.5 (5.1)
Severity of attacks, mean (SD)						
Nb episodes last year	6.5 (5.5)	7.0 (5.1)	6.5 (5.7)	5.9 (4.4)	6.5 (5.6)	6.5 (4.8)
Pain intensity before treatment (VAS)	73.3 (11.4)	74.8 (13)	75 (13.3)	74 (12.6)	74.1 (12.4)	74.2 (12.6)
Classification of gout– n (%)						
monoarticular	51 (45.1)	51 (44.3)	66 (58.9)	71 (62.3)	117 (52.0)	122 (53.3)
oligoarticular	37 (32.7)	50 (43.5)	23 (20.5)	28 (24.6)	60 (26.7)	78 (34.1)
polyarticular	25 (22.1)	14 (12.2)	23 (20.5)	15 (13.2)	48 (21.3)	29 (12.7)
Contraindication, intolerance, and/or inefficacy						
NSAID	107 (94.7)	113 (98.3)	97 (86.6)	96 (84.2)	204 (90.6)	209 (91.2)
Colchicine	27 (23.9)	39 (33.9)	67 (59.8)	59 (51.8)	94 (41.7)	98 (42.7)
NSAID and colchicine	22 (19.5)	38 (33.0)	54 (48.2)	46 (40.4)	76 (33.7)	84 (36.7)
Urate lowering therapy in progress n (%)						
Yes	57 (50.4)	63 (54.8)	32 (28.6)	40 (35.1)	89 (39.6)	103 (45.0)
Presence of tophi– n (%)						
Yes	44 (38.9)	45 (39.1)	20 (17.9)	23 (20.2)	64 (28.4)	68 (29.7)
Uricaemia (mg/dl)						
median (min-max)	8.1 (2-13)	8.6 (3-17)	8.3 (3-13)	8.2 (3-13)	8.0 (2-13)	8.0 (3-17)

Canaki = canakinumab, TA = triamcinolone acetonide

- Treatment discontinuations:

Among the patients included, 91.6% of patients completed 12 weeks of the study. Treatment discontinuations affected:
- in Study H2356, 6 patients in the canakinumab group (3 lost to follow-up, 2 for administrative reasons, 1 due to withdrawal of consent) versus 10 in the TA group (4 due to insufficient efficacy, 3 due to withdrawal of consent, 1 for administrative reasons, 1 death and 1 lost to follow-up)
- in Study 2357, 13 patients in the canakinumab group (6 due to withdrawal of consent, 5 lost to follow-up, 1 death, 1 laboratory abnormality) versus 11 in the TA group (4 due to withdrawal of consent, 3 lost to follow-up, 1 due to administrative reasons, 1 laboratory abnormality, 2 due to protocol deviation).

- Analysed population

In Study H2356, the FAS analysis focused on 228 of 230 randomised patients (two randomised patients in the canakinumab group but not treated).
In Study H2357, the analysis did not include one patient in the canakinumab group and three patients in the TA group). The patients for whom the basal value of pain intensity and/or the value at 72 hours was not available were not included in the FAS analysis for this endpoint. No additional analysis was carried out on the whole randomised population.

- Results for the primary endpoints

The superiority of canakinumab 150 mg over triamcinolone acetonide 40 mg was shown in the two studies in terms of the two co-primary endpoints:

Pain intensity at 72 hours

The reduction of the pain intensity at 72 hours, measured by VAS (0-100 mm), was more significant in the canakinumab group than in the triamcinolone acetonide group: difference of -10.7 mm [15.4;-6], pooled results from the two studies, p < 0.0001.

Table 2. Results on the pain intensity (co-primary endpoint in mm, mean ± SD) in Studies H2356 and H2357 (FAS population)

	Study H2356		**Study H2357**		**Grouped data**	
FAS population	**Canaki N = 113**	**TA 40 mg N = 115**	**Canaki N = 112**	**TA 40 mg N = 114**	**Canaki N = 225**	**TA 40 mg N = 229**
Before treatment	73.3 ± 1.1	74.8 ± 1.2	74.9 ± 1.3	73.6 ± 1.2	74.1 ± 0.8	74.2 ± 0.8
at 72 hours **N analysed**	28.1 ± 2.4 N = 112*	39.5 ± 2.4 N = 111*	22.1 ± 2.3 N = 111*	31.9 ± 2.4 N = 109*	25 ± 1.7	35.7 ± 1.7
Difference versus inclusion (p value)	**-11.4 [-18.2; -4.6] (p = 0.0005)**		**-9.8 [-16.3; -3.2] (p = 0.0018)**		**-10.7 [-15.4; -6] (p < 0.0001)**	

* only the patients who had a VAS on D0 and at 72 hours were included in the analysis

Time to onset of the first new attack

The Kaplan-Meier method was used to estimate the probability of onset of an attack of gout within 12 weeks, in each of the two treatment groups. This probability was significantly lower in patients treated with canakinumab 150 mg (17%) than in those treated with TA 40 mg (37%), grouped data from two studies, p = 0.0001.

Table 3. Results on the probability of onset of the 1st new attack at 12 weeks in Studies H2356 and H2357 (FAS population)

	Study H2356		**Study H2357**		**Grouped data**	
FAS population	**Canaki N = 113**	**TA N = 115**	**Canaki N = 112**	**TA N = 114**	**Canaki N = 225**	**TA 40 mg N = 229**
At 12 weeks Probability (%, 95% CI)	19 (13-27)	37 (28-46)	14 (9-22)	38 (30-48)	17 (12-22)	37 (31-44)
HR (p)	**0.45 [0.26; 0.76] (p = 0.0014)**		**0.32 [0.18; 0.58] (p < 0.0001)**		**0.38) (p < 0.0001)**	

HR: hazard ratio

- Results for a secondary endpoint:

The proportion of patients who received rescue treatment was lower in the canakinumab group than in the triamcinolone group during the two studies. According to the results of the pooled analysis from the two studies, it was 37.3% in the canakinumab group versus 54.6 in the TA group (OR = 0.47, p = 0.001).

Other analyses:

Post-hoc analyses were carried out as part of the procedure for granting Marketing Authorisation in different sub-groups considered by the CHMP as likely to derive particular benefit from canakinumab treatment. These analyses were motivated by the characteristics of the population treated with canakinumab in the studies (only 40% taking urate lowering therapy, 42% who had a contraindication, intolerance or did not respond adequately to colchicine). The CHMP questioned the fact that these patients had not received optimal treatment for their gout.

An analysis was conducted in the sub-group of patients who cannot be treated either with NSAIDs or colchicine because of a contraindication, intolerance or inefficacy.

The results in this sub-group are superimposable to those of the general study population (difference of -12.6 mm on the VAS at 72 hours [-20.8, -4.3], p = 0.0015 and probability of a new

attack at 12 weeks lower with canakinumab than with TA (HR 0.27; 95% CI, [0.14; 0.54], p < 0.0001).

An analysis was conducted in the sub-group of patients treated with urate lowering therapy. In this sub-group, no difference was shown between canakinumab and TA in terms of pain and onset of a new attack.

Finally, an analysis was carried out in a sub-group of patients who cannot be treated either with NSAIDs or colchicine because of a contraindication, intolerance or inefficacy. They were treated or not treated with urate lowering therapy because of a contraindication or prior failure to respond to these treatments. Of the 456 patients included in Studies 2356 and 2357, 101 (22% of the patients included) were considered as meeting these criteria (canakinumab 150 mg: 50, TA 40 mg: 51). The results in this sub-group were superimposable to those of the general study population (difference of -10.2 mm on the VAS at 72 hours [-19.9, -0.4], p = 0.0208 and probability of a new attack at 12 weeks lower with canakinumab at 16.6% vs 35.3% with TA (HR 0.39; 95% CI, [0.17; 0.91], p < 0.0151).

These analyses, not included in the protocol, had a low level of evidence.

The data for patients in whom the use of corticosteroids is inappropriate is not available.

<u>24-week extension data:</u>
175 patients (90 canakinumab and 85 TA) from Study H2356 and 160 (84 canakinumab and 76 TA) from Study H2357 participated in the 12-week extension phase (2356 E1 and 2357 E1) during which, in case of a new attack, they received, double-blind, the same treatment as they did during the pivotal phase, i.e. canakinumab 150 mg or TA 40 mg. A total of 149 patients were re-treated at least once (60 canakinumab and 89 TA).
The results at 6 months suggested a probability of onset of a new attack, estimated using the Kaplan-Meier method, which was significantly lower in the patients treated with canakinumab 150 mg (32%) than those in the TA 40 mg group (56%), HR = 0.44, p = 0.0001 (grouped data).

09.2 Safety/Adverse effects

The safety of canakinumab in the treatment of gouty arthritis attacks was examined in four studies (two phase II studies and two phase III studies) and focused on 1085 patients, including 253 treated with 150 mg of canakinumab, dose recorded by the Marketing Authorisation. Around 87% of these patients received a single dose of canakinumab.
The incidence of adverse events (AE) was higher in the canakinumab 150 mg group (56.2%) than in the triamcinolone acetonide 40 mg group (44.1%).
The most common AEs with canakinumab were headaches (4%), arterial hypertension (4%) and back pain (3.6%). Thirteen (13) serious AEs, including two infections, were reported in patients treated with canakinumab as opposed to seven in the TA group. Five deaths, including three in the canakinumab group, were reported. The imputability score for the treatment was not recorded.

If we limit ourselves to data from the two phase III studies and their 24-week extensions (225 patients treated with canakinumab, including 23.7% who received at least two injections), the overall incidence of AEs was 66.2% with canakinumab versus 52.8% with TA. Infections were reported in 20.4% of patients treated with canakinumab versus 12.2% in those treated with TA. The infections were as follows: nasopharyngitis, upper respiratory tract infections, bronchitis, of mild to moderate severity.
Vertigo was reported in 2% of patients in the canakinumab group versus 0.7% in the TA group.
No severe reaction to the canakinumab injection has been reported, but two mild reactions have been reported.
Given the data, the immunogenic potential of canakinumab seems low. The appearance of anti-canakinumab antibodies was observed in around 1% of patients with no clinical consequence.

Two cases of malignant tumours have been reported in the context of studies carried out on gout, including one case of prostate cancer considered as not linked to treatment in a patient treated with canakinumab (one in the comparator group).
The risk management plan includes the monitoring of infections, neutropenia and thrombopenia, malignant tumours, vertigo, immunogenicity, the increase in uricaemia and lipid and hepatic abnormalities.

09.3 Summary & discussion

Efficacy
In two controlled, randomised, double-blind clinical studies with an identical study design, the efficacy of a single dose of 150 mg of canakinumab was compared with that of a single intramuscular injection of 40 mg of triamcinolone acetonide (TA) in patients with multiple attacks of gout but who, for some of them, were able to receive the usual treatment for an attack, in particular colchicine, and who did not have optimal urate lowering therapy.
The choice of triamcinolone acetonide administered intramuscularly as a comparator (while the 2012 ACR guidelines[5] favour oral corticosteroids, Grade A) and the low dose used (40 mg instead of the 60 mg recommended followed by oral corticosteroids with prednisone or prednisolone according to the 2012 ACR guidelines) are questionable. This choice was however considered by the EMA as acceptable in the absence of data demonstrating that another comparator would have been more appropriate[6].
A total of 456 patients, predominantly men (> 90%), who had an average age of 53 years, with an average BMI of 32 kg/m^2 and many comorbidities (59.5% had hypertension, 15% had diabetes, and 87% renal failure) were included in these two studies. These patients suffered from frequent attacks of gout. They had on average 6.5 attacks of gout in the year prior to their randomisation. The proportion of patients aged 75 years and older was very low: 13 patients, i.e. less than 3% of the patients included.
Among the patients randomised to the canakinumab group, only 40% were receiving urate lowering therapy, which reflects non-optimal management of their disease. Moreover, although 91% of patients had a contraindication to NSAIDs, only 42% had a contraindication to colchicine and 34% to both treatments. We could therefore consider that 65% of patients included in the study were likely to receive conventional treatment for attacks of gout with NSAIDs and/or colchicine.

In the general population of these two studies, the superiority of canakinumab 150 mg over TA 40 mg was demonstrated for the two co-primary endpoints (grouped data):
- a difference of -10.7 mm [-15.4; -6] on the VAS 0-100 mm at 72 hours was shown in favour of canakinumab, p < 0.00001;
- the probability of onset of a new attack of gout within 12 weeks of the treatment ending was significantly lower with canakinumab (17%) than with TA (37%), p = 0.00001.

The proportion of patients who had recourse to a rescue treatment (paracetamol and/or codeine and oral prednisolone if necessary), secondary endpoint, was lower in the canakinumab group (37.3%) than in the TA group (54.6%), p = 0.001.

The data from the comparative double-blind follow-up phase of these two studies suggested a maintained efficacy for canakinumab at 6 months with a probability of onset of a new attack lower with canakinumab (32%) than with TA (56%), p = 0.0001.
An analysis was conducted in a sub-group of patients in situations where no further therapeutic options are likely to derive particular benefit from canakinumab treatment. This sub-group, defined a posteriori, included patients who cannot be treated either with NSAIDs or colchicine (because of a contraindication, intolerance or inefficacy). They were treated or not treated with urate lowering

[5] Khanna D, Khanna PP, Fitzgerald JD. 2012 ACR guidelines for management of gout. Part 2. Athritis Care Res 2012; 64: 1447-1461.
[6] Cf EPAR.

therapy because of a contraindication or prior failure to respond to these treatments. Of the 456 patients included in the two studies, 101 patients, i.e. only 22% of the patients included, met these criteria. In this sub-group, results similar to those observed in the general study population were shown (difference of -10.2 mm on the VAS at 72 hours [-19.9, -0.4], p = 0.0208 and probability of a new attack at 12 weeks lower with canakinumab at 16.6% versus 35.3% with TA (HR 0.39; 95% CI, [0.17; 0.91], p < 0.0151).
This analysis in a sub-group not included in the initial study protocol has a low level of evidence.
The data for patients in whom the use of corticosteroids is inappropriate is not available.

Safety
The safety of canakinumab was overall satisfactory in all the studies performed in the gouty arthritis indication. In the two phase III studies and their extensions at 24 weeks, the incidence of adverse events (AE) was 66.2% with canakinumab versus 52.8% with TA. Infections have been reported in 20.4% of patients treated with canakinumab versus 12.2% of those treated with TA: they were rhinopharyngitis, upper respiratory tract infections, and bronchitis, of mild to moderate severity.
The risk management plan includes the monitoring of infections, neutropenia and thrombopenia, malignant tumours, vertigo, immunogenicity, the increase in uricaemia and lipid and hepatic abnormalities.

09.4 Planned studies

In the indication for gouty arthritis, the RMP provides for the implementation of a follow-up register for treated patients.

010 THE MEDICINE'S THERAPEUTIC USE

The Marketing Authorisation population of canakinumab (ILARIS) is restricted to patients with gout situations where no further therapeutic options are available for the treatment of attacks: patients who do not respond adequately to NSAIDs or colchicine and corticosteroids or who cannot be treated with these drugs. Given the therapeutic need in these patients, the likely efficacy of canakinumab despite the low level of evidence of the demonstration of its efficacy in this population (*post hoc* sub group analyses) and its possible adverse effects, canakinumab (ILARIS) is a therapeutic option. The Committee states that ILARIS is a last-line treatment of gouty attacks and should only be used after considering the real therapeutic need.
Once remission is obtained, the urate lowering therapy should be optimised and combined with hygiene and dietary measures. An interval of 3 months should be observed between two injections of canakinumab. The Committee issues a reminder that ILARIS should not be administered during an active infection.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

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

011.1 Actual Benefit

◗ In patients with frequent attacks and who do not respond adequately to the usual treatments, or who cannot receive these treatments, advanced-stage gout is the cause of disability and a marked deterioration in quality of life, linked to joint or kidney damage (lithiasis, nephropathy).

◗ ILARIS is intended as symptomatic therapy.

◗ Its efficacy/adverse effects ratio is high.

◗ Public health benefit

Gout is a frequent, incapacitating condition. However, the public health burden represented by the ILARIS indication indicated in patients with frequent attacks and for whom NSAIDs and colchicine cannot be used is low because of the restricted number of patients concerned.
Improving the management of gout is a public health need which is an established priority (Pain Management Improvement Plan 2006 – 2010, Quality of Life Improvement Plan for Patients with Chronic Disorders 2007-2011).
Given the available data versus corticosteroids, the impact of ILARIS on morbidity is moderate.
An impact on quality of life can be expected in view of the reduction in symptoms. However, in the absence of data, this impact cannot be quantified.
The transferability of the data to current clinical practice is acceptable.
Therefore, ILARIS provides a partial response to the therapeutic need.
It is not expected that ILARIS will benefit public health in this indication.

◗ This proprietary medicinal product is a symptomatic last-line treatment for acute attacks in patients who had an inadequate response, an intolerance or a contraindication to a previous NSAID or colchicine treatment and in whom the use of corticosteroids is deemed inappropriate.

◗ There are no treatment alternatives with a Marketing Authorisation for these patients.

Consequently, the Committee considers that the actual benefit of ILARIS is substantial in the Marketing Authorisation indication.

011.2 Improvement in actual benefit

In view of:
- the therapeutic need for treatment of attacks in patients with gout who do not respond adequately to NSAIDs and colchicine and who cannot receive corticosteroids;
- the likely efficacy of canakinumab in these patients but the low level of evidence of available data (*post-hoc* sub group analysis) and possible adverse effects;
the Transparency Committee considers that ILARIS provides a minor improvement in actual benefit (level IV) in the treatment of gouty arthritis attacks in a population restricted only to those patients who have frequent gouty attacks who do not respond adequately to NSAIDs, colchicine and corticosteroids or who cannot receive these drugs.

012 TARGET POPULATION[7,8]

Given its Marketing Authorisation wording, the target population of ILARIS is made up 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.
This population is restricted and difficult to assess due to a lack of accurate epidemiological data.

In 1999, the prevalence of gout was 1.4% in the United Kingdom[9]. This figure is confirmed in another study conducted[10] between 2000 and 2005 in the United Kingdom and Germany.
On this basis, we can estimate the population with gout in France to be around 600,000.
The proportion of patients with gout who cannot be treated with NSAIDs, colchicine or corticosteroids is very restricted and would represent less than 1% of the population of patients with gout. Consequently, this population can be estimated to be at most 6000 patients in France.
In practice, it is observed that many patients with gout who are difficult to treat are offered alternative preventative solutions before having recourse to a monoclonal antibody: use of low doses of colchicine (0.5 or 1 mg/d) and NSAIDs (ex diclofenac 25 mg x2/d) with risks that the rheumatologists know how to control. In the event of a situation without recourse, anti-IL1 treatment can be initiated in a hospital.
Thus, among the 6000 patients with gout which is difficult to treat in France, only 10% would be likely to be treated with ILARIS (expert opinion).

Consequently, the population likely to derive benefit from ILARIS treatment would be 600 patients.

013 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.

◗ Specific requests inherent to reimbursement
The Committee issues a reminder that ILARIS has exception drug status.

◗ Request for data
The Committee wishes, within 2 years, to have data on the characteristics of patients treated in France with gouty arthritis collected on the basis of a cohort study.

[7] Chalès G. De l'hyperuricémie à la goutte: épidémiologie de la goutte. Revue du Rhumatisme 2011; 78: S109- S115.
[8] Lioté F, Lancrenon S, Lanz S et al. GOSPEL: Prospective survey of gout in France. Part I: Design and patient characteristics (n=1003) Joint Bone Spine; 79 :464-470.
[9] Mikuls TR, Farrar JT, Bilker WB, et al. Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. Ann Rheum Dis 2005; 64:267-272.
[10] Annemans L et al. Gout in the UK and Germany: prevalence, comorbidities and management in clinical practice. Ann Rheum Dis 2008;67:960-966.