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TRANSPARENCY COMMITTEE

OPINION

9 January 2013

The opinion adopted by the Transparency Committee on 4 July 2012
was given a hearing on 5 December 2012 and
observations were examined on 9 January 2013

Examination of the dossier for a medicinal product included for a 5-year period starting on 27 May 2006 (Official Gazette of 28 December 2007)

CHONDROSULF 400 mg, hard capsule
B/84 (CIP code: 335 917-3)

CHONDROSULF 400 mg, granules for oral solution in sachets
B/84 (CIP code: 335 915-0)

Applicant: GENEVRIER

Chondroitin sulfate

ATC code: M01AX25

Date of Marketing Authorisation: 25 January 1993 (hard capsules) and 29 June 1993 (sachets)
Amendment: 21 May 2008 (modification of the wording of the indication following the re-assessment of the benefit/risk ratio of slow-action symptomatic anti-arthritic agents)

Reasons for request:
Renewal of inclusion on the list of medicines refundable by National Health Insurance.
Re-assessment of the actual benefit following the Transparency Committee conclusions in its opinions of 26 November 2008 and reiterated in its opinion of 21 September 2011.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Chondroitin sulfate

1.2. Indication

“Symptomatic treatment with delayed effect for osteoarthritis of the hip or knee.”

1.3. Dosage

“Three capsules or 3 sachets of 400 mg, which is 1,200 mg per day, divided into three doses per day. The sachets or capsules are to be taken with food.”

2 REMINDER OF THE COMMITTEE’S OPINIONS AND CONDITIONS OF INCLUSION

Committee Opinion of 3 March 1993

Inclusion (hard capsule):

“The therapeutic indication has been retained based on the results from multi-centred trials comparing CHONDROSULF with a placebo which demonstrated efficacy for pain and an improvement in functional indices.
In a treatment study, the efficacy was in the same order as NSAIDs (diclofenac). Although NSAIDs have an immediate action, CHONDROSULF has a delayed action which starts to appear after one month, is apparent at two months and continues for a prolonged period of time. There are no treatment studies showing a chondroprotective action, or long-term sustained efficacy, or demonstration of a reduction of flares for patients with osteoarthritis. There are many adverse effects, which are generally harmless and do not lead to discontinuation of treatment.
As for diacerein, the problem is knowing how chondroitin sulfate will fit into the therapeutic strategy for osteoarthritis. In the current state of the dossier, the therapeutic benefit is clear in the case where:

- The product is initially co-prescribed with an immediate action symptomatic treatment, in patients whose health requires permanent treatment with these therapies,
- And if, after one to two months, it is possible to gradually withdraw the NSAIDs to avoid the drawbacks of these types of products.

If the product is used according to the instructions stated, it is possible to consider that there is a modest, type III improvement in actual benefit (IAB), in terms of efficacy and safety of use. The Committee notes that the carry-over effect allows possible therapeutic windows.”

Committee Opinion of 26 May 1993

Inclusion (sachet):

“In the category of anti-arthritics, CHONDROSULF belongs to the slow-action symptomatic group of medicinal products. Its benefit is in the substitution of NSAIDs, saving on their use and thus avoiding the complications linked to taking them. The Transparency Committee considers that this substitution is a consequence of the efficacy of CHONDROSULF and is a true therapeutic benefit. NSAIDs belong to a different therapeutic category (fast action symptomatic medicinal products) and cannot be considered as reference products.”

Committee Opinion of 8 January 1997

“Given the nature of the therapeutic indications of CHONDROSULF, its benefit/risk ratio and other available treatments, the actual benefit of CHONDROSULF justifies its continued reimbursement.”

Committee Opinion of 19 November 1999 - Re-assessment

The actual benefit of these proprietary medicinal products is low.

Committee Opinion of 20 December 2000

Renewal of inclusion:

Actual benefit:

These medicinal products concern the condition characterised by a progression towards a disability and/or a marked deterioration in quality of life.
These proprietary medicinal products fall under the category of symptomatic treatments.
The efficacy/adverse effects ratio for these proprietary medicinal products in this indication is modest.
These medicinal products are second-line therapies.
Alternative treatments are available.

The actual benefit of this medicinal product is low.

Conclusion:

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Insurance in the indication and at the dosage in the Marketing Authorisation.
Reimbursement rate: 35%

Committee Opinion of 2 April 2003

Re-assessment of actual benefit:

Proprietary medicinal products containing chondroitin sulphate (CHONDROSULF) are symptomatic treatments with a delayed action enabling significant reductions in the use of analgesics and NSAIDs after three months of use. The “chondro-modulator” activity of these proprietary medicinal products has not been clearly demonstrated clinically. Despite being well tolerated, the efficacy/adverse effects ratio is moderate. Due to their delayed action and the lack of evidence supporting their efficacy, these proprietary medicinal products are second-line treatments. Combination with paracetamol or NSAIDs is more likely to be necessary at the start of treatment (4 to 8 weeks). Alternative medicinal products exist. The actual benefit of these proprietary medicinal products is moderate.

Committee Opinion of 20 June 2007

Renewal of inclusion:

Actual benefit:

Osteoarthritis is characterised by a progression towards a disability and/or a deterioration in quality of life.
CHONDROSULF provides symptomatic treatment with a delayed effect.
The efficacy/adverse effects ratio for this medicinal product is moderate.
Due to their delayed action, these proprietary medicinal products are second-line treatments.
There are treatment alternatives.
The actual benefit provided by CHONDROSULF is moderate.

Conclusion:

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Insurance in the indication and at the dosage in the Marketing Authorisation.
The Transparency Committee will re-examine this medicinal product in view of the results from the re-assessment of its benefit/risk ratio by the Marketing Authorisation Committee.
Reimbursement rate: 35%

Committee Opinion of 26 November 2008

Re-assessment of the actual benefit at the request of the Committee following the re-assessment of the benefit/risk ratio by the Marketing Authorisation Committee.

Actual benefit:

“Symptomatic osteoarthritis of the hip and knee is characterised by pain and functional incapacity that are likely to progress into a chronic condition. Eventually surgical intervention may be required, with the fitting of a prosthesis.

These proprietary medicinal products are symptomatic treatments with a delayed effect.

Public health benefit:

Osteoarthritis of the knee and hip are a substantial public health burden.

The reduction in functional limitations and incapacities brought about by osteoarthritis, as well as the improvement in the quality of life of those affected is a public health need. The response to this need is not purely medicinal.

Available data on pain and algo-functional indices do not enable conclusions to be drawn on the existence of an impact of chondroitin sulfate on the improvement in quality of life and on the reduction in functional limitations: absence of quality of life data and small effect on symptoms.

The theoretical benefit of slow action anti-inflammatories, in terms of public health, lies in the reduction in the use of NSAIDs, which may enable a reduction in the frequency of intestinal adverse effects, which are particularly harmful in elderly patients. Evidence of this benefit for chondroitin sulfate was not demonstrated in the data.

Consequently, CHONDROSULF 400 mg is not expected to benefit public health.

These proprietary medicinal products have little effect in improving the symptoms of osteoarthritis. The efficacy/adverse effects ratio is modest.

Above all, the management of osteoarthritis is based on making lifestyle and dietary adjustments (losing weight, taking regular physical exercise) and non-pharmacological changes (physiotherapy, wearing orthotics, using walking sticks, etc.). Symptomatic treatment mainly comprises the use of analgesics and oral NSAIDs. These proprietary medicinal products are of limited therapeutic benefit.

The actual benefit of CHONDROSULF 400 mg, hard capsule and granules for oral solution, is low."

Conclusion:

"The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Insurance and on the list of medicines approved for use by hospitals and various public services.

This favourable opinion is under the condition that a study is carried out within two years with the aim of demonstrating the impact of prescribing CHONDROSULF 400 mg in reducing the use of NSAIDs.

Reimbursement rate: 35%"

Committee Opinion of 21 September 2011

Re-assessment of the actual benefit following referral from the Director of Social Security:

"Due to its modest level of efficacy and limited therapeutic use, the actual benefit of CHONDROSULF 400 mg, hard capsules and granules remains low in the Marketing Authorisation indications.
The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Insurance in the indications and at the dosages in the Marketing Authorisation while waiting for the results from the 3A-PEGASE study.

Reimbursement rate: 15%"

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2012)

M : Musculo-skeletal system
M01 : Antiinflammatory and antirheumatic products
M01A : Antiinflammatory and antirheumatic products, non-steroids
M01AX : Other antiinflammatory and antirheumatic agents, non-steroids
M01AX25 : Chondroitin sulfate

3.2. Medicines in the same therapeutic category

These are other slow action symptomatic anti-arthritics (SASAAs):

Active ingredient	**Proprietary medicinal product**	**Form**	**Indication**
Diacerein	ART 50 mg	hard capsule	Symptomatic treatment with delayed effect for osteoarthritis of the hip or knee
Diacerein	ZONDAR 50 mg	hard capsule	Symptomatic treatment with delayed effect for osteoarthritis of the hip or knee
Glucosamine	FLEXEA 625 mg	tablet	Relief of symptoms in mild to moderate osteoarthritis of the knee
Glucosamine	DOLENIO 1178 mg	tablet	Relief of symptoms in mild to moderate osteoarthritis of the knee
Glucosamine	OSAFLEXAN 1178 mg	powder for oral solution in single-dose sachets	Relief of symptoms in mild to moderate osteoarthritis of the knee
Glucosamine	STRUCTOFLEX 625 mg	hard capsule	Relief of symptoms in mild to moderate osteoarthritis of the knee
Glucosamine	VOLTAFLEX 625 mg	film-coated tablet	Relief of symptoms in mild to moderate osteoarthritis of the knee
Avocado and soybean oil unsaponifiables	PIASCLEDINE 300 mg	hard capsule	Symptomatic treatment with delayed effect for osteoarthritis of the hip or knee

For all of these proprietary medicinal products, the actual benefit is low while waiting for the results from the observational study (PEGASE), the aim of which is to show that these medicinal product enable savings to be made in the use of NSAIDs.

3.3. Medicines with a similar therapeutic aim

Other medicinal treatments for osteoarthritis of the hip or knee: analgesics, oral and topical NSAIDs, intra-articular corticosteroid injections and intra-articular hyaluronic acid injections (medicinal product or medical device).

4 UPDATE ON THE DATA AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Efficacy

The applicant provided a new randomised, double-blind clinical study[1] that lasted three months, with the aim of demonstrating the equivalence of CHONDROSULF 1200 mg taken in one single dose (oral capsule in sachet) to CHONDROSULF 400 mg 3x/day in 353 patients with osteoarthritis of the knee. A placebo arm was scheduled in the protocol as an internal control group. The primary efficacy endpoint was the change in Lequesne index[2] (functional scale between 0 and 24 points) between inclusion and Day 91.
On inclusion, in the ITT population, the Lequesne index was 11.2 in the CHONDROSULF 400 mg group and 11.1 in the placebo group. After 91 days, there was a more significant reduction in the index for the CHONDROSULF 400 mg 3x/day group than in the placebo (-3.7 points versus -1.5 points, $p < 0.0001$).

4.2. Adverse effects

New pharmacovigilance data (PSUR covering the period from 05/11/2004 to 30/08/2008) did not highlight any particular concerns.

4.3. Conclusion

A new study that compared two dosage regimens, 1200 mg chondroitin sulfate per day taken as one dose or split into three doses in 353 patients with osteoarthritis of the knee, was provided. This was a randomised, double-blind equivalence study, which also included a placebo arm. After 91 days of treatment, the Lequesne algo-functional index had decreased more significantly in the CHONDROSULF 400 mg group than in the placebo group (-3.7 points versus -1.5 points, $p < 0.0001$), however this difference of 2.2 points (on a 24 point scale) may be considered as minimal.

Updated pharmacovigilance data has not highlighted any new issues.

[1] Zegels B, Crozes P, Uebelhart D, Bruyère O, Reginster JY. Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. Osteoarthritis Cartilage. 2013 Jan; 21(1):22-7.

[2] The Lequesne algo-functional index, expressed by the total of the pain-related scores, the maximum distance walked and difficulties in performing activities of daily living, enables the functional decline felt by the patient to be assessed. It is graded from 0 to 24.

5 MEDICINAL PRODUCT USAGE DATA

5.1. Observational study: PEGASE study

AIM AND METHOD

In 2008, the Transparency Committee began the re-assessment of all slow action symptomatic anti-arthritics (SASAAs); they considered that, in light of their low efficacy, the potential benefit of SASAAs lies in a possible reduction in the use of NSAIDs. This is why their favourable opinion regarding their continued reimbursement was on the condition that "a study was implemented and carried out within two years, with the aim of showing the impact of the prescription of ART 50 mg/ ZONDAR 50 mg, CHONDROSULF and PIASCLEDINE in terms of the reduction in the use of NSAIDs."

In response to the request by the Transparency Committee for the study, the companies marketing ART 50 mg/ZONDAR 50 mg, CHONDROSULF and PIASCLEDINE initially presented results from an interim analysis, then secondly, the results of the final analysis from a combined observational study (the "PEGASE" study).
The results from the final analysis were submitted by the laboratory company marketing CHONDROSULF on 14 November 2012 and have been included in this opinion.

The aim of this cohort study patients with osteoarthritis of the knee or hip, whether they were being treated with SASAAs or not, was to measure the impact of the use of SASAAs on the use of NSAIDs and to describe the usage profile for SASAAs during the follow-up period.

The PEGASE study, which started including patients in 2010, was conducted on a sample of GPs or private rheumatologists practising in mainland France identified randomly from telephone lists.

This cohort comprised patients aged 18 years or older, presenting with osteoarthritis of the knee or hip (or both) diagnosed according to ACR criteria[3,4]. They were included consecutively, during a consultation for a pain episode of their osteoarthritis, from when new treatment with a SASAA or any other new osteoarthritis treatment (control) regardless of the type - pharmacological (NSAID or analgesics, infiltration) or non-pharmacological (health/dietary measures, physiotherapy, orthotics, other forms of physical therapy) - was started.
Patients on SASAAs or hyaluronic acid for more than 3 months, with arthritis, tendinitis of the lower limbs or radicular pain were specifically not included.

The follow-up period lasted up to 16 months after inclusion, until lost to follow-up, death, withdrawal from the study or up to the end of the study (number achieved or major event concerning the life of the product).

Data were collected by doctors at inclusion and during an annual consultation appointment carried out between 12 and 16 months after inclusion and for certain patients by standard telephone follow-up in the month following inclusion, then at 4, 8, 12 and 16 months.
Patients were questioned about their consumption of SASAAs and NSAIDs, over the two-month period by indicating the number of days treatment was taken in these two months

[3] Altman, R et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986 Aug; 29 (8): 1039-49.

[4] Altman, R et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum. 1991 May; 34 (5): 505-14.

(more or less every day, for 31 to 60 days in total, for 17 to 30 days, for 6 to 16 days, for 1 to 7 days, never).

In order to take into account the treatment dynamics during the follow-up period (discontinuation of treatment, potential substitutions, etc.), a treatment time-population analysis was conducted. Thus, the periods of exposure to SASAAs were subdivided, across the whole follow-up period, into two-month analysis time units (ATU).

All exposure was considered as binary (exposed/not exposed) for each SASAA in the two-month unit (independent of any combination). The risk of presenting the event of interest was considered as constant within each ATU.

The event of interest was the use of systemic NSAIDs,[5] which was considered as binary (taken: yes/no) within each ATU.

The aim of the primary analysis was to compare the use of NSAIDs in the two-month periods of exposure to a SASAA with the two-month periods of no SASAA exposure, on the understanding that during the previous two-month period there was no exposure to any SASAAs.

In total, 3,000 person-months of exposure for each SASAA and 4,500 person-months of non-exposure were initially planned to enable the difference in risk of the use of NSAIDs of 15% to be detected (which is an RR = 0.85, 80% power, 95% confidence). The mean anticipated follow-up period was 9 months.

Description of the PEGASE cohort:

Of the 24,107 GPs and 1,236 private rheumatologists contacted to participate in the study, 2,860 agreed to participate and 617 (521 GPs and 96 rheumatologists) included at least one patient.

On the 8 March 2012, 3,803 patients meeting the inclusion and non-inclusion criteria were included in the interim analysis.

On 4 October 2012, a total of 5,485 patients meeting the inclusion and non-inclusion criteria were included. Only the sub-population of patients included outside the competitive recruitment for those taking glucosamine were considered in the analysis, i.e. 4,555 patients.

The main patient characteristics at inclusion were:
- 63.8% of patients were female;
- the mean age at inclusion was 66.8 years;
- in the majority of cases, the level of education of the patients was below the baccalaureate (2,279/3,521 i.e. 64.7%) and a large proportion of them (2,819 /3,525 i.e. 80.0%) were retired or with no professional activity at the time of inclusion;
- the mean BMI was 28.0 [standard deviation: 5.0];
- of the 4,539 patients with a diagnosis, the majority of patients presented with osteoarthritis of the knee (78.9%), of the hip (16.2%) or both (4.6%);
- osteoarthritis had been present for less than a year for 26.0% of patients, for 1 to 5 years for 41.2% and for more than 5 years for 32.3% of patients;
- the median number of pain flare-ups over the last 6 months was 2.0 [range: 0.0 - 12.0];
- the mean pain score (measured from 0 to 10 on a VAS) was 5.5 [standard deviation 1.8];
- disability at inclusion (Lequesne algo-functional index) was significant to very significant (46.4%) or even unbearable (19.0%);

[5] NSAIDs used in the analysis: diclofenac, diclofenac + misoprostol, aceclofenac, etodolac, ibuprofen, nabumetone, flurbiprofen, ketoprofen, alminoprofen, fenoprofen, naproxen, nimesulide, celecoxib, etoricoxib, meloxicam, piroxicam, tenoxicam, indometacin and sulindac.

- the main co-morbidities presented were cardiovascular disease (61.0%), musculo-skeletal disorders (60.7%), endocrine (33.4%) and intestinal disorders (24.8%) and osteoarthritis in other parts of the body (41.9%);
- a limited number of patients (2.6%) declared that they were allergic to NSAIDs;
- more than one in ten patients declared having had physiotherapy (11.6%) or orthotics (12.6%);
- 6.1% of patients declared that they wore a prosthesis.

The characteristics of the population presented at the interim report stage were similar to those of the final report population described below.

State of progress of the cohort at the interim report stage:
On the date database freeze (8 March 2012), the mean cohort follow-up period was 7.2 months (n = 2,907), with 2,907, 2,239, 1,417 and 636 patients having a follow-up period of 4, 8, 12 and 16 months respectively.

A total of 1,258/3,803 (33%) patients were never exposed to any SASAAs during the follow-up period.

Table 1: Summary of the level of progress of the cohort on 8 March 2012 (interim report):

	ART 50 mg/ ZONDAR 50 mg/ diacerein	CHONDROSULF	PIASCLEDINE	Not exposed to any SASAA
Number of patients participating on the date of interim report	424	580	723	1,258
Mean follow-up time on the date of the interim report (months)	9.0	9.6	8.7	ND
Mean duration of exposure (months)	6.3	6.5	6.9	ND
"Approximate" time-population on the date of the interim report (patient-months)	2,671	3,770	4,988	ND
Expected time-population according to protocol (patient-months)	3,000	3,000	3,000	4,500

On the date of the final report, the mean follow-up time of the cohort was 9.71 months.
A total of 4,223, 3,523, 2,752, 1,770, 931 and 426 patients had a follow-up period of 4, 8, 12, 16, 20 and 24 months respectively.

A total of 1,288/4,555 (28.3%) patients were not exposed to any SASAA during the follow-up period.

RESULTS

The results presented below only concern CHONDROSULF.

On the date of the interim report, among the 620 patients who received a prescription for CHONDROSULF, 40 (6.5%) eventually refused follow-up and 519 patients who had agreed to participate had data from at least one follow-up on the date of the interim report.
Nevertheless, among these, 365 patients (i.e. 70.3%) reported taking CHONDROSULF during the follow-up period and were considered in the interim analysis.

On the date of this analysis, the mean exposure duration to CHONDROSULF for these patients was 6.5 months, corresponding to 2,364 patients-months of accumulated exposure (i.e. 1,182 ATU).

On the date of the final report, among the 780 patients who received a prescription for CHONDROSULF, 54 (6.9%) eventually refused follow-up and 719 patients who had agreed to participate had data from at least one follow-up on the date of this report.
Nonetheless, only 541 patients (i.e. 75.2%) reported taking CHONDROSULF during follow-up and accumulated 3,780 patients-months of exposure in the study (i.e. 1,890 ATU).

Characteristics of patients exposed to CHONDROSULF differed to those of patients who were never exposed to any SASAAs during follow-up. On the whole patients were younger (66.1 years versus 69.4 years on average), commonly had a higher level of education (41.1% versus 30.2%), reported fewer cardiovascular (59.1% versus 67.2%) and endocrine co-morbidities (30.9% versus 36.3%), used orthotics less frequently (12.3% versus 15.8%) and had fewer prostheses (5.7% versus 9.1%).
A history of osteoarthritis (>5 years) was more common in the non-exposed patients (38.2% versus 29.1%) while the number of pain flare-ups in the 6 months prior to inclusion, the pain scale and the Lequesne index were similar in both groups.

The differences seen at the stage of the final report between the characteristics of patients exposed to CHONDROSULF and those of patients who had never been exposed to any SASAAs during the follow-up period were stated at the time of the interim analysis.

Results for the use of NSAIDs

- **Primary analysis**

- Results from the interim report

On 8 March 2012, the analysis units were divided as follows: 1,182 were for two months exposure to CHONDROSULF, 5,549 were for two months of non-exposure to any SASAAs and 482 were not documented. Accumulative total of 1,680 ATUs for the use of NSAIDs were counted.

Table 2: Association between all the ATUs for incident exposure to CHONDROSULF and the ATUs for the use of NSAIDs during the follow-up period (n=6,403)

	No. of ATUs for CHONDROSULF	% use of NSAIDs within ATUs	OR* (95% CI)
No SASAA (reference**)	5,241	**25.3**	1
All exposure durations ***	1,162	**23.5**	**0.93 [0.74-1.17]**
• Exposure from 0 to 4 months after starting	310	24.2	0.98 [0.71-1.35]
• Exposure from 4 to 8 months after starting	388	24.7	1.11 [0.74-1.66]
• Exposure of + 8 months after starting	464	22.0	0.69 [0.43-1.11]

* Odds Ratio estimated based on Generalized Estimating Equation (GEE) type multi-variate logistic regression model taking into account the autocorrelation between each ATU and adjusted for age (continuous variable), sex (binary), pain scale (continuous), the number of osteoarthritis pain flare-ups (binary), the Lequesne score (binary), the history of osteoarthritis (binary), the level of education (binary), the use of physiotherapy/orthotics/prosthesis (yes/no), the taking of specific and non-specific osteoarthritis treatments (yes/no), the taking of hyaluronic acid (yes/no), the existence of co-morbidities, risk factors for not taking NSAIDs and the treatment arm in the previous two months, defined according to a variable classification (1st treatment with SASAA considered, already used in the past, not known).

**Two-months periods of non-exposure to any SASAAs, on the understanding that during the previous two months there was no SASAA exposure (n=5,241/5,549).

*** 13 two-month periods for which it was not possible to determine the precise duration of exposure after starting treatment.

Thus, during the study, the frequency of use of NSAIDs was 23.5% for the two months of exposure to CHONDROSULF and 25.3% for the two-month period of non-exposure to any SASAAs respectively.

The two-month period of NSAID exposure indicates that patients using NSAIDS have a different profile compared with non-users: on average they are younger (65.6 years versus 68.1 years), are more often female (67.0 % versus 62.0 %), with a history of osteoarthritis of more than 1 year (77.8 % versus 70.8 %), a higher mean pain score (5.3 versus 4.7), a higher algo-functional score (63.6% versus 51.2% highlighting a significant to very significant disability). These patients are also more likely to be treated with physiotherapy, use orthotics or have prostheses (26.3% versus 23.9%).

The overall results, which lack detail, are also presented and compare the two-month exposure to three anti-arthritics (n = 3,265) to the two-month periods of non-exposure. These results are similar to those presented for each individual medicinal product (OR = 0.99 [0.85-1.15]).

- Results from the final report

On the 4 October 2012, the analysis units were divided as follows: 1,890 were for two months exposure to CHONDROSULF and 9,243 were for two months of non-exposure to any SASAAs. Accumulative total of 2,757 ATUs for the use of NSAIDs were counted.

Table 3: Association between all the ATUs for exposure to CHONDROSULF and the ATUs for the use of NSAIDs during the follow-up period (n=11,133)

	No. of ATUs of CHONDROSULF	% use of NSAIDs within ATUs	OR* (95% CI)
No SASAA (reference**)	**9,243**	**24.1**	1
All durations of exposure	**1,890**	**22.1**	**0.94 [0.77-1.14]**
• Exposure from 0 to 4 months after starting	1,006	24.9	1.01 [0.83-1.24]
• Exposure from 4 to 8 months after starting	486	19.5	0.76 [0.56-1.04]
• Exposure of + 8 months after starting	398	18.1	0.71 [0.48-1.06]

* Odds Ratio estimated based on Generalized Estimating Equation (GEE) type multi-variate logistic regression model taking into account the autocorrelation between each ATU and adjusted for age (continuous variable), sex (binary), pain scale (continuous), the number of osteoarthritis pain flare-ups (binary), the Lequesne score (binary), the history of osteoarthritis (binary), the level of education (binary), the use of physiotherapy/orthotics/prosthesis (yes/no), the taking of specific and non-specific osteoarthritis treatments (yes/no), the taking of hyaluronic acid (yes/no) and the existence of a morbidity risk factor for not taking NSAIDs.
**Two-month periods of non-exposure to any SASAAs.

Thus, during the study, the frequency of use of NSAIDs was 22.1% for the two months of exposure to CHONDROSULF and 24.1% for the two month period of non-exposure to any SASAAs respectively.
The final results from the primary analysis thus confirm the results from the interim analysis and the absence of a difference in NSAID use between the two groups, whether SASAAs were taken or not.

The sensitivity analysis, taking into account the of carry-over effect time, defined as a period of two months following the discontinuation of treatment when the treatment was taken for at least two consecutive two-month periods, gave similar results.
This sensitivity analysis is only based on the carry-over time and not the latent time of the effect, as initially stated in the protocol.

The patient profiles of NSAID users were different to those of non-users. The differences noted in the interim report are continued through in the final report.

- **Secondary analyses**

In the final report, the secondary analyses are presented by the applicant.

A secondary analysis was carried out on the sub-group of patients who started treatment with CHONDROSULF on inclusion in the study and had not used a slow action anti-arthritic in the three months prior to the inclusion date.[6]
This analysis was combined with a sensitivity analysis, taking or not taking the carry-over effect into account, and a stratified analysis taking into account the duration of exposure to CHONDROSULF.

[6] The study protocol was amended on 23/09/2010 in order to change the exclusion criteria including patients taking SASAAs or who had received a hyaluronic acid injection **more than 3 months previously**.

Table 4: Association between all the ATUs for exposure to CHONDROSULF and the ATUs for the use of NSAIDs during the follow-up period only for patients who started CHONDROSULF treatment on inclusion in the study:

		No. of ATUs for CHONDROSULF	% use of NSAIDs within ATUs	OR* (95% CI)
Analysis not taking carry-over effect into account	No SASAA (reference**)	**9,243**	**24.1**	1
	All durations of exposure	**1,039**	**19.5**	**0.89 [0.71-1.13]**
	• 0 to 4 months	533	24.2	1.04 [0.82-1.33]
	• 4 to 8 months	266	16.2	**0.64 [0.42-0.97]**
	• More than 8 months	240	12.9	**0.49 [0.28-0.88]**
Analysis with carry-over effect***	No SASAA (reference**)	**9,243**	**24.1**	1
	All durations of exposure	**1,125**	**19.0**	**0.88 [0.7-1.1]**
	• 0 to 4 months	525	24.2	1.05 [0,82-1.34]
	• 4 to 8 months	321	16.5	0.72 [0.51-1.01]
	• More than 8 months	279	12.2	**0.50 [0.33-0.78]**

* Odds Ratio estimated based on Generalized Estimating Equation (GEE) type multi-variate logistic regression model taking into account the autocorrelation between each ATU and adjusted for age (continuous variable), sex (binary), pain scale (continuous), the number of osteoarthritis pain flare-ups (binary), the Lequesne score (binary), the history of osteoarthritis (binary), the level of education (binary), the use of physiotherapy/orthotics/prosthesis (yes/no), the taking of specific and non-specific osteoarthritis treatments (yes/no), the taking of hyaluronic acid (yes/no), the existence of co-morbidities, risk factors for not taking NSAIDs and the treatment arm in the previous two months, defined according to a variable classification (1st treatment with SASAA considered, already used in the past, not known).
**Two-month periods of non-exposure to any SASAAs.
*** The carry-over effect was considered as a period of two months following the discontinuation of treatment when treatment was taken for at least two consecutive two-month periods.

Since inclusion of patients with a prescription for less than three months of slow-action anti-arthritics was authorised in the protocol (amendment of 23/09/2010), a secondary analysis of patients new to or previously receiving treatment was integrated into the protocol.
The analysis presented in the final report is only based on the sub-group of patients who started CHONDROSULF treatment on inclusion in the study. Analysis of prevalent patients, i.e. those who started during the three months prior to inclusion, is not presented, although initially planned for in the protocol.

In addition, this stratified sub-group analysis was carried out despite the non-significance of the results from the primary analysis on the total study population, and can therefore only be considered as exploratory.
The various analyses initially taking into account the carry-over effect and the duration of exposure per four-month period led to a number of statistical tests being carried out and resulted in an alpha risk control that was not corrected.

Furthermore, statistically significant results were only reported for durations of exposure over eight months and only concern a limited number of ATUs (in the order of 25%).
This limited number of ATUs suggests a low duration of exposure to SASAAs in the cohort, especially above 8 months, which could be explained either by interrupted follow-up of patients in the cohort or by discontinuation of treatment. No information on the potential lost to follow-ups was presented.
The absence of informative elements regarding these different points also limits the interpretation of these results.
Consequently, and given the limitations stated previously, the Committee cannot take these new analyses into consideration.

Results for pain and functional state:

The results from the *post hoc* secondary analysis carried out for pain (VAS score from 0 to 10 categorised as 0-4 / 5-10) and functional impact (modified Lequesne algo-functional index – telephone version - categorised by the median of the observed distribution in modest or average disability / significant, very significant or unbearable disability) are presented below:

Table 5: Association between all the ATUs for exposure to CHONDROSULF and the ATUs for pain (VAS ≥5) during the follow-up period (n=10,753)

		No. of ATUs for CHONDROSULF	% two-month period of pain within ATUs	OR* (95% CI)
Analysis taking into account carry-over effect***	No SASAA (reference**)	**8,837**	**60.7**	1
	All durations of exposure	**1,916**	**58.7**	**1.07 [0.9-1.23]**
	• 0 to 4 months after starting	985	66.9	1.20 [0.98-1.48]
	• 4 to 8 months after starting	516	52.1	0.82 [0.67-1.00]
	• More than 8 months after starting	**415**	**47.2**	**0.68 [0.53-0.87]**

* Odds Ratio estimated based on Generalized Estimating Equation (GEE) type multi-variate logistic regression model taking into account the autocorrelation between each ATU and adjusted for age (continuous variable), sex (binary), the history of osteoarthritis (binary), the level of education (binary), the use of physiotherapy/orthotics/prosthesis (yes/no), the taking of specific and non-specific osteoarthritis treatments (yes/no), the taking of hyaluronic acid (yes/no) and the existence of a morbidity risk factor for not taking NSAIDs.
**Two-month periods of non-exposure to any SASAAs.
*** The carry-over effect was considered as a period of two months following the discontinuation of treatment when treatment was taken for at least two consecutive two-month periods.

Table 6: Association all the ATUs for exposure to CHONDROSULF and the ATUs with significant disability or more during the follow-up period (n=10,896)

		No. of ATUs for CHONDROSULF	% two-month periods with ≥ significant disability within ATUs	OR* (95% CI)
Analysis taking into account carry-over effect***	No SASAA (reference**)	**8,955**	**58.4**	1
	All durations of exposure	**1,941**	**54.5**	**0.91 [0.8-1.04]**
	• 0 to 4 months after starting	987	58.7	0.97 [0.8-1.17]
	• 4 to 8 months after starting	**524**	**47.3**	**0.74 [0.62-0.87]**
	• More than 8 months after starting	430	53.5	0.85 [0.68-1.05]

* Odds Ratio estimated based on Generalized Estimating Equation (GEE) type multi-variate logistic regression model taking into account the autocorrelation between each ATU and adjusted for age (continuous variable), sex (binary), the history of osteoarthritis (binary), the level of education (binary), the use of physiotherapy/orthotics/prosthesis (yes/no), the taking of specific and non-specific osteoarthritis treatments (yes/no), the taking of hyaluronic acid (yes/no) and the existence of a morbidity risk factor for not taking NSAIDs.
**Two-month periods of non-exposure to any SASAAs.
*** The carry-over effect was considered as a period of two months following the discontinuation of treatment when treatment was taken for at least two consecutive two-month periods.

These analyses, carried out on a *post-hoc* basis, could not be used by the Committee. Furthermore, they did not enable the clinical relevance of these results to be determined.

CONCLUSION

In its Opinion of 26 November 2008, within the context of a low AB, there was a condition to the Transparency Committee's recommendation of maintaining reimbursement, the implementation which was performance of a study with the aim of demonstrating the impact of prescribing CHONDROSULF on the reduction in the use of NSAIDs.

The interim results from the PEGASE study, despite being from a secondary interim analysis not initially stated in the protocol, were confirmed in the final analysis.

The primary results observed were:
- an absence of taking CHONDROSULF treatment, even though it was prescribed, in nearly 30% of patients at the time of the interim report and in 24.8% of patients at the time of the final report,
- an approximate rate of 25% in the use of NSAIDs across the whole population with osteoarthritis of the knee or hip,
- a similar frequency of use of NSAIDs in the ATUs for exposure to CHONDROSULF (22.1%) versus the ATUs for non-exposure to SASAAs (24.1%).

These results enable the absence of an impact of SASAAs, and CHONDROSULF in particular, on the use of NSAIDs to be highlighted.
Secondary sub-group and stratified analyses provided within the context of the definitive report can not be taken into account due to the fact they are only exploratory.

5.2. Prescribing data

According to IMS prescription data (moving annual total November 2011), 813,000 prescriptions were issued for CHONDROSULF. This medicinal product was mainly prescribed for osteoarthritis in 85% of cases (12% for osteoarthritis of the knee and 2% for osteoarthritis of the hip).

Considering previous Committee conclusions, the Low AB, and analysis of data from the PEGASE study that demonstrated and absence of a difference in the use of NSAIDS based on the taking of SASAAs or not, the Committee has concluded:

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual clinical benefit

Symptomatic osteoarthritis of the hip and knee is characterised by pain and functional incapacity that are likely to evolve into a chronic condition. Eventually surgical intervention may be required, with the introduction of a prosthesis.

These proprietary medicinal products are symptomatic treatments with a delayed effect.

Public health benefit:

Osteoarthritis of the knee and hip are a substantial public health burden.

The reduction in functional limitations and incapacities brought about by osteoarthritis, as well as the improvement in quality of life of those affected, represent a public health need that is already an established priority in the Law of 9 August 2004 on public health policy (Objective 85). However, the response to this need is not limited to treatment with medication.

Available data on pain and algo-functional indices do not enable conclusions to be drawn on the existence of an impact of chondroitin sulfate on the improvement in quality of life and on the reduction in functional limitations: absence of quality of life data and limited effect on functional incapacity.

The theoretical benefit, in terms of public health, of slow action anti-inflammatories may lie in the reduction in the use of NSAIDs, which is likely to reduce the frequency of intestinal adverse effects, which are particularly harmful in elderly patients.

Both the interim and definitive results from the PEGASE study show a limited use of NSAIDs in the population with osteoarthritis of the knee or hip and a very similar use of NSAIDs regardless of the exposure to slow-action anti-arthritics.

Thus, the theoretical benefit in terms of public health of treatment with slow action anti-arthritics on the use of NSAIDs is not confirmed in current medical practice.

Consequently, CHONDROSULF is not expected to benefit public health.

The effects of chondroitin sulfate on pain and functional incapacity linked to osteoarthritis are minimal. It has not been shown whether chondroitin sulfate will enable savings to be made in the use of NSAIDs. The efficacy/adverse effect ratio for CHONDROSULF is low.

Above all, the management of osteoarthritis is based on making health and dietary adjustments (losing weight, taking regular physical exercise) and non-pharmacological changes (physiotherapy, wearing orthotics, using walking sticks etc.). Symptomatic treatment mainly comprises the use of analgesics and oral NSAIDs. Slow action symptomatic anti-arthritics, especially chondroitin sulfate, have minimal effect on the symptoms of osteoarthritis and it has not been demonstrated that they enable a reduction the use of NSAIDs.

As with other slow-action symptomatic anti-arthritics, this proprietary medicinal product is of no therapeutic benefit.

The actual benefit of CHONDROSULF 400 mg capsules and granules is insufficient to justify reimbursement by National Insurance.

6.2. Therapeutic use

The initial measures implemented in the treatment of symptomatic osteoarthritis of the lower limbs are health- and diet-based (losing excess weight, participating in regular physical activity when not suffering with pain flare-ups or stiffness, when reduction in activity is needed) and non-pharmacological (physiotherapy, wearing of orthotics, using walking sticks, etc.).
Treatment should be targeted to the individual, taking into consideration the risk factors associated with the knee (obesity, restricted mobility, physical activity) and general risk factors (age, combination of medication, etc.), the intensity of the pain and the resulting disability, the presence of signs of inflammation (effusions), and the extent of joint damage.

During symptomatic phases, treatment mainly comprises taking analgesics, starting with paracetamol, and during acute episodes, short periods with oral NSAIDs at the minimum effective dose in patients who are not responding to paracetamol. Due to the gastrointestinal risk, coxibs are preferred.

Localised treatment may also be used, such as topical NSAIDs, intra-articular corticosteroid injections, especially during phases of stiffness, or hyaluronic acid.

Slow action anti-arthritics (chondroitin sulfate, avocado and soybean oil unsaponifiables, diacerein and glucosamine) have a minimal effect on both pain and functional incapacity. They did not demonstrate that they were able to reduce the use of NSAIDs, which are the cause of very notable and often serious adverse effects, especially in the elderly. In addition, the benefit/risk ratio for diacerein was considered as unfavourable in a recent assessment by the Marketing Authorisation Committee (July 2012). Consequently, these proprietary medicinal products are of no therapeutic benefit.

The place of glucosamines in the therapeutic strategy for the symptomatic treatment of mild to moderate osteoarthritis of the knee will only be determined following the results of the PEGASE observational study, which aims to demonstrate their impact on the use of NSAIDs.

Surgery (arthroplasty, introduction of a prosthesis) is only for cases of painful and debilitating osteoarthritis, which has seen radiological progression, and which is unresponsive to other usual treatment measures.

6.3. Transparency Committee recommendations

The Transparency Committee does not recommend continued inclusion on the list of medicines refundable by National Health Insurance.