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TRANSPARENCY COMMITTEE

Opinion
20 November 2013

OSAFLEXAN 1178 mg, oral powder for solution in single-dose sachets

Box of 30 single-dose sachets (CIP: 34009 397 018 2 0)

Box of 90 single-dose sachets (CIP: 34009 575 860 6 5)

Applicant: ROTTAPHARM S.A.R.L.

INN	Glucosamine (sulfate)
ATC code (2012)	M01AX05 (other non-steroidal anti-rheumatic anti-inflammatory drugs)
Reason for the review	Re-assessment of the actual benefit pursuant to the findings of the Transparency Committee in its opinion of 10 March 2010.
List(s) concerned	National Health Insurance (French Social Security Code L.162-17) B/30 only Hospital use (French Public Health Code L.5123-2) B/30 and 90
Indication(s) concerned	"Relief of symptoms in mild to moderate osteoarthritis of the knee."

Actual Benefit	Insufficient Actual Benefit
Therapeutic Use	Due to the very modest efficacy on pain and functional disability on the one hand, and the absence of a demonstrated impact in terms of reduced consumption of NSAIDs on the other hand, OSAFLEXAN has no place in the treatment of mild to moderate osteoarthritis of the knee.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	06 October 2009 (mutual recognition)
Prescribing and dispensing conditions / special status	List II

ATC Classification	2012	
	M	Musculo-skeletal system
	M01	Anti-inflammatory and anti-rheumatic drugs
	M01A	Non-steroidal anti-inflammatory and anti-rheumatic drugs
	M01AX	Other non-steroidal anti-rheumatic and anti-inflammatory drugs
	M01AX05	glucosamine

02 BACKGROUND

During the application for inclusion on the national health insurance and hospital use lists for OSAFLEXAN, the Committee found that its AB was low and gave a favourable opinion for inclusion, on the condition that a study was set up and conducted within two years of marketing (deadline of 30 June 2013) to show the impact of OSAFLEXAN prescription in terms of reducing NSAID consumption (opinion of 10 March 2010).

On 26 November 2008, a similar opinion was rendered for the medicinal products: ART 50 mg and ZONDAR 50 mg (diacerein), CHONDROSULF (chondroitin sulfate) and PIASCLEDINE (unsaponifiable components of avocado and soybean oils). In its opinions of 9 January 2013, the Committee evaluated the results of a study (PEGASE) that did not show reduction in NSAID consumption related to the prescription of these four medicinal products; it therefore concluded insufficient actual benefit.

Due to the late arrival on the market of proprietary medicinal products based on glucosamine, the Committee re-assessed the AB for OSAFLEXAN, after the 2-year period set, on the basis of the results of the PEGASE study in response to the Committee's request in its 2010 opinion.

03 THERAPEUTIC INDICATIONS

"Relief of symptoms in mild to moderate osteoarthritis of the knee. "

04 DOSAGE

"One 1500 mg sachet per day. The powder must be dissolved in a glass of water (250 ml). OSAFLEXAN is not indicated in the treatment of acute pain. Relief of symptoms, especially pain relief, may not be experienced until after several weeks of treatment and in some cases even longer.

If no relief of symptoms is experienced after 2-3 months of treatment, continued treatment with OSAFLEXAN should be re-assessed.

OSAFLEXAN may be taken with or without food.
Dosage and administration methods in special populations:

Children and adolescents: OSAFLEXAN should not be used in children and adolescents below age 18 due to the lack of data on safety and efficiency.

Elderly: No specific study has been conducted in the elderly, but from clinical experience, no dosage adjustment is necessary when treating elderly patients otherwise in good health. A considerable proportion of patients above age 65 were included in three "pivotal" studies.

Renal and/or hepatic impairment: no study has been conducted in patients with renal and/or hepatic impairment, so no recommendation can be made. "

05 THERAPEUTIC NEED

The first steps to take in treating osteoarthritis symptoms of the lower members are hygiene and dietary rules (weight loss, regular physical activity except during flare-ups of pain or congestion where reduced activity is necessary) and non-pharmacological (physical therapy, wearing orthotics, using canes, etc.).

Treatment must be individualised and include risks 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 based on chondroitin sulfate, unsaponifiable components of 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, in particular in the elderly. Consequently, they have no therapeutic use. It should be noted that the risk/benefit ratio for diacerein was deemed unfavourable by the MA Committee (July 2012).

Surgery (arthroplasty, prosthesis 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.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Active ingredient	Proprietary medicinal product	Company	Presentation	Indication	AB	Date of opinion	Reimbursement
Glucosamine (hydrochloride)	FLEXEA 625 mg	Expanscience	tablet	Relief of symptoms in mild to moderate osteoarthritis of the knee.	Low, on the condition that a study is conducted within two years to show the impact of prescribing glucosamine in terms of reducing NSAID consumption	22 July 2009	yes
	STRUCTOFLEX 625 mg	Pierre Fabre Médicament	hard capsule			30 June 2010	
	VOLTAFLEX 625 mg	Novartis Santé Familiale S.A.S.	tablet			10 March 2010	
Glucosamine (sulfate)	DOLENIO 1178 mg	Biocodex	tablet			13 January 2010	
Chondroitin (sulfate)	CHONDROSULF 400 mg	Genévrier	hard capsule and oral granulate for solution in sachet	Delayed-effect symptomatic treatment of hip and knee osteoarthritis.	Insufficient	09 January 2013	
Diacerein	ART 50 mg	Negma-Lerads	hard capsule			09 January 2013	
	ZONDAR 50 mg	Pharma 2000	hard capsule			09 January 2013	
Unsaponifiable components of avocado and soybean oil	PIASCLEDINE 300 mg	Expanscience	hard capsule			09 January 2013	

06.2 Other health technologies

Not applicable

► Conclusion

The most relevant comparators are other glucosamine-based proprietary medicinal products.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Brand Name	Reimbursement
Germany	DONA	No
Austria	DONA	No
Belgium	DONACOM	No
Bulgaria	DONA	No
Cyprus	DONAROT	No
Denmark	DONACOM	No
Spain	XICIL / HESPERCORBIN / ANDUR	
Estonia	ARTHRYL	No
Finland	ARTHRYL	No
Greece	DONAROT / VIARTRIL	No
Hungary	DONA	No
Ireland	DONA / VIARTRIL	No
Italy	DONA / VIARTHRYL-S	No
Latvia	ARTHRYL	No
Lithuania	ARTHRYL	No
Luxembourg	DONA	No
Norway	DONACOM	No
Netherlands	DONACOM	No
Poland	ARTHRYL	No
Portugal	VIARTRIL-S	Yes (69%)
Czech Republic	DONA	Yes (70%)
Romania	DONA	Yes (50%)
United Kingdom	GLUSARTEL	Yes (100% by insurance)
Slovakia	DONA	No
Slovenia	DONA	No
Sweden	onACOM	No

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion	10 March 2010 (inclusion)
Indication	"Relief of symptoms in mild to moderate osteoarthritis of the knee. "
AB	<p>Symptomatic osteoarthritis of the knee is characterised by pain and functional disability that can become chronic. It may eventually require surgical treatment with a prosthesis implant.</p> <p>This proprietary medicinal product is intended for symptomatic treatment.</p> <p><u>Public health benefit:</u></p> <p>The public health burden of osteoarthritis of the knee is moderate. The reduction in functional limitations and disability induced by osteoarthritis, as well as the improvement in quality of life in people who suffer from it, represent a public health need. The response to this need is not only drug-based.</p> <p>The available data regarding pain and algofunctional indexes do not permit concluding the existence of an impact of glucosamine on improving quality of life and reducing functional limitations: no quality of life data, little effect on symptoms.</p> <p>The theoretical benefit, in public health terms, of slow-acting osteoarthritis drugs resides in reducing NSAID consumption, which reduces the frequency of adverse digestive effects that are particularly detrimental in the elderly. For glucosamine, this benefit has not been proven by evidence. Consequently, OSAFLEXAN 1178 mg is not expected to benefit public health.</p> <p>This proprietary medicinal product is not very effective in relieving knee osteoarthritis symptoms. The efficacy/adverse effects ratio is modest.</p> <p>Treatment of osteoarthritis of the lower members relies above all on hygiene and dietary rules (weight loss, regular physical exercise) and non-pharmacological measures (physical therapy, wearing orthotics, using canes, etc.). Symptomatic treatment mainly relies on oral analgesics and NSAIDS. This proprietary medicinal product has a limited place in the symptomatic treatment of mild to moderate knee osteoarthritis.</p> <p>Due to its modest efficacy and limited role in therapeutic use, the actual benefit of OSAFLEXAN 1178 mg, oral powder for solution in single-dose sachets, is low.</p>
Improvement Actual Benefit	in OSAFLEXAN 1178 mg, oral powder for solution in single-dose sachets, does not provide improved actual benefit (IAB V) with regard to other slow-acting osteoarthritis drugs.
Studies requested	A favourable opinion for inclusion on the list of medicines refundable by national health insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosage in the MA, on the condition that a study is conducted within two years to show the impact of OSAFLEXAN prescription in terms of reduced NSAID consumption.

09 ANALYSIS OF AVAILABLE DATA

09.1 Efficacy

The company has not provided any new clinical efficacy data.

09.2 Safety/Adverse effects

The company has provided new safety data: PSUR covering the period from 01/04/2010 to 31/03/2013. These data are not likely to change the known safety profile of glucosamine.

09.3 Usage/prescription data

Observational study: PEGASE study

OBJECTIVES AND METHOD

Since 2008, the Transparency Committee has re-assessed all delayed-effect symptomatic treatments for hip and knee osteoarthritis included on the list of reimbursable medicinal products (ART 50, ZONDAR, CHONDROSULF and PIASCLEDINE) and, in 2009-2010, examined the various applications for inclusion of glucosamine-based proprietary medicinal products and other delayed-effect symptomatic treatments with a similar indication (relief of symptoms related to mild to moderate osteoarthritis of the knee): DOLENIO, FLEXEA, OSAFLEXAN, STRUCTOFLEX and VOLTAFLEX. Due to their low efficacy on pain and joint function, the Committee believed that the potential benefit of these treatments, in particular glucosamine, would reside in a possible reduction of NSAID consumption.

Its favourable opinion for continued listing or inclusion of these proprietary medicinal products depended on setting up and conducting a study, within two years after marketing (deadline of 30 June 2013), to show their impact in terms of reducing NSAID consumption.

To meet the Transparency Committee's request dated on 13 January 2010, Rottapharm participated in the PEGASE study.

As a reminder, PEGASE is a cohort study of patients with knee or hip arthritis, treated or not treated by delayed-effect symptomatic osteoarthritis medicines, including glucosamine-based medicines, which aimed to measure their impact on NSAID use and describe their usage profile during follow-up.

This study, which began including patients in March 2010, was conducted on a sample of generalist physicians or rheumatologists in private practice in metropolitan France and identified at random from telephone lists.

This cohort comprised patients aged 18 years or older, presenting with osteoarthritis of the knee or hip (or both) according to the ACR criteria.^{1,2} They were included consecutively, during a consultation for a pain episode of their osteoarthritis, from when new treatment with a symptomatic delayed-effect osteoarthritis medicine or any other new osteoarthritis

¹ 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;29:1039-49.

² Altman, R et al: The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* 1991;34:505-14.

treatment (control) regardless of the type - pharmacological (NSAID or analgesics, infiltration) or non-pharmacological (lifestyle/dietary measures, physiotherapy, orthotics, other forms of physical therapy) - was started.

Patients already treated by a delayed-effect symptomatic osteoarthritis medicine or hyaluronic acid for more than 3 months, with [rheumatoid] arthritis, tendinitis of the lower limbs or radicular pain were specifically not included.

The follow-up period lasted up to 24 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, as well as during a standard telephone follow-up at 1, 4, 8, 12, 16, 20 and 24 months after inclusion.

Patients were questioned about their consumption of delayed-effect symptomatic medicines for osteoarthritis and NSAIDs over two-month periods indicating the number of days on treatment in the two months in question (every day, or nearly every day, 31 to 60 days in all, 17 to 30 days, 6 to 16 days, 1 to 7 days, never).

In order to take into account the treatment dynamics during follow-up (discontinuation of treatment, potential substitutions, etc.), a treatment time-population analysis was conducted. Thus, the periods of exposure to delayed-effect symptomatic medicines for osteoarthritis are divided into analysis time units (ATU) of two months over the entire follow-up.

All exposure was considered as binary (exposed/not exposed) for each delayed-effect symptomatic medicine for osteoarthritis in a unit of two months (independent of any combination).

Only uses reported during patient questioning were considered as exposures to delayed-effect symptomatic osteoarthritis medicines. Doctors' prescriptions without reported consumption in the interview were not considered to be exposures.

The event of interest was systemic NSAID³ consumption which was considered as binary (consumption yes/no) within each ATU.

The risk of the event of interest occurring was considered constant in each ATU.

The primary analysis sought to compare NSAID use in the two-month periods of exposure to glucosamine (regardless of any combination with another compound) with two-month periods of non-exposure to any delayed-effect symptomatic osteoarthritis medicine, given that during the previous two-month period there was no exposure to any of them.

As of October 2012, due to the failure to reach inclusion objectives related to the late arrival of glucosamine-based proprietary medicinal products on the market, the patient inclusions and follow-ups are continuing in the PEGASE study for patients exposed to glucosamine on the one hand and patients not exposed to any delayed-effect symptomatic osteoarthritis medicine on the other hand

The failure to reach the inclusion goals for patients specifically taking glucosamines by 4 October 2012 led to amending the protocol regarding the procedure for recruiting new patients to favour patients on glucosamines.

³ NSAIDs included in the analysis: diclofenac, diclofenac + misoprostol, aceclofenac, etodolac, ibuprofen, nabumetone, flurbiprofen, ketoprofen, alminoprofen, fenoprofen, naproxen, nimesulide, celecoxib, etoricoxib, meloxicam, piroxicam, tenoxicam, indomethacin, sulindac.

Thus, patients taking glucosamines were recruited in several waves from the start of the study.

Therefore, in order to take different recruitment periods into account, the study's scientific committee considered three types of control times defined after the fact:

- 1) the control time for patients recruited and followed before freezing the PEGASE database on 4 October 2012, the date of freezing the database for final analysis as specified by the original protocol for other symptomatic delayed-effect osteoarthritis medicines;
- 2) the control time for these same patients, including their follow-up after 4 October 2012;
- 3) the control time for new patients, recruited and followed after 4 October 2012;

Given these different control time options, the scientific committee for the study expressed (without knowledge of the results) its preference for **comparison B** defined below but requested the presentation of three analyses:

- Comparison A, not specified in the protocol, focuses on all the available control times for the study period (before and after 4 October 2012).
- Comparison B, not specified in the protocol, focuses on the control times for patients recruited before 4 October 2012 and censored at that date and patients recruited after that date.
- Comparison C, specified in the protocol, focuses only on the control times for patients recruited before 4 October 2012 to later compare the results obtained previously with other delayed-effect symptomatic osteoarthritis treatments.

The selected primary analysis focused on the comparison using all the available control times over the study period: **Comparison A, not specified in the protocol**. Sensitivity analyses were performed on the basis of comparisons with other control times defined above.

Secondary analyses performed at the request of the scientific committee sought to compare the impact on pain (measured by VAS) and disability (measured by the Lequesne algofunctional index) in two-month periods of glucosamine exposure *versus* two-month periods with no exposure to any delayed-effect symptomatic osteoarthritis medicine. These analyses do not appear in the analysis plan filed by the companies and were performed *post hoc*.

In all, 500 two-month periods of exposure for each glucosamine and 10,000 two-month periods of non-exposure were planned to detect an 18% difference in NSAID use risk (or RR = 0.82, power 80%, confidence 95%).

Description of the PEGASE cohort

Out of 38,014 generalist physicians and 1236 private rheumatologists contacted to participate in the study, 4052 agreed to participate in the study and 745 (642 generalist physicians and 96 rheumatologists) included at least one patient.

On 22 April 2013 (date the database was frozen), a total of 6451 patients meeting the inclusion and non-inclusion criteria were included.

The main characteristics of patients at inclusion are the following:

- female 63.5%;
- mean age 66.2 years, [standard deviation: 12.0];
- less than secondary school education 58.6%
- working 74.4%
- mean body mass index 28.0 [standard deviation: 5.0];
- known diagnoses were knee arthritis (79.4%), hip arthritis (16.4%) both (4.3%);
- osteoarthritis present for < 1 year (25.3%) , from 1 to 5 years (41.2%), > 5 years (30.3%)
- median number of pain flare-ups in the past 6 months 2.0 [range: 0.0 - 12.0];
- mean pain score (measured from 0 to 10 on the VAS) 5.6 [standard deviation: 1.8];
- disability (Lequesne algofunctional index) significant to very significant (35.3%), unbearable (18.8%);
- main co-morbidities musculo-skeletal disorders (58.9%), cardiovascular disease (57.2%), other osteoarthritis locations (42.7%), endocrine (32.2%) and gastrointestinal disorders (23.2%).
- allergy to NSAIDs 2.3%
- use of physical therapy (11.7%) or orthotics (11.7%)
- wearing prostheses 5.5%

On the date of the final report,

- the mean follow-up of the cohort was 11.72 months.
- 5824, 4729, 3725, 2425, 1703 and 1154 patients had a follow-up at 4, 8, 12, 16, 20 and 24 months, respectively.
- 21% of patients (1373/6451) were never exposed to any delayed-effect symptomatic osteoarthritis medicine during the PEGASE cohort follow-up period.

RESULTS:

The results presented below only concern OSAFLEXAN

Among the 315 patients who received an OSAFLEXAN prescription at inclusion or during the follow-up (i.e.,4.9% of the PEGASE cohort), 56 (19.5%) eventually refused follow-up and 72 (22.9%) reported not taking or immediately discontinuing the prescribed treatment. Furthermore, 226 patients who agreed to participate had at least one follow-up visit.

On the date of the final report, the mean duration of OSAFLEXAN exposure in these patients was 10.0 months corresponding to 2262 patient-months of cumulative exposure.

The characteristics of patients exposed to OSAFLEXAN differed from those of patients who were never exposed to any slow-acting symptomatic osteoarthritis medicine during follow-up. The exposed patients

- were younger on average (64.4 *versus* 69.1 years old);
- more commonly had a higher education level (48.1% *versus* 30.7%);
- were more often retired or had no occupation (30.9 *versus* 14.8);
- had fewer cardiovascular (49.5% *versus* 63.6%) and endocrine (29.5% *versus* 35.6%) co-morbidities, but more musculo-skeletal disorders (63.2% *versus* 58.8%);

- used orthotics (8.0% *versus* 15.3%) and prostheses (4.4% *versus* 8.7%) less frequently.

Fewer of them had a history of osteoarthritis of more than 5 years (27.1% vs. 37.7%)

The mean number of pain flare-ups in the past 6 months before inclusion, the pain scale and the Lequesne index were similar in both groups.

Results regarding NSAID consumption:

➤ **Primary analysis and sensitivity (see Table 1)**

On 22 April 2013, the date the PEGASE database was frozen for glucosamine-based proprietary medicinal products, the analysis units were divided as follows: 481 were for two-month periods of OSAFLEXAN exposure (inclusion goal not reached due to the product's small market share), the number of two-month periods of non-exposure to medicines with indications similar to OSAFLEXAN varied depending on the choice of control time considered. The number of non-documented ATUs was not specified. A cumulative total of 90 NSAID-use ATUs were counted.

The two-month periods of NSAID exposure indicate that the patients using NSAIDs had a different profile compared with non-users:

- younger on average (65.4 *versus* 67.3 years old),
- more often women (67.8% *versus* 62.2%),
- more common history of osteoarthritis > 1 year (78.6% *versus* 72.9%),
- higher mean pain score (5.2 *versus* 4.5),
- higher algofunctional index (67.3% *versus* 52.5% expressing a significant to very significant disability).
- more frequent use of physical therapy, orthotics or prostheses (26.7% *versus* 23.3%).

Global results comparing two-month periods exposed to all glucosamines with two-month periods of non-exposure were not presented. It would have been useful to have this global analysis since the statistical power of the results presented for OSAFLEXAN is lower than the goal set beforehand, insofar as the inclusion objectives have not been achieved due to the the product's low market share.

During the study, the frequency of NSAID use was, respectively, 18.7% for two months of exposure to OSAFLEXAN and 21.6% for two-month periods of non-exposure to any delayed-effect symptomatic osteoarthritis treatment, i.e., according to analysis A selected as the primary one, no difference in NSAID use between the groups exposed to OSAFLEXAN and not exposed to any delayed-effect symptomatic osteoarthritis medicine (OR = 0.74 95% CI [0.54-1.01]) (see Table 1).

Sensitivity analysis B led to a similar result (22.1 % *versus* 18.7%, OR = 0.79, 95% CI = [0.57; 1.1]). In analysis C, the difference observed (23.8% *versus* 18.7%) was statistically significant (OR = 0.64, 95% CI = [0.45; 0.92]).

An analysis according to the duration of use per 4-month period was also done (see Table 1).

Table 1: Association between all the exposure to OSAFLEXAN ATUs and the NSAID use ATUs during the follow-up period

			Number of OSAFLEXAN ATUs	% NSAID use within the ATUs	OR* (95% CI)
Analysis A: all control two-month periods included (primary analysis not specified in the protocol)	No delayed-effect symptomatic osteoarthritis treatment (reference**)		15,756	21.6	1
	All exposure durations***		481	18.7	0.74 [0.54-1.01]
	• Exposure from 0 to 4 months after starting		271	20.7	0.77 [0.55-1.07]
	• Exposure from 5 to 8 months after starting		124	12.9	0.59 [0.33-1.09]
	• Exposure for more than 8 months after starting		86	20.9	0.94 [0.42-2.1]
Analysis B: all control two-month periods included with censure at 4/10/2012 (not specified in the protocol)	No delayed-effect symptomatic osteoarthritis treatment (reference**)		13,870	22.1	1
	All exposure durations ***		481	18.7	0.79 [0.57-1.1]
	• Exposure from 0 to 4 months after starting		271	20.7	0.85 [0.61-1.2]
	• Exposure from 5 to 8 months after starting		124	12.9	0.55 [0.29-1.03]
	• Exposure for more than 8 months after starting		86	20.9	0.95 [0.39-2.35]
Analysis C: only control two-month periods included before 4/10/2012 (specified in the protocol)	No delayed-effect symptomatic osteoarthritis treatment (reference**)		9237	23.8	1
	All exposure durations ***		481	18.7	0.64 [0.45-0.92]
	• Exposure from 0 to 4 months after starting		271	20.7	0.73 [0.49-1.07]
	• Exposure from 5 to 8 months after starting		124	12.9	0.46 [0.24-0.88]
	• Exposure for more than 8 months after starting		86	20.9	0.83 [0.36-1.9]

* Odds Ratio estimated based on a Generalised Estimating Equation (GEE) type multivariate logistic regression model taking into account the autocorrelation between each ATU and adjusted for age (continuous variable), sex (binary), pain scale (binary), the number of osteoarthritis pain flare-ups (three categories), 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 comorbidities and risk factors for not taking NSAIDs.

**Two-month periods of non-exposure to any delayed-effect symptomatic osteoarthritis treatment given that during the preceding two months there was no exposure to a delayed-effect symptomatic osteoarthritis treatment.

➤ Other sensitivity analyses

Several other sensitivity analyses were presented by the company. They led to non-significant results concordant with those of primary analysis A and those of sensitivity analysis B.

A first sensitivity analysis was done taking into account 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: OR = 0.79, 95% CI = [0.60-1.05].

This sensitivity analysis is only based on carry-over effect time and not the latent time of the effect as initially specified by the protocol.

A second sensitivity analysis was carried out on the subgroup of patients who started treatment with OSAFLEXAN on inclusion in the study and had not used any other delayed-effect osteoarthritis symptomatic treatment in the three months prior to the inclusion date:⁴ OR = 0.72, 95% CI = [0.49-1.07].

However, since inclusion of patients with a prescription for less than three months of slow-action osteoarthritis medicines was authorised in the protocol (amendment of 23/09/2010), an analysis of patients new to or previously receiving treatment was integrated into the protocol. Only the analysis on the subgroup of incident patients was presented.

A third sensitivity analysis was done considering so-called "unclassified" two-month periods, defined as being three two-month periods of OSAFLEXAN exposure compared with the incident analysis, and led to similar results: OR = 0.77, 95% CI = [0.57-1.04].

Finally, an analysis stratified by whether or not NSAIDs were taken previously (evaluated in the first two months following the painful osteoarthritis episode) indicates a relative risk of NSAID consumption, without carry over effect, of 1.28 (95% CI = [0.68-2.43]) in the case of prior NSAID consumption and 0.61 (95% CI = [0.31-1.18]) in the absence of prior NSAID consumption.

➤ Secondary analyses

Results relating to pain (see Table 2) and functional status (see Table 3)

The results of the *post hoc* secondary analyses conducted on pain (VAS score from 0 to 10 categorised by 0-4 / 5-10) and functional impairment (modified Lequesne algofunctional index - telephone version - categorised by the median of the observed distribution of modest or medium disability / significant, very significant or unbearable disability) are presented below:

Table 2: Association between all the exposure to OSAFLEXAN ATUs and the pain ATUs (VAS ≥5) during follow-up

		Number of OSAFLEXAN ATUs	% of two-month period of pain (5-10) within the ATUs.	OR* (95% CI)
Analysis A: all control two-month periods included	No delayed-effect symptomatic osteoarthritis treatment (reference**)	15,196	59.0	1
	All exposure durations	476	59.5	1.18 [0.89-1.55]
	• 0 to 4 months after starting	271	65.7	1.21 [0.89-1.65]
	• 4 to 8 months after starting	120	50.8	1.00 [0.54-1.82]
	• More than 8 months after starting	85	51.8	0.68 [0.33-1.41]

⁴ The study protocol was amended on 23/09/2010 in order to change the exclusion criterion relating to patients taking delayed-effect symptomatic osteoarthritis medicines or who received a hyaluronic acid injection **more than 3 months earlier**.

Table 3: Association between all the exposure to OSAFLEXAN ATUs and the ATUs with significant or greater disability during follow-up

		Number of OSAFLEXAN ATUs	% two-month periods with significant disability within the ATUs.	OR* (95% CI)
Analysis A: all control two-month periods included	No delayed-effect symptomatic osteoarthritis treatment (reference**)	14,701	55.6	1
	All exposure durations	340	55.9	1.28 [0.87-1.89]
	• 0 to 4 months after starting	135	59.3	1.29 [0.78-2.15]
	• 4 to 8 months after starting	120	55.0	1.18 [0.71-1.97]
	• More than 8 months after starting	85	51.8	1.06 [0.46-2.47]

*Odds Ratio estimated based on a Generalised Estimating Equation (GEE) type multivariate 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 physical therapy/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 and risk factor for not taking NSAIDs.

**Two-month periods of non-exposure to any delayed-effect symptomatic osteoarthritis treatment.

An analysis according to the duration of use per 4-month period was also done .

These *post hoc* analyses could not be used by the Committee. However, no significant impact on pain and functional impairment was observed between the groups exposed to OSAFLEXAN and the non-exposed groups.

Conclusion:

The results of the PEGASE study presented are concordant (except for sensitivity analysis C) and confirm that OSAFLEXAN has no impact in terms of reducing NSAID consumption. The absence of the following components limits the interpretation of these results:

- The decision to choose analysis A as the primary analysis is questionable insofar as it was neither specified in the protocol nor the option preferred by the study scientific committee.
- Statically significant results are only observed for one of the two sensitivity analyses (analysis C). Analysis C, although specified in the protocol, is not the most relevant and least biased methodological choice given the time lag between the recruitment of non-exposed and exposed patients. Indeed, the majority of patients exposed to glucosamine-based medicines were included in a period after 04/10/2012, unlike the non-exposed patients.
- An analysis pertaining to subjects recruited concomitantly would have been more rigorous in order to avoid selection bias related to any changes in practices and/or conditions for reimbursement occurring over time.
- Moreover, analyses by subgroup performed as a function of duration of exposure could only be considered as exploratory. Indeed, they led to conducting multiple statistical tests leading to an alpha risk for consumption that was not corrected. Furthermore, these analyses by subgroup were conducted despite the non-significance of the results of the main analysis on the total study population. Therefore, they can only be considered as exploratory.
- The limited number of ATUs, especially beyond 8 months, suggests a short OSAFLEXAN exposure in the cohort, which could be explained either by a truncated follow-up of the cohort patients or by treatment discontinuations.
- No information on any losses to follow-up was presented.

Consequently, given the above-mentioned limits, the Committee believes that the PEGASE results concerning OSAFLEXAN, like those of other delayed-effect osteoarthritis symptomatic treatments evaluated in this study, confirm the absence of a difference in NSAID consumption between the group exposed to glucosamine and the group not exposed to any delayed-effect symptomatic osteoarthritis treatment.

09.4 Summary & discussion

No new clinical efficacy data were submitted.

The updated safety data (PSUR) are not likely to change the known safety profile of glucosamine.

In its opinion of 10 March 2010, the Transparency Committee made its favourable opinion for inclusion on the list for reimbursement, given a low AB, dependent on setting up and conducting, within two years, a study to show the impact of OSAFLEXAN prescription in terms of reducing NSAID consumption.

The main results of the PEGASE study observed are:

- not taking prescribed OSAFLEXAN by 22.9% of patients;
- an NSAID consumption rate of around 22% in the entire population with knee or hip osteoarthritis;
- a reduction in terms of frequency of NSAID use in the analysis time units (ATUs) of OSAFLEXAN exposure compared with that observed in ATUs with no exposure to any symptomatic delayed-effect osteoarthritis medicines, only appearing statistically significant in one analysis (sensitivity analysis C) of the three done due to the time lag between recruiting non-exposed patients and patients exposed to medicines based on glucosamines:
 - 18.7% *versus* 21.6%, OR = 0.74, 95% CI = [0.54-1.01] in the primary analysis (not initially specified in the protocol) considering all the control times available over the study period (before and after 4 October 2012);
 - 18.7% *versus* 22.1%, OR = 0.79, 95% CI = [0.57-1.1] in the analysis considering control times for patients recruited before 4 October 2012 and censored on that date and patients recruited after that date (initially not specified in the protocol);
 - 18.7% *versus* 23.8%, OR = 0.64, 95% CI = [0.45-0.92], or a statistically significant difference in the only analysis (initially specified in the protocol) considering just the control times of patients recruited before 4 October 2012, therefore a period prior to the recruitment of the majority of patients on glucosamine. However, this difference is not really clinically relevant.

These results raise the question of the relevance of these multiple analyses, potentially allowing an incorrect positive conclusion to be reached. Furthermore, the time lag between recruiting patients on glucosamine and those on other delayed-effect symptomatic medicines for hip and knee osteoarthritis could have biased this analysis (changes in practices and/or reimbursement conditions).

Because the multiplicity of tests could potentially lead to an incorrect positive conclusion, the lack of concordance among analyses A, B and C and the not very clinically relevant effect observed in the only analysis that showed a statistically significant effect (sensitivity analysis C), it could not be concluded that OSAFLEXAN has an impact on NSAID use.

Secondary analyses by subgroup and stratified analyses cannot be taken into consideration because of their exploratory nature.

As a result, OSAFLEXAN has not been proven to contribute to reducing NSAID consumption in osteoarthritis patients.

010 THERAPEUTIC USE

Due to the very modest efficacy on pain and functional disability on the one hand, and the absence of a demonstrated impact in terms of reduced consumption of NSAIDs on the other hand, OSAFLEXAN has no place in the treatment of mild to moderate osteoarthritis of the knee.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

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

011.1 Actual benefit

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

► This medicinal product is a symptomatic treatment

► Public health benefit

The public health burden of osteoarthritis of the knee is moderate.

Reduction of functional limitations and disabilities induced by osteoarthritis, as well as improvement in the quality of life of people affected with it, represent a public health need included in the priorities established in the public health policy act of 9 August 2004 (objective 85). However, the response to this need is not limited to drug treatment.

The available data regarding pain and algofunctional indexes do not permit concluding the existence of an impact of glucosamine-based proprietary medicinal products on improving quality of life and reducing functional limitations: no quality of life data, little effect on functional disability.

The theoretical benefit, in public health terms, of medicines indicated in the treatment of osteoarthritis symptoms resides in reducing NSAID consumption, which would likely reduce the frequency of adverse digestive effects that are particularly detrimental in the elderly.

The results of the PEGASE study do not confirm the impact of OSAFLEXAN on reducing NSAID consumption.

Consequently, OSAFLEXAN does not benefit public health.

► This proprietary medicinal product is not very effective in relieving knee osteoarthritis symptoms. The efficacy/adverse effects ratio is modest.

► 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 canes, etc.). Symptomatic treatment mainly relies on oral analgesics and NSAIDs. Glucosamine-based proprietary medicinal products, including OSAFLEXAN, are not very effective on pain and functional disability and it has not been proven that they reduce NSAID use. Consequently, OSAFLEXAN has no role in the treatment of mild to moderate osteoarthritis of the knee.

Taking account of these points, the Committee considers that the actual benefit of OSAFLEXAN is insufficient in the relief of symptoms of mild to moderate osteoarthritis of the knee for reimbursement by National Health Insurance.

The Committee renders an unfavourable opinion for continued inclusion on the list of medicines refundable by National Health Insurance (for the box of 30) and on the list of medicines approved for hospital use (for the box of 30 and 90) in the indication "Relief of symptoms in mild to moderate osteoarthritis of the knee" and at the dosages in the Marketing Authorisation.