HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion
19 November 2014

HYALGAN 20 mg/2 ml, solution for intra-articular injection in prefilled syringe
B/1 (CIP: 34009 335 657 1 8)

Applicant: EXPANSCIENCE

INN	Sodium hyaluronate
ATC code (2014)	M09AX01 (anti-osteoarthritic)
Reasons for the review	**Re-assessment of the actual benefit at the Committee's request, in accordance with Article R. 163-21 of the Social Security Code.** **Renewal of inclusion**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)**
Reimbursable indication	**"Treatment of patients with gonarthrosis, after failure of analgesics and failure of or intolerance to non-steroidal anti-inflammatories (NSAIDs)".**

Actual Benefit:	**Low in the treatment of painful flare-ups of gonarthrosis, after failure of or intolerance to analgesics and NSAIDs**
Improvement in Actual Benefit	**N/A**
Therapeutic use	**HYALGAN has a limited role in the management of flare-ups of gonarthrosis in patients in whom the usual analgesic and NSAID treatments have proved ineffective or in patients intolerant to these treatments (see section 08.2).**
Recommendations	**The Transparency Committee recommends continued inclusion on the list of medicines reimbursed and approved for hospital use.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	08.10.1992 (national procedure)
Prescribing and dispensing conditions /special status	List I Management or reimbursement by National Health Insurance is conditional on these injections being prescribed and carried out exclusively by a rheumatologist, an orthopaedic surgeon, or by a specialist in physical medicine and rehabilitation, up to a limit of three injections per year and per knee.

ATC Classification	M	Musculo-skeletal system
	M09AX	Other drugs for disorders of the musculo-skeletal system
	M09AX01	hyaluronic acid

02 BACKGROUND AND HISTORY OF THE ASSESSMENT

Review of the proprietary medicinal product HYALGAN included again on the list of medicines refundable by National Health Insurance for a period of 5 years starting on 12.01.2010 (automatic renewal).

The proprietary medicinal product HYALGAN is the only hyaluronic acid solution for intra-articular injection with the status of a medicinal product indicated in gonarthrosis with effusion.

Ten (10) other viscoelastic solutions of hyaluronic acid of variable molecular weight have the status of medical devices (MD) and are included on the list of products and services qualifying for reimbursement (LPPR).

The reimbursable indication[1] of HYALGAN is similar to that of hyaluronic acid-based medical devices: “Treatment of patients with gonarthrosis, after failure of analgesics and failure of or intolerance to NSAIDs”.

In fact, in 2004, the Committee recommended the inclusion of HYALGAN on the list of medicinal products reimbursable by National Health Insurance and approved for hospital use “on condition that:

- the number of reimbursable injections is limited to three per year and per knee,
- the injections are prescribed and carried out exclusively by a rheumatologist, an orthopaedic surgeon, or by a specialist in physical medicine and rehabilitation.”

The actual benefit provided by HYALGAN was considered substantial.

As regards therapeutic use, the Committee regarded it as a second-line treatment: “hyaluronic acids are more particularly used in cases of painful gonarthrosis, or where oral treatments have failed or are contraindicated. HYALGAN is a second-line treatment the proper use of which requires the involvement of a competent doctor experienced in the management of osteoarthritis and in giving intra-articular injections. There is no proof of the usefulness of giving several courses

[1] Official Gazette of 12 January 2005.

of HYALGAN a year. These local treatments are particularly useful for avoiding the continuous consumption of NSAIDs, especially in patients with gastrointestinal risk factors".
As regards the improvement in actual benefit (IAB), the Opinion stated: "The efficacy of HYALGAN is of the order of that of medical devices that contain hyaluronic acid and are indicated in gonarthrosis. In addition, its safety of use, which has been the subject of studies required for medicinal product development, seems to be better established."
The efficacy data taken into account were as follows:[2]

- The Carrabba 1995 study, a double-blind comparison of HYALGAN with placebo and with arthrocentesis in 100 patients with gonarthrosis with effusion (20 patients per group) for the relief of pain on day 35 and day 60 (primary endpoint). The superiority of HYALGAN (three injections and five injections) over placebo has been demonstrated (difference between day 0 and day 60 of -4.6 in the placebo group, -1.3 in the arthrocentesis group, -8.3 in the HYALGAN one injection group, -16.3 in the HYALGAN three injection group (a difference of 11.7 points versus placebo) and -21.2 in the HYALGAN five injection group.
- Altman 1998 study, no difference was shown between naproxen 1 g a day and five injections of HYALGAN in terms of pain on walking assessed in week 26 for patients who completed the study (333/495); the analysis was not made as ITT.
- Jones 1995 study: the efficacy of HYALGAN five injections was compared with that of triamcinolone hexacetonide 20 mg in 63 patients. No difference between the two groups was found as regards pain assessed at week 4 and week 29 (ITT analysis).
- Sala 1995 study in 36 patients which showed the superiority of HYALGAN versus placebo in the relief of pain on a VAS from day 90 onwards.

It must be pointed out that, on the basis of the Committee's current assessment standards, the level of evidence for the results of these studies that led the Committee to classify the AB of HYALGAN as substantial seems very low.

In 2010, as part of the statutory 5-yearly renewal of its inclusion on the list of reimbursable medicinal products, the Transparency Committee, in the light of knowledge about the value of this proprietary medicinal product in the management of gonarthrosis, wondered whether or not to change the substantial actual benefit with regard to and in keeping with the assessments made of medicinal products with comparable performance, i.e. moderate, in disorders of "moderate" severity. Classification of the actual benefit as no longer substantial at that time seemed scientifically logical and well-founded, but would have automatically led to unfairness of treatment between different hyaluronic acid-based healthcare technologies by recommending a level of reimbursement lower than the one for medical devices. However, since the efficacy of HYALGAN was no less than that of the best medical devices available, which were reimbursed at 65% on account of a "sufficient" expected clinical benefit assigned by the National Committee for the Assessment of Medical Devices and Health Technologies (CNEDiMTS), it risked giving rise to inequality of treatment between these different forms of treatment that were nevertheless equivalent, and disrupting competition. A note was sent to the Social Security Directorate to inform it of that fact.
Against this background, and concerned to apply equal treatment to hyaluronic acid-based medical devices, the Committee retained the substantial AB for HYALGAN.

The clinical data taken into account in this Opinion were as follows:[3]

- The Bellamy meta-analysis of 2006 which compared hyaluronic acids (HYALGAN and MD) with placebo, injectable corticosteroids and NSAIDs. The superiority of HYALGAN (3-5 injections) to placebo was confirmed with a difference of 6.2 points on the VAS at 100 mm (not clinically significant) and 1.5 points on the Lequesne index. Given the poor methodological quality of the studies, no conclusion could be drawn from a comparison of HYALGAN with injectable corticosteroids. A single study comparing HYALGAN with an NSAID (study by Altman et al taken into account in 2004) was used. The results of this

[2] Transparency Committee Opinion of 22 December 2004.
[3] Transparency Committee Opinion of 28 April 2010.

meta-analysis must be interpreted with caution because of the methodological reservations (low level of evidence of the studies included, no test of heterogeneity).
- The Reinchenbach meta-analysis which did not show any difference between HYALGAN and the SYNVISC MD in acting on pain.
- The results of a clinical study versus placebo (Tsai et al 2003) carried out in a Taiwanese population between 2001 and 2002 in 198 patients as part of the Marketing Authorisation process in Taiwan in 2003 were supplied. The superiority of HYALGAN to placebo was demonstrated on the primary endpoint which was pain on walking 15 m (VAS 0-100 mm). A difference of 8.07 mm (95% CI [2.98; 13.16]; p=0.002) was shown in comparison with placebo.

In November 2013, the CNEDiMTS recommended against the maintenance of reimbursement (inadequate AB) for hyaluronic acid-based medical devices indicated in knee osteoarthritis.

Following this Opinion and in pursuance of Article R.163-21 of the Social Security Code, the office of the Transparency Committee wished to re-assess the actual benefit provided by HYALGAN in pursuance of Article R.163-21.

Since the previous assessment by the Transparency Committee, new data, including meta-analyses likely to change the Committee's assessment, have been published. It against this background that the Transparency Committee decided of its own volition to re-assess the AB of HYALGAN.

Because of a procedural shortcoming, the CNEDiMTS is continuing its assessment of hyaluronic acid-based medical devices.

03 THERAPEUTIC INDICATION

“Symptomatic treatment of painful gonarthrosis with effusion.”

The only therapeutic indication for which National Health Insurance cover is provided is limited to:
“Treatment of patients with gonarthrosis, after failure of analgesics and failure or intolerance to nonsteroidal antiinflammatories (NSAIDs)”.

04 DOSAGE

“Intra-articular use. For use in adults only.
Injections must be given using a strictly aseptic technique. It is important to aspirate before injecting, to ensure that the tip of the needle is not in a blood vessel.
The dosage is one intra-articular injection of 20 mg/2 ml a week, for not more than 5 weeks.”

05 THERAPEUTIC NEED

The first steps to take in treating symptomatic osteoarthritis of the lower extremities are diet- and lifestyle- based (weight loss, regular physical activity except during flare-ups of pain or congestion where reduced activity is necessary) and non-pharmacological (physical therapy, wearing orthoses, using sticks, etc.).
Treatment must be individualised and include risk factors related to the knee (obesity, mechanical stress, physical activity) and general risk factors (age, multiple medications, etc.), the intensity of the pain and the disability that it causes, the presence of inflammatory signs (effusion), and the degree of structural impairment.

During symptomatic phases, treatment mainly includes analgesics, starting with paracetamol, and during acute flares, short courses of oral NSAIDs at the minimum effective dose in patients who do not respond to paracetamol. Local analgesic treatments, especially topical NSAIDs and intra-articular corticosteroid injections, can also be used, especially during congestive phases.

Medicines such as chondroitin sulfate, unsaponifiable avocado and soybean oil, diacerein and glucosamine have minimal effects only on pain and functional disability. It has not been demonstrated that they reduce NSAID consumption, which causes very notable and often serious adverse effects, particularly in the elderly. Consequently, they have no role in the therapeutic strategy. The Transparency Committee issued an Opinion recommending their deletion from the list of reimbursable medicinal products.

Surgery (arthroplasty, prosthetic implant) is reserved for radiologically advanced osteoarthritis that is painful and disabling and resistant to the usual therapeutic measures.

There is therefore currently no primary treatment that can change the progression of osteoarthritis.

In conclusion, there is a medical need in the management of osteoarthritis.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

There is no other hyaluronic acid-based medicinal product included on the list of reimbursable medicinal products.

Taking account of its indication as per the Marketing Authorisation, the other medicinal products comparable to HYALGAN are other symptomatic treatments of gonarthrosis included on the list of reimbursable medicinal products: analgesics, NSAIDs and corticosteroids for intra-articular injection.
Taking account of its reimbursable indication (second-line after failure of NSAIDs and analgesics), injectable corticosteroids are, according to the guidelines, reserved for congestive flare-ups of osteoarthritis (characterised by more inflammatory pain, the presence of articular effusion and by a risk of rapid chondrolysis); there is no medicinal alternative to HYALGAN.

06.2 Other health technologies

The most relevant comparators are other viscoelastic solutions of hyaluronic acid for intra-articular injection with the status of medical devices (MD). These products are indicated in the "symptomatic treatment of gonarthrosis, after failure of analgesics and failure of or intolerance to NSAIDs". This indication corresponds to the reimbursable indication of HYALGAN (but not to the indication in its Marketing Authorisation, which is broader), the molecular weight of which is between 0.5 and 0.7 million daltons.

Product	Description/composition/molecular weight	Distributor
ADANT	10 mg/ml viscoelastic solution of hyaluronic acid in prefilled syringe of 2.5 ml **molecular weight 0.6-1.2 million daltons**	DAIICHI SANKYO FRANCE S.A.S.
ARTHRUM	20 mg/ml solution of hyaluronic acid for intra-articular injection **molecular weight 2.3-3.3 million daltons**	LCA S.A.
DUROLANE	viscosupplement, single injection of non-animal hyaluronic acid (NASHA), 20 mg/ml **cross-linked hyaluronic acid-90**	BIOVENTUS
EUFLEXXA	10 mg/ml viscoelastic solution of hyaluronic acid for intra-articular injection **molecular weight 2.4-3.6 million daltons**	BIO-TECHNOLOGY GENERAL Ltd
GO-ON	10 mg/ml viscoelastic solution of hyaluronic acid **molecular weight 1.4 million daltons**	ROTTAPHARM S.A.R.L
OSTENIL	10 mg/ml hyaluronic acid for intra-articular injection **molecular weight 1.2 million daltons**	TRB CHEMEDICA S.A.S.
SINOVIAL	8 mg/ml of sodium hyaluronate solution for intra-articular injection **molecular weight 0.8-1.2 million daltons**	LABORATOIRE GENEVRIER
STRUCTOVIAL	hyaluronic acid solution for intra-articular injection **molecular weight 2.2-2.7 million daltons**	PIERRE FABRE MEDICAMENT
SYNOCROM	10 mg/ml viscoelastic solution of hyaluronic acid for intra-articular injection **molecular weight 1.6 million daltons**	CROMA
SYNVISC ONE[4]	8 mg/ml hyaluronic acid **cross-linked hyaluronic acid-6**	GENZYME SAS

Conclusion

The clinically relevant comparators are the other hyaluronic acids with the status of medical devices.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

According to information supplied by the applicant, HYALGAN is reimbursable only in the following six European countries: United Kingdom*, Greece, Hungary, Ireland, Slovakia, Czech Republic.
It should however be noted that the NICE recommendation of 2014[19] does not favour reimbursement of hyaluronic acids and that HYALGAN is not reimbursed in 22 European countries, including Germany, the Netherlands, Belgium, Spain and Italy.

08 ANALYSIS OF AVAILABLE DATA

In the 2004 Opinion on the inclusion of HYALGAN, the Committee's conclusions on the efficacy and safety data supplied were as follows:

[4] Not yet re-assessed by the CNEDiMTS.

"The relief of pain on movement was greater in the groups with HYALGAN three and five injections than in the placebo and arthrocentesis groups.
There is a gain in efficacy for HYALGAN five injections compared with HYALGAN three injections but it must be offset by the constraints and potential risks associated with additional injections.
There was no difference between the HYALGAN and naproxen groups in the assessment of pain on walking 50 paces.
There was no difference between HYALGAN and triamcinolone hexacetonide in efficacy against pain in an activity defined by the patient at 4 weeks. The results at 29 weeks, which were favourable to HYALGAN in the per protocol analysis, are however difficult to interpret because of the large number of dropouts from the study."

In the last Opinion given by the Committee in 2010, the data supplied showed modest efficacy of HYALGAN. The conclusions of the Transparency Committee were as follows:
"The new data available, subject to their methodological limitations, confirm:
- the superiority of HYALGAN in comparison with placebo in the treatment of gonarthrosis. The difference on the 0-100 mm VAS was modest and not clinically significant (6.2 mm);
- the efficacy of HYALGAN, which is of the order of that of medical devices containing hyaluronic acid which were assessed in gonarthrosis, and accepted for reimbursement."

Since that assessment, several systematic reviews and meta-analyses assessing the efficacy of all hyaluronic acids and four clinical studies including a group treated with HYALGAN have become available.

08.1 Efficacy

The new efficacy data supplied by the applicant consist of:

- **five (5) meta-analyses or systematic reviews**
  - Miller et al 2013[5]
  - Colen 2012[6]
  - Rutjes et al. 2012[7]
  - Bannuru et al. 2011[8] and
  - Bannuru et al. 2009[9].
- **two (2) clinical studies**
  - an independent clinical study from the company EXPANSCIENCE (Jorgensen A et al 2010[10]) which compared HYALGAN with placebo, the results of which are negative and,
  - a non-inferiority study which compared GO-ON (a hyaluronic acid-based medical device) with HYALGAN[11].

[5] Miller LE, Block JE et al. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. Clin Med Insights Arthritis Musculoskelet Disord. 2013; 6: 57-63.
[6] Colen S, van den Bekerom MP, Mulier M et al. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. BioDrugs. 2012; 26: 257-68.
[7] Rutjes AWS, Juni P, da Costa BR et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Int Med. 2012; 157: 180-91.
[8] Bannuru RR, Natov NS, Dasi UR et al. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis-meta-analysis. Osteoarthritis Cartilage. 2011; 19: 611-9.
[9] Bannuru RR, Natov NS, Obadan IE et al. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Arthritis Rheum. 2009; 61: 1704-11.
[10] Jorgensen A, Stengaard-Petersen K, Simonsen O, et al. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicentre, randomized, placebo-controlled, double-blind study of 337 patients followed for 1 year. Annals Rheum Dis 2010; 69: 1097-102.

Two other studies and two meta-analyses have been identified by the Medicines Assessment Department of HAS:

- a non-inferiority study (not published but assessed in July 2009 by the National Committee for the Assessment of Medical Devices and Health Technologies (CEPP), now CNEDiMTS) comparing the medical device ARTHRUM with HYALGAN;
- a non-inferiority study[12] comparing the medical device SYNVISC with HYALGAN,
- an unpublished meta-analysis supplied to HAS as part of the CNEDiMTS assessment also took into account the "Affinity Health meta-analysis";[13]
- a meta-analysis by Bannuru 2013[14] which compared hyaluronic acids with NSAIDs.

Non-inferiority studies comparing medical devices with HYALGAN were the result of a request from post-inclusion data made by CNEDiMTS.

It should be noted that no new study has been carried out by the company distributing the proprietary medicinal product HYALGAN.

Published studies assessing hyaluronic acids other than HYALGAN and those for which the hyaluronic acid assessed is not specified were not taken into account, in particular:

- the Petrella 2010 study in which the hyaluronic acid assessed was not specified;
- a recent negative Japanese study published in 2014; the non-inferiority of a high molecular weight hyaluronic acid (2700 kD) from Chugai Pharmaceutical by comparison with an NSAID (loxoprofen) was not demonstrated in 200 patients.
- the results of a study available only in the form of an abstract comparing a special hyaluronic acid (Fermathron plus, molecular weight 2.2 M daltons) with placebo, the superiority of three injections was not demonstrated by comparison with placebo; the authors thus do not recommend the use of three injections of hyaluronic acid in patients with mild to moderate gonarthrosis.

8.1.1 Results of meta-analyses and systematic reviews

They are described from the newest to the oldest ones.

- Unpublished "Affinity Health" meta-analysis of 2013[15] assessing the effects of hyaluronic acids versus placebo supplied to CNEDiMTS.

The aim of this meta-analysis was to assess the efficacy versus placebo of viscosupplementation in knee osteoarthritis, including studies versus placebo and studies with an active control.
The primary efficacy endpoint was pain assessed 3 months after the end of treatment or, failing that, at the next measurement.
We included controlled, randomised studies of high methodological quality defined by unpredictable randomisation[16] and blinding[17] of patients and investigators.

[11] Berenbaum F, Grifka J, Cazzaniga S, et Al. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Ann Rheum Dis. 2012; 71: 1454-60.
[12] Raman R et al. Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee - a prospective randomized clinical trial. Knee. 2008; 15: 318-24.
[13] This meta-analysis (MA) was done by Michel Cucherat at the request of a group of manufacturers to reply to the Rutjes MA (used as the main basis for the CNEDiMTS re-assessment) which, according to them, took account of all studies, whatever their methodological quality, and not the latest post-inclusion studies.
[14] Bannuru et al. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: A systematic review and meta-analysis. Seminars in Arthritis and Rheumatism 43 2014; 43 : 593-9.
[15] Viscosupplementation in the treatment of knee osteoarthritis – "Meta-analysis of randomised studies of greater methodological quality" – final report final V1.0 of 2 October 2013 prepared for the company "Affinité Santé" by Michel Cucherat.

The meta-analysis covered **14 studies**. Of the 14 studies used, 8 assessed a viscosupplementation treatment versus placebo and 6 assessed one viscosupplementation treatment versus another viscosupplementation treatment. The safety data were not documented.

8 studies versus placebo:

Study	Treatment evaluated	Subjects randomised	Weekly No. of injections
Shichikawa 1983	Not specified	114 / 114	5
Puhl 1993	ARTZAL	102 / 107	5
Altman 2004	DUROLANE	172 / 174	1
Petrella 2006	Not specified	53 / 53	3
Lundsgaard 2008	HYALGAN	84 / 84	4
Altman 2009	EUFLEXXA	293 / 295	3
Chevalier 2010	SYNVISC	124 / 129	1
Navarro-Sarrabia 2011	ADANT	149 / 152	5

6 non-inferiority studies (versus other viscosupplementation treatment):

Study	Treatment evaluated	Comparator	Subjects randomised	Weekly No. of injections
Kirchner 2006	EUFLEXXA	SYNVISC	160 / 161	3
Berenbaum 2012	GO-ON	HYALGAN	217 / 209	3
Ostenil study (Nov 11) *	OSTENIL	SYNVISC	116 / 106	3
Pavelka 2011	SINOVIAL	SYNVISC	192 / 189	3
Maheu 2011	STRUCTOVIAL	SYNVISC	139 / 140	3
Durolane study (Oct 12) *	DUROLANE	ARTZAL	175 / 174	1 / 5

* unpublished study

One hundred (100) studies were not included, mainly for reasons of methodological quality. It should be noted that some of these studies are however included in other published meta-analyses described below.

The results are presented not by product but overall. In a direct comparison versus placebo, the overall analysis of the endpoint pain shows a weak effect of viscosupplementation (-0.21 [95% CI, -0.32 to -0.10]). An extrapolation was made of the efficacy of treatment evaluated by comparison with placebo, using the results of the non-inferiority study of treatment evaluated versus an active control and the results of the study of active treatment versus placebo (Bucher method). This indirect comparison (putative placebo type) led the authors to associate viscosupplementation with a reduction in pain after the end of treatment corresponding to an effect size of -0.30 [95% CI, -0.44 to -0.16]. The clinical relevance of this effect is small.

[16] To be as effective as possible, randomisation must be unpredictable. Otherwise, there is a risk of selection bias. For example, if the nature of the treatment the next patient will receive is predictable, the investigator can delay the time of a patient's inclusion until he/she will receive the treatment which, consciously or unconsciously, the investigator wanted him/her to receive. The lists or envelopes giving the type of treatment in clear text give rise to this type of problem. Only a centralised randomisation procedure guarantees that it is unpredictable.

[17] The double-blind design avoids bias due to the observer (subjective interpretation of the results and heterosuggestion) and to the patient (autosuggestion).

Looking specifically at HYALGAN, a single study versus placebo (Lundsgaard 2008[18]) was included in this meta-analysis because it met the predefined methodological quality criteria but it is not conclusive. This is consistent with the recent NICE guideline[19] on osteoarthritis which considered that only the Lundsgaard study contained no serious bias in assessing the effect of HYALGAN versus placebo in terms of the percentage of responders in gonarthrosis. It should be noted that, in this study, the proportion of patients with stage IV gonarthrosis according to the Kellgren and Laurence classification (which does not correspond to the main target population for hyaluronic acids) was 36.9% in the HYALGAN group, 32.5% in the 2 ml physiological saline group and 38.8% in the 20 ml physiological saline group. In addition to this study versus placebo, a comparative study[11] versus a medical device (GO-ON) was included (it is described below).

The studies versus placebo that were not included in this meta-analysis for want of sufficient methodological quality for HYALGAN include:

- the studies Grecomoro 1987, Bragantini 1987, Corrado 1995 and Sala 1995 because the patient blinding, investigator blinding and the unpredictability of randomisation cannot be evaluated
- studies Cohen 1994, Creamer 1994, Huskisson 1999, Bunyaratavej 2001, Jubb 2003, Tsai 2003 and Huang 2011 because patient blinding and the unpredictability of randomisation cannot be evaluated
- the studies Henderson 1994, Altman 1998 and Carrabba 1995 because the unpredictability of randomisation cannot be evaluated;
- the study Dougados 1993; the investigator was not blinded
- the study Huang 2005; the patient was not blinded and the unpredictability of randomisation could not be evaluated;
- the Jorgensen 2010 study; the unpredictability of randomisation could not be evaluated;
- the study Listrat 1997: the patient and the investigator were not blinded and the unpredictability of randomisation could not be evaluated.

One comparative study was not included: the study Roman 2008 comparing ADANT (n=30) with HYALGAN (n=19) because the patient blinding, investigator blinding and the unpredictability of randomisation could not be evaluated.

Overall, the results of this meta-analysis do not allow any conclusions to be drawn about the efficacy of HYALGAN in the management of gonarthrosis.

- Systematic review and meta-analysis, Miller et al 2013[5]

This systematic review and meta-analysis (MA), covered **29 studies, including 18 performed with HYALGAN**, the aim of which was to assess the efficacy and safety of injections of hyaluronic acids approved in the USA[20] in symptomatic gonarthrosis.

The efficacy endpoints were pain and function, assessed at two points: 4-13 weeks and 14-26 weeks. Safety was also assessed.
The results for the endpoint pain showed a mean standardised difference of 0.43 (95% CI: 0.26 to 0.60) at 4-13 weeks and of 0.38 (95% CI: 0.21 to 0.55) at 14-26 weeks in comparison with placebo ($p<0.001$). The results for the endpoint function showed a mean standardised difference of 0.34 (95% CI: 0.16 to 0.51) at 4-13 weeks and of 0.32 (95% CI: 0.18 to 0.45) at 14-26 weeks in comparison with placebo ($p<0.001$).
No statistically significant difference was found in terms of safety as regards severe AEs, severe AEs linked to treatment and dropouts on account of adverse effects.

[18] Lundsgaard et al. Intra-articular sodium hyaluronate 2 ml versus physiological saline 20 ml versus physiological saline 2 ml for painful knee osteoarthritis: a randomized clinical trial. Scand J Rheumatol 2008; 37: 142-50.
[19] NICE. Osteoarthritis, care and management in adults - February 2014.
[20] This work was funded by a coalition of companies marketing viscosupplementation in the USA.

However, the methodological quality of the studies was considered moderate (JADAD score of 3 [2-5]), since 0 = very weak and 5 = rigorous. Moderate to substantial heterogeneity (substantial for the endpoint pain (I^2=73-5%) and moderate for the endpoint function (I^2=54-69%) and publication bias (only articles published in English comparing hyaluronic acids approved in the US versus placebo were taken into account for the endpoint pain) were found. There was no analysis of sensitivity. As regards adverse effects, the analysis made using only the published studies seems to be of little relevance; an independent, blinded analysis of attributability for the treatments received should have been made (using a relevant classification for severe AEs).

In view of these methodological limitations, this systematic review and meta-analysis cannot be used to draw any formal conclusion about the efficacy and safety of injections of hyaluronic acid in the treatment of gonarthrosis.

- Systematic review and meta-analysis, Bannuru 2013[14] (effect versus NSAIDs)

The aim of this new systematic review and meta-analysis was to assess the efficacy of viscosupplementation by comparison with that of NSAIDs in the treatment of gonarthrosis. It covered **five clinical studies, only one of which evaluated HYALGAN** (with a dose regimen of five injections, which does not correspond to the one validated).
This systematic review suggested that there was no difference in efficacy between hyaluronic acids and NSAIDs. However, the methodological quality of studies was poor; randomisation was considered acceptable for just one study. As regards the only study evaluating HYALGAN that was included, the authors considered that the risk of bias was not "not clear" because of randomisation and performance of the ITT analysis that are "not clear".

- Systematic review and meta-analysis, Rutjes 2012[7]

The aim of this systematic review and meta-analysis was to assess the benefits and risks of viscosupplementation in adults with symptomatic gonarthrosis.
The primary efficacy endpoint was pain at ± 3 months (assessed 3 months after the end of treatment or, failing that, at the nearest measurement time) and the primary safety endpoint was the occurrence of inflammatory flare-ups. **It covered 89 clinical studies** (the number of studies relating to HYALGAN is not given). It should be noted that 81 studies included in this meta-analysis (MA) were excluded from the previous MA (Affinity Health) because of problems with methodological quality.
The main analysis of the endpoint reduction in pain suggested a moderate effect size of viscosupplementation (-0.37 [95% CI, -0.46 to -0.28]). This result was at the limit of the minimum value for the clinically relevant difference defined beforehand (effect size of -0.37 corresponding to 9 mm on a visual analogue scale (VAS) at 100 mm).
The safety assessment suggested that the risk of inflammatory flare-ups evaluated in six clinical studies was increased but not statistically significant (relative risk of 1.51 [0.84; 2.72]. However, the risk was statistically increased in terms of serious AEs (1.41 [95% CI, 1.02-1.97], p=0.039), discontinuations of treatment on account of AEs (1.33 [1.01-1.74] p=0.04) and local adverse effects (1.34 [1.13-1.60] p=0.001), although the available data do not allow the mechanism to be understood (14 studies). Attributabililty to the treatment was not discussed.

Methodological limitations linked primarily to the poor quality of the studies included were revealed. In fact, the study selection criteria defined by the authors were: the following "randomised or semi-randomised studies". Thus, only 13 studies out of the 89 included (15%) reported adequate secrecy of assignment to treatment, 17 studies (19%) made an ITT analysis of the results, in 16 (18%) the patient was adequately blinded and in 48 (54%) the evaluation was made by a suitably blinded method.
Differences were revealed between the studies included in the meta-analysis (test of heterogeneity significant, p<0.001). Interaction tests were performed and showed a correlation between the effect size and the size of the study (the effect size was nil whereas the size of the study was large, more than 100 patients per group) and between the effect size and the blinded assessment of the primary endpoint (the effect size was nil when the evaluation was made blinded).

A limited analysis of large studies (more than 100 patients per arm) evaluated blind (i.e. 18 studies with a total of 5094 patients) showed an effect size of less than the value for the minimum clinically relevant difference (-0.11 95% CI [-0.18 to -0.04]); the differences between studies disappeared.

Publication bias was also revealed (asymmetric funnel plot).

Safety data are little reported in the clinical studies, which limits the validity of the conclusions about safety.

Overall, the results of this meta-analysis do not allow any formal conclusion to be drawn about the efficacy and safety of hyaluronic acids such as HYALGAN in the treatment of gonarthrosis because of the numerous methodological limitations identified.

- Systematic review and meta-analysis, Colen 2012[6]

The aim of this systematic review and meta-analysis was to compare the efficacy in gonarthrosis of intra-articular injections of hyaluronic acid with placebo in controlled, randomised studies with the primary endpoint pain, assessed on a VAS at 3 months' follow-up. It covered **74 clinical studies, 25 of which assessed HYALGAN**. The reduction in pain achieved after treatment with hyaluronic acid was 40-50% at 3 months and, after the intra-articular injection of placebo, was of the order of 30% (range 16-44%), which means that the mean difference observed was modest (-10.20 [-15.97; -4.42]), its clinical relevance was considered debatable by the authors. The high heterogeneity of the studies included was however identified (I^2 =92%).

The available data suggested efficacy of HYALGAN and SYNVISC (the two most widely evaluated hyaluronic acids) versus placebo that was at best weak:

- the size of effect for HYALGAN[21] versus placebo was evaluated at -0.61 [-0.92; -0.29], but with strong heterogeneity identified (I^2 =86%)
- that of SYNVISC was -0.89 [-1.98; 0.21], also with strong heterogeneity identified (I^2 =97%).

Because of contradictory data, the strong heterogeneity of the studies and the endpoints evaluated, the authors were unable to conclude that one particular hyaluronic acid, despite differences in terms of molecular weight, concentration or injected volume, was more effective than another.

Given the identified limitations of this systematic review, particularly the strong heterogeneity of the studies analysed (open, single-blind studies could be included since double-blind was not defined as a study selection criterion) and a period of follow-up limited to 3 months, the results of this meta-analysis do not allow a distinction to be made between hyaluronic acids, the efficacy of which is at best weak in comparison with placebo.

- Meta-analysis, Bannuru 2011 (effect versus placebo)[8]

The aim was to assess the effect of viscosupplementation versus placebo in patients with gonarthrosis.
The primary efficacy endpoint was pain assessed at 7 times between 2 and 24 weeks. The safety of hyaluronic acids was not assessed.
It covered **54 clinical studies** (the number of studies relating to HYALGAN is not specified). The results suggested a modest clinical improvement in pain with hyaluronic acids starting from the 4th week (standardised effect of 0.31 95% CI [0.17-0.45]) with a peak at 8 weeks (0.46, 95% CI [0.28-0.65] then a tendency for the effect to be reduced (0.25, 95% CI [0.15-0.36] at 12 weeks, and a residual effect detectable at 24 weeks (0.21, 95% CI [0.10-0.31]).

[21] 11 studies published between 1987 and 2010, 734 patients treated with HYALGAN and 732 with placebo.

The quality of the studies used was considered to be very variable: only 16 studies (30%) met the criteria defined by the authors to rate them as being "of good methodological quality" (inclusion of more than 100 patients, suitable double-blind and randomisation procedures, intention-to-treat analysis).

A high level of heterogeneity was found, including an analysis limited to "studies of good methodological quality". Publication bias cannot be ruled out, in the absence of a funnel plot. Safety was not assessed in this meta-analysis.

Overall, the results of this meta-analysis do not allow any formal conclusion to be drawn about the efficacy and safety of hyaluronic acids such as HYALGAN in the treatment of gonarthrosis because of the numerous methodological limitations identified.

- Systematic review and meta-analysis, Bannuru 2009 (effect versus corticosteroids)[9]

The aim was to assess the effect of viscosupplementation versus corticosteroids in patients with gonarthrosis. The primary efficacy endpoint was pain assessed at 2, 4, 8 and 12 weeks.
It covered **seven clinical studies** (606 patients), of which five were performed with HYALGAN, four compared HYALGAN with methylprednisolone acetate, one study compared HYALGAN with triamcinolone hexacetonide; in the other two studies, the hyaluronic acid was ORTHOVISC and SYNVISC.

The results suggested the superiority of corticosteroid injections over hyaluronic acid at 2 weeks in terms of the reduction in pain (size of effect -0.39 95% CI [-0.65; -0.12]), the absence of any difference between the two treatments after four weeks (size of effect -0.01 [-0.23; 0.21]), the superiority of hyaluronic acid as regards pain at week eight (size of effect 0.22 [-0.05; 0.49], and at weeks 12 (0.35 [0.03; 0.66] and 26 (0.39 [0.18; 0.59]. Weak heterogeneity was found (I^2<50%).

Out of the seven studies, just one had been performed double-blind, three were open, for five studies secrecy of assignment to treatment was not specified, and only five studies underwent intention-to-treat analysis.

Overall, this meta-analysis comparing hyaluronic acid with corticosteroids in intra-articular injection for the treatment of gonarthrosis included studies of inadequate methodological quality, which virtually invalidates its conclusions.

<u>General conclusion on meta-analyses and systematic reviews</u>
The seven available meta-analyses were made on a variable number of clinical studies (ranging from 5 to 89) of variable but mostly poor methodological quality. The studies included were heterogeneous, performed at different periods, on differing populations, with greatly varying endpoints, endpoint analysis periods and statistical methods. This explains the great heterogeneity shown. Publication bias cannot be ruled out, even though unpublished data were used in some meta-analyses. **Leaving aside these methodological limitations, most of these meta-analyses suggest a symptomatic effect that is at best weak of injections of hyaluronic acid, including HYALGAN, on pain and functional impairment in gonarthrosis.**

- **<u>Results of clinical studies</u>**

Four new clinical studies, one of them a study versus placebo, and three studies assessing the non-inferiority of a medical device (MD): GO-ON, ARTHRUM or SYNVISC to HYALGAN have been performed since the last Opinion of the Transparency Committee.
The literature search identified:

- some unpublished studies comparing medical devices with HYALGAN, supplied to CEPP (National Committee for the Assessment of Medical Devices and Health Technologies, the former name of CNEDiMTS)

<u>Independent Danish study of HYALGAN versus placebo, Jorgensen et al 2010[10]</u>
In this controlled, randomised, double-blind study, 337 patients with symptomatic gonarthrosis and a Lequesne score ≥ 10 were randomised to receive one intra-articular injection a week of

HYALGAN (n=167) or placebo (saline, n=170) for 5 weeks and were followed for up to 1 year. The primary efficacy endpoint was the time to relapse (time between the reduction of 1 point in the Lequesne score[22] in comparison with baseline and the time when the Lequesne score increases (again) by 1 point). No statistically significant difference was found between HYALGAN and placebo (172.2 days with HYALGAN versus 204.3 days with placebo). It should be noted that the time before relapse could not be assessed for 53% of the patients in the HYALGAN group and 59% of the patients in the placebo group because these patients were mostly rated as still improved at the end of the study (at 1 year). No statistically significant difference was found between the two groups in the secondary endpoints, particularly the reduction in pain assessed on a 50 mm VAS (difference of 0.07 [-0.33; 0.46] at 3 months) and the use of paracetamol (difference of -0.23 [-0.54; 0.14] at 3 months.
According to the authors, the strong placebo effect noted in this study, about 58% for the primary endpoint, is consistent with that described in other clinical studies, where it ranged from 50 to 70%. According to them, the injection itself, the aspiration of synovial fluid, patient training and the psychological effect are possible explanations for the strong placebo effect.

This study was included in the recent meta-analyses Rutjes, Colen and Miller.

Berenbaum study 2012[10] (GO-ON)
The main aim of this controlled, randomised, double-blind study was to demonstrate the non-inferiority of the MD GO-ON by comparison with HYALGAN in the symptomatic treatment of gonarthrosis. The primary efficacy endpoint was the reduction in the WOMAC pain score at 6 months (assessed on a VAS of 0-100 mm). The non-inferiority hypothesis was as follows: GO-ON would be regarded as non-inferior to HYALGAN if the lower limit of the difference between the two treatments was greater than the non-inferiority threshold set at - 9mm on the WOMAC pain scale of 0 to 100 mm.

For 3 consecutive weeks, patients received one injection a week of HYALGAN or GO-ON.

Out of the 437 randomised patients, 343 (78.5%) were analysed in the per-protocol population (PP). In the main PP analysis, the non-inferiority of GO-ON to HYALGAN was demonstrated: the improvement in the WOMAC pain score was 25.8 ± 19.9 in the GO-ON group (n=171) and 20.6 ± 20.8 in the HYALGAN group (n=172), a difference of 5.2; 95% CI [0.9; 9.6]. The ITT analysis confirmed this result, with a difference of 4.5% [0.5; 8.5].
No conclusion can be drawn from the analysis of superiority that was made, because of the non-clinically relevant size of effect observed.
Adverse events that were treatment-related were reported in 2.7% of patients in the GO-ON group and 3.3% of patients in the HYALGAN group. Most were local effects such as pain, haematoma or smarting at the injection site.

During the study, a comparable proportion of patients (no statistically significant difference) took concomitant treatment with paracetamol and/or NSAIDs: 166/217 (77%) in the GO-ON group versus 154/209 (74%) in the HYALGAN group.

This study did not have a placebo group, which means that the internal validity of its results cannot be confirmed, particularly as the effect size is small and the level of evidence in demonstrating the effect of HYALGAN versus placebo is low.

Study of SYNVISC versus HYALGAN (not published)[23]
The CEPP's conclusions were as follows: "A comparative, randomised, single-blind clinical study had the main aim of comparing SYNVISC (199 patients included) with HYALGAN (193 patients included) as regards the change in the knee pain score (measured on a VAS graduated from 0 to 10 cm) at 26 weeks (6 months). The analysis shows that the difference between groups is statistically significant in favour of SYNVISC at 26 weeks (3.3 for the SYNVISC group versus

[22] Lequesne index (score from 0 to 24 points, classified in five degrees of severity; 1-4 points: slight disability / 14 points or more: extreme disability).
[23] HAS CEPP. SYNVISC Opinion of 6 October 2009.

0.7 for the HYALGAN group; p=0.02). One patient in the SYNVISC developed, 5 days after the 3rd injection, the clinical picture of pseudoseptic arthritis, no microbe found, which necessitated hospitalisation. There are methodological reservations to counterbalance the conclusions of this study favourable to SYNVISC. The pain score for the HYALGAN reference group had not improved at 26 weeks in comparison with D0 (6.6 at D0 and 5.9 at 26 weeks), a difference of 0.7 point, NS. Thus, the reference did not show its usual efficacy under the conditions in which the study was performed. Analysis of the protocol shows, in particular, that patients knew which treatment they had been given. Overall, the results of this study cannot be interpreted."

ARTHRUM versus HYALGAN (not published)[24]
The CEPP's conclusions were as follows: "This unpublished study was intended to demonstrate the non-inferiority of ARTHRUM H 2% (99 patients included) versus HYALGAN (94 patients included) in the reduction on the WOMAC pain index (Likert scale[25]). Patients were followed up until the end of the study (D180 or discontinuation of treatment). In the primary per-protocol analysis, the confidence interval for the intergroup difference in the mean change in the subscore WOMAX A was [-2.93; -0.46]. The upper limit of the 95% confidence interval for that difference was less than the non-inferiority limit set at 1.94, the non-inferiority of ARTHRUM H 2% by comparison with HYALGAN was demonstrated for the WOMAC A score at the end of the study in the per-protocol population. The secondary, intention-to-treat analysis reported a 95% confidence interval of [-2.62; -0.33]. Since the upper limit was lower than the fixed non-inferiority limit, the non-inferiority of ARTHRUM H 2% by comparison with HYALGAN was confirmed. The analysis of superiority showed a clinical difference between the groups of -1.47 ± 0.58 [-2.62; -0.33] with p=0.012, in the intention-to-treat population. On the other hand, the claimed superiority was difficult to accept since the difference observed, of 1.47, was less than the non-inferiority limit of 1.94 which was initially set in the protocol as a non-clinically relevant difference. In addition, using the effect size concept, estimated to be 0.34, it was possible to conclude that the effect size was at best small."

Conclusion from the results of these clinical studies
In a Danish study published in 2010, HYALGAN was no different to placebo in terms of the time to relapse assessed using the Lequesne index (primary efficacy endpoint) in 337 patients with gonarthrosis who were followed up for 1 year.
The results of studies comparing medical devices with HYALGAN (some of which have not been published) showed their non-inferiority; however, none of these studies included a placebo group, which means that their internal validity cannot be guaranteed. Claims concerning superiority were not considered acceptable because of the methodological limitations revealed (single-blind assessment, clinical relevance of the difference observed, etc.).

08.2 Safety/Adverse effects

Data from clinical studies
Safety data were very limited in the meta-analyses described above. The main aim of these meta-was not to assess the safety of hyaluronic acids. The literature search did not identify any specific meta-analysis.

World pharmacovigilance data
In the time between when it first went on the market in Italy in 1987 and 31 May 2014, 47,671,049 units of HYALGAN were sold around the world. Between 1987 and 15 June 2014, a total of 2088 adverse events (AEs) were reported. Among the AEs reported, the systems and/or organs most commonly affected were:

- "*General disorders and administration site conditions*" with 506 AEs, mainly local reactions of the joint treated which were generally benign, short-lived and without lasting effects;

[24] CEPP. ARTHRUM Opinion of 7 July 2009.
[25] Five-level scale where 0 = no pain, 1 = minimal pain, 2 = moderate, 3 = severe, 4 = very severe.

- "*Skin and subcutaneous tissue disorders*" with 119 AEs reported, mainly allergic symptoms, particularly rash, erythema and pruritus.

The following were also observed:
- 23 cases of headaches or migraine and 10 cases of syncope or presyncope;
- 4 cases of anaphylactoid reactions, all with a favourable outcome;
- 13 cases of inflammatory reactions defined by the investigators as "pseudoseptic reactions" and 10 cases of synovitis
- cases of septic arthritis attributed not to contamination of the product but to a risk inherent in any intra-articular injection of a constituent when aseptic technique is not perfectly observed.

No clear French data were provided.

In conclusion
The analysis of the safety data did not reveal any pharmacovigilance signal. The safety profile of HYALGAN is unchanged.

08.3 Usage/prescription data

According to the IMS-EPPM data (moving annual total, autumn 2013), there were 120,500 prescriptions for the proprietary medicinal product HYALGAN, mainly in gonarthrosis (90% of prescriptions).
According to the data from GERS, the Group for the Collection and Compilation of Statistics (moving annual total, May 2014), 307,578 boxes of HYALGAN were sold in pharmacies.

According to a CEGEDIM study[26] performed by the company EXPANSCIENCE using the Thalès database and devoted to the management of gonarthrosis in 2012 by rheumatologists in private practice, 65.5% of the gonarthrosis patients treated with HYALGAN were women and had an average age of 69.3 years. The mean dosage of HYALGAN was 4.6 injections a year, 43% of patients received three injections, 18.8% four injections and 12% more than six injections. No details are given of the number of knees treated per patient.

Dosage of HYALGAN in patients treated for gonarthrosis in 2012

Mean number of injections/year	N (%)
1	3555 (10.4)
2	1019 (3)
3	14,718 (43.2)
4	6423 (18.8)
5	213 (0.6)
6	3982 (11.7)
>6	4195 (12.3)

An epidemiological study[27] was performed in 2013 by CEMKA eval for EXPANSCIENCE.
Its aim was to compare the level of medicinal products indicated in osteoarthritis and in particular NSAIDs in a group of patients with gonarthrosis and starting treatment with HYALGAN versus another group of patients starting a treatment indicated in osteoarthritis apart from hyaluronic acid (oral and topical NSAIDs, long-acting osteoarthritis drugs, corticosteroid analgesics) but not

[26] Epidemiological survey based on the LPD-Thalès database, management of osteoarthritis of the knee by rheumatologists in private practice. Year 2012. Internal report
[27] Cemka Eval – Study of the effects of HYALGAN on the consumption of NSAIDs and other associated treatments in the context of treating gonarthrosis – 2013.

necessarily prescribed for osteoarthritis. Only patients with gonarthrosis, followed up by rheumatologists in private practice, who had received HYALGAN or another medicine indicated in osteoarthritis in 2011, were included in the study.
On the basis of the only report provided, it is not possible to draw any conclusions about the impact of HYALGAN on the use of other osteoarthritis medicines, particularly oral NSAIDs, because of methodological limitations and uncertainties. In particular, the comparability of the two populations on the initiation of treatment, in terms of the severity of the gonarthrosis, the time since diagnosis of the condition and other associated diseases likely to give rise to, in particular, nonspecific treatments such as NSAIDs or analgesics, is uncertain, and has not been analysed in the report. The level of NSAID use did not take account of prescriptions by general practitioners during the 1-year follow-up period, which is a severe limitation. Its exclusion from the analysis of initial prescriptions raises questions, since such prescriptions may contain treatments prescribed for several months.
Finally, the method used to select patients in the database is not described in enough detail (no flow chart).
Overall, it is not possible to attribute any reduction in the consumption of NSAIDs to treatment with HYALGAN on the basis of this report.

08.4 Summary and discussion

Since the last assessment of HYALGAN (the only hyaluronic acid with the status of a medicinal product) in 2010 by the Transparency Committee, no new clinical study has been performed by the company EXPANSCIENCE.
In an independent Danish study published in 2010, HYALGAN was no different to placebo in terms of the time to relapse assessed using the Lequesne index in 337 patients with gonarthrosis who were followed up for 1 year.
In two studies comparing medical devices with HYALGAN, their non-inferiority was demonstrated; in the absence of a placebo group it is not possible to guarantee the internal validity of each of these studies.

Since the efficacy of hyaluronic acids is controversial, numerous meta-analyses have been performed. Thus, seven meta-analyses, including six published since the Committee's previous opinion and an unpublished meta-analysis performed in 2013 are available. They were performed on a variable number of clinical studies (ranging from 5 to 89) of variable but mostly poor methodological quality which included HYALGAN among the hyaluronic acids evaluated. The studies included were varied, performed at different periods, on differing populations, with greatly varying endpoints, endpoint analysis periods and statistical methods. This explains the great heterogeneity seen between the various results. Publication bias cannot be ruled out, even though unpublished data were included in some meta-analyses.

Leaving aside these methodological limitations, most of these meta-analyses suggest a symptomatic effect that is at best <u>weak</u> of injections of hyaluronic acid, including HYALGAN, on pain and functional impairment in gonarthrosis.
The great heterogeneity of the effects of hyaluronic acid-based treatments revealed by these analyses calls into question the relevance of the meta-analysis approach and leads to one assessment per product being favoured.

From this point of view, an analysis of specific studies to assess the size of the effect inherent in HYALGAN highlights what are mostly old studies which were therefore performed using methodological standards which do not comply with current guidelines. The result is at best a low level of evidence of their results.
Thus, the most recent "Affinité Santé" meta-analysis performed in 2013, which has not been published, covering a selection of studies on the basis of their quality, included for HYALGAN only one study versus placebo which met the quality criteria defined as unpredictable randomisation and double-blinding (patient and investigator) and a non-inferiority study versus an MD.

In the Danish placebo-controlled, randomised, double-blind study independent of industry, published by Lundsgaard in 2008,[18] no statistical difference was found between HYALGAN and saline (2 ml and 20 ml) given by intra-articular injection for the relief of pain on movement assessed on a VAS of 0-100 mm in 251 subjects aged 59 years or more with painful gonarthrosis (at least 20 mm on a VAS of 0-100 mm). It should be noted that the proportion of patients with stage IV gonarthrosis according to the Kellgren and Laurence classification (which does not correspond to the main target population for hyaluronic acids) was 36.9% in the HYALGAN group, 32.5% in the 2 ml physiological saline group and 38.8% in the 20 ml physiological saline group. The reduction in pain on movement was 5.46 mm 95% CI [0.08; 11] with HYALGAN versus 3.87 mm [-1.69; 9.4] with 20 ml saline.
In another Danish study[10] (Jorgensen et al 2010) not included in the "Affinité Santé" meta-analysis of 2013 but relevant in the context of this re-assessment since it was published after the Committee's last assessment, no statistically significant difference was found between HYALGAN and placebo in the primary endpoint. It should be noted that the time before relapse could not be assessed for 53% of patients in the HYALGAN group and 59% of patients in the placebo group because these patients were mostly rated as still improved at the end of the study (at one year). As in the Lundsgaard study of 2008, a strong placebo effect of the order of 58% was noted in this study. This strong placebo effect is consistent with that described in other clinical studies, where it ranged from 50 to 70% and could be linked to the injection itself, the aspiration of synovial fluid, patient education and the psychological effect.
In the study of the non-inferiority of HYALGAN versus a GO-ON medical device, the lack of a placebo group means that its internal validity cannot be guaranteed. Other non-inferiority studies were performed versus other medical devices without including a placebo group. However, in view of a strong placebo effect and a weak effect of the medicinal product, it is necessary, in a study versus an active comparator, to have a placebo group.

The analysis of safety does not yield any new information. The use of HYALGAN is above all associated with local adverse effects with a reporting frequency that is low given the number of injections given around the world.

The available epidemiological data do not allow any conclusion to be drawn about a positive impact of HYALGAN on the reduced use of other osteoarthritis medicines, particularly oral NSAIDs, because of methodological limitations and uncertainties.

08.5 Planned studies

No studies are planned.

09 THERAPEUTIC USE

09.1 International guidelines

There are several guidelines on the management of osteoarthritis, some of which have been updated recently. Whereas the earlier versions (up to 2010) gave hyaluronic acids a role in the pharmacological management of osteoarthritis, the recent updates are more balanced: some are unfavourable, limiting the acids' role to a specific population, and others make them subject to certain conditions.

The recommendations of EULAR (the European League Against Rheumatism) on the pharmacological management of gonarthrosis will not be mentioned since they have not been updated since 2003[28] and appear to be obsolete.

OARSI[29] (Osteoarthritis Research Society International) guidelines for the non-surgical management of knee osteoarthritis – March 2014

The OARSI guidelines were updated in March 2014. No consensus emerged on hyaluronic acids. The guideline concerning injections of hyaluronic acid in knee osteoarthritis has been rated as uncertain[30] and as inappropriate in cases of osteoarthritis affecting other joints.

The experts considered that, despite the controversy about the efficacy and safety of hyaluronic acids, a positive effect on pain had been shown by various analyses but that no consensus had been reached on whether or not hyaluronic acids should be recommended. It is pointed out in the rationale that the divergent conclusions of the meta-analyses and the differing safety results influenced the votes of the panel of experts.

NICE[19]

In the update to its recommendations on the management of osteoarthritis in 2014, NICE (the National Institute for Health and Care Excellence) does not recommend injections of hyaluronic acid in the management of osteoarthritis.

American Academy of Orthopaedic Surgeons (AAOS) in 2013[31]

This society does not recommend (strong recommendation) the use of hyaluronic acids in the treatment of symptomatic gonarthrosis.

ACR[32] (American College of Rheumatology)

In 2012, the ACR, in its update on gonarthrosis, does not recommend hyaluronic acids as 1st-line treatment of gonarthrosis, but in patients aged ≥ 75 years in whom paracetamol has failed, recommends NSAIDs (preferably topical) and corticosteroids, and only under certain conditions (not clearly specified).

The wording of these recommendations is not clear.

ESCEO 2014[33]

An algorithm was published recently (May 2014) by this learned society, which believes that hyaluronic acids have a role, just like intra-articular corticosteroids, after the failure of oral NSAIDs.

[28] Jordan et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003; 62; 1145-55.

[29] McAlidon et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and cartilage 2014; 22; 363-88.

[30] To clarify, the "Uncertain" classification is not intended here to be a negative recommendation or to preclude use of that therapy. Rather it requires a role for physician patient interaction in determining whether this treatment may have merit in the context of its risk-benefit profile and the individual characteristics, co-morbidities and preferences of the patient.

[31] AAOS (American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee evidence-based guideline 2nd edition Adopted by the American Academy of Orthopaedic Surgeons Board of Directors 2013.

[32] Hochberg MC et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012; 64: 465-474.

[33] The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis.

09.2 Role of HYALGAN in the therapeutic strategy

The Transparency Committee took into account the medical need in the management of gonarthrosis.
It considered that the information available allowed the recording of at best a weak efficacy for HYALGAN versus the intra-articular injection of saline (used as placebo in the clinical studies).
It regretted the lack of any study with a rigorous methodology demonstrating a substantial size of effect for HYALGAN versus placebo, despite the substantial lag in terms of marketing and the failure to demonstrate any savings on NSAIDs or any convincing impact on the use made of surgery.
However, given:
- the limited number of treatment alternatives available,
- the admittedly weak efficacy versus placebo (existence of responder patients according to the experts)
- the absence of any safety signal,

the Committee believes that HYALGAN retains a role in the treatment strategy for osteoarthritis, but that role is limited.

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

◗ Symptomatic knee osteoarthritis is characterised by pain and functional disability that can become chronic. It may eventually require surgical treatment with a prosthesis implant.

◗ HYALGAN is intended as symptomatic treatment.

◗ The therapeutic effect of HYALGAN is at best weak on the symptoms of gonarthrosis, taking into account the results of the clinical studies available, most of which are of poor methodological quality. In particular, its superiority versus placebo was not demonstrated in two clinical studies published in 2008 and 2010. In addition it has not been shown that this proprietary medicinal product would allow a saving on NSAIDs. Its safety is satisfactory. Consequently, its efficacy/adverse effects ratio is low.
◗ Treatment of osteoarthritis of the lower extremities relies above all on diet and lifestyle measures (weight loss, regular physical exercise) and non-pharmacological measures (physical therapy, wearing orthotics, using sticks, etc.). Symptomatic treatment mainly relies on oral analgesics and NSAIDs.

Taking into account:
- the medical need and the limited number of alternatives available in the management of gonarthrosis;
- the fact that the efficacy of HYALGAN versus placebo is at best weak;
- the absence of any pharmacovigilance signal identified with this proprietary medicinal product, despite its 26 years on the market;

the Transparency Committee believes that HYALGAN has a limited role in the therapeutic strategy for gonarthrosis, as 2nd-line treatment, i.e. after the failure of or intolerance to analgesics or NSAIDs.

◗ Public health benefit: the public health burden of osteoarthritis is substantial. However, the data available cannot demonstrate the effect of HYALGAN on the consumption of medicines

with substantial adverse effects; its effect on the symptoms of osteoarthritis is at best weak. Consequently, this medicinal product cannot have any impact on public health.

Taking account of these points, the Committee considers that the actual benefit provided by HYALGAN is low in the treatment of painful flare-ups in patients with gonarthrosis, after failure of or intolerance to analgesics and NSAIDs.

010.2 Transparency Committee recommendations:

The Committee recommends continued 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 patients with gonarthrosis, after failure of analgesics and failure of or intolerance to non-steroidal anti-inflammatories (NSAIDs)".

- **Proposed reimbursement rate: 15%**

- **Packaging:** Appropriate for the prescription conditions.