FLEXEA 625 mg, tablet
Box of 60 tablets (CIP: 34009 380 534 2 5)
Box of 180 tablets (CIP: 34009 380 535 9 3)

Applicant: EXPANSCIENCE

<table>
<thead>
<tr>
<th>INN</th>
<th>Glucosamine (hydrochloride)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (2012)</td>
<td>M01AX05 (other non-steroidal anti-rheumatic anti-inflammatory drugs)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Re-assessment of the actual benefit pursuant to the findings of the Transparency Committee in its opinion of 22 July 2009.</td>
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<tr>
<td>List(s) concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17) only for the box of 60</td>
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<tr>
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<td>Hospital use (French Public Health Code L.5123-2) for boxes of 60 and 180</td>
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<td>Indication(s) concerned</td>
<td>&quot;Relief of symptoms in mild to moderate osteoarthritis of the knee.”</td>
</tr>
<tr>
<td>AB</td>
<td>Insufficient Actual Benefit</td>
</tr>
<tr>
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<td>-----------------------------</td>
</tr>
<tr>
<td>Therapeutic Use</td>
<td>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, FLEXEA has no place in the treatment of mild to moderate osteoarthritis of the knee.</td>
</tr>
</tbody>
</table>
**01 ADMINISTRATIVE AND REGULATORY INFORMATION**

<table>
<thead>
<tr>
<th>Marketing Authorisation (procedure)</th>
<th>12/07/2007 (under the name ENDOSTA, mutual recognition) amendments of 24/12/2009, 08/03/2010 (name change), 05/12/2011 and 09/02/2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing and dispensing conditions / special status</td>
<td>List II</td>
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</table>

**ATC Classification**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>2012</td>
<td>M Musculo-skeletal system</td>
</tr>
<tr>
<td>M01</td>
<td>Anti-inflammatory and anti-rheumatic drugs</td>
</tr>
<tr>
<td>M01A</td>
<td>Non-steroidal anti-inflammatory and anti-rheumatic drugs</td>
</tr>
<tr>
<td>M01AX</td>
<td>Other non-steroidal antirheumatic and anti-inflammatory drugs</td>
</tr>
<tr>
<td>M01AX05</td>
<td>glucosamine</td>
</tr>
</tbody>
</table>

**02 BACKGROUND**

During the application for inclusion on the national health insurance and hospital use lists for FLEXEA, 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 FLEXEA prescription in terms of reducing NSAID consumption (opinion of 22 July 2009).

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 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 FLEXEA, 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 2009 opinion.

**03 THERAPEUTIC INDICATIONS**

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

**04 DOSAGE**

"1250 mg of glucosamine once daily for relief of symptoms.

Glucosamine is not indicated for the treatment of acute painful symptoms. 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, continued treatment with glucosamine should be re-assessed."
The tablets can be taken with or without food.

Dosage and administration methods in special populations:

**Children and adolescents**

FLEXEA should not be used in children under 18 years of age.

**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.

**Renal or hepatic impairment**

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

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**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 individualized 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. The risk/benefit ratio for diacerein was deemed unfavourable by the MA Committee (July 2012). These medicinal products have not proven 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.

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

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Proprietary medicinal product</th>
<th>Company</th>
<th>Presentation</th>
<th>Indication</th>
<th>AB</th>
<th>Date of opinion</th>
<th>Reimbursement</th>
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<tbody>
<tr>
<td>Glucosamine (hydrochloride)</td>
<td>STRUCTOFLEX 625 mg</td>
<td>Pierre Fabre Médicament</td>
<td>hard capsule</td>
<td>Relief of symptoms in mild to moderate osteoarthritis of the knee.</td>
<td>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</td>
<td>30 June 2010</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VOLTAFLEX 625 mg</td>
<td>Novartis Santé Familiale S.A.S.</td>
<td>tablet</td>
<td></td>
<td></td>
<td>10 March 2010</td>
<td></td>
</tr>
<tr>
<td>Glucosamine (sulfate)</td>
<td>OSAFLEXAN 1178 mg</td>
<td>Rottapharm S.A.R.L</td>
<td>oral powder for solution in single-dose sachets</td>
<td></td>
<td></td>
<td>10 March 2010</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DOLENIO 1178 mg</td>
<td>Biocodex</td>
<td>tablet</td>
<td></td>
<td></td>
<td>13 January 2010</td>
<td></td>
</tr>
<tr>
<td>Chondroitin (sulfate)</td>
<td>CHONDROSULF 400 mg</td>
<td>Genévrier</td>
<td>hard capsule and oral granulate for solution in sachet</td>
<td>Delayed-effect symptomatic treatment of hip and knee osteoarthritis.</td>
<td>Insufficient</td>
<td>9 January 2013</td>
<td></td>
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<tr>
<td>Diacerein</td>
<td>ART 50 mg</td>
<td>Negma-Lerads</td>
<td>hard capsule</td>
<td></td>
<td>9 January 2013</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>ZONDAR 50 mg</td>
<td>Pharma 2000</td>
<td>hard capsule</td>
<td></td>
<td>9 January 2013</td>
<td></td>
<td></td>
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<tr>
<td>Unsaponifiable components of avocado and soybean oil</td>
<td>PIASCLEDINE 300 mg</td>
<td>Expanscience</td>
<td>hard capsule</td>
<td></td>
<td></td>
<td>9 January 2013</td>
<td></td>
</tr>
</tbody>
</table>

#### 06.2 Other health technologies

Not applicable

**Conclusion**

The most relevant comparators are other glucosamine-based proprietary medicinal products.
### SUMMARY OF PREVIOUS ASSESSMENTS

| Date of opinion (reason for request) | 22 July 2009 (inclusion) under the name ENDOSTA 625 mg tablet |
| Indication | "Relief of symptoms in mild to moderate osteoarthritis of the knee." |
| AB (wording) | Symptomatic osteoarthritis of the knee is characterized by pain and functional disability that can become chronic. It may eventually require surgical treatment with a prosthesis implant. This proprietary medicinal product is intended for symptomatic treatment. **Public health benefit:** The public health burden of osteoarthritis of the knee is moderate. Reduction in the functional limitations and disability induced by osteoarthritis, as well as improvement in the quality of life in people who suffer from it, represent a public health need. The response to this need is not only drug-based. 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. The theoretical benefit, in public health terms, of slow-acting osteoarthritis drugs resides in reducing NSAID consumption, which reduces the frequency of adverse digestive reactions that are particularly detrimental in the elderly. For glucosamine, this benefit has not been proven by evidence. Consequently, ENDOSTA is not expected to 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 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. Due to its modest efficacy and limited role in therapeutic use, the actual benefit of ENDOSTA 625 mg, tablet, is low. |
| Improvement in Actual Benefit (wording) | ENDOSTA 625 mg, tablet, 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 medicinal products reimbursable by national health insurance and the list of medicinal products approved for hospitals and various public services in the indications and at the dosages of the MA, on the condition that a study is conducted within two years to show the impact of ENDOSTA 625 mg prescription in terms of reduced NSAID consumption. |

| Date of opinion (reason for request) | 21 September 2011 (re-assessment of the Actual Benefit following the petition to the Transparency Committee of 16 June 2011 by the French Social Security Directorate pursuant to Article R 163-19/6° of the social security code). |
| Indication | "Relief of symptoms in mild to moderate osteoarthritis of the knee." |
| AB (wording) | Symptomatic osteoarthritis of the knee is characterized by pain and functional disability that can become chronic. It may eventually require surgical treatment with a prosthesis implant. This proprietary medicinal product is intended for symptomatic treatment. **Public health benefit:** The public health burden of osteoarthritis of the knee is moderate. Reduction in the functional limitations and disability induced by osteoarthritis, as well as improvement in the quality of life in people who suffer from it, represent a public health need. The response to this need is not only drug-based. 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. The theoretical benefit, in public health terms, of slow-acting osteoarthritis drugs resides in reducing NSAID consumption, which reduces the frequency of adverse digestive reactions that are particularly detrimental in the elderly. For glucosamine, this benefit has not been proven by evidence. Consequently, ENDOSTA is not expected to 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 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. Due to its modest efficacy and limited role in therapeutic use, the actual benefit of ENDOSTA 625 mg, tablet, is low. |
| Improvement in Actual Benefit (wording) | ENDOSTA 625 mg, tablet, 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 medicinal products reimbursable by national health insurance and the list of medicinal products approved for hospitals and various public services in the indications and at the dosages of the MA, on the condition that a study is conducted within two years to show the impact of ENDOSTA 625 mg prescription in terms of reduced NSAID consumption. |
disability that can become chronic. It may eventually require surgical treatment with a prosthesis implant.

This proprietary medicinal product is intended for symptomatic treatment.

**Public health benefit:**

| 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. |

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.

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, FLEXEA 625 mg is not expected to 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. This proprietary medicinal product has a limited place in the symptomatic treatment of mild to moderate knee osteoarthritis.

Due to its modest efficacy and limited role in therapeutic use, the actual benefit of FLEXEA 625 mg mg, tablet, remains low in the MA indications.

**Studies requested**

Favourable opinion for continued inclusion on the list of medicines refundable by national health insurance in the indications and at the dosages in the Marketing Authorisation while awaiting the results from the 3A-PEGASE study.
08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The company has not provided any new clinical efficacy data.

08.2 Safety/Adverse effects

The company has not provided any new safety data.

08.3 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 an MA for a similar indication (relief of symptoms related to mild to moderate osteoarthritis of the knee): DOLENIO, FLEXEA, OSAFLEXAN, STRUCTOFLEX and VOLTA FLEX. 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 all delayed-effect symptomatic treatments for osteoarthritis 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 22 July 2009, Expanscience participated in the PEGASE study.

As a reminder, PEGASE is a cohort study of patients with knee or hip arthritis, either treated or not treated by delayed-effect symptomatic 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 general practitioners or rheumatologists in private practice in mainland 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) diagnosed according to 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 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 loss 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 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 (irrespective of any combination). Only uses reported during patient questioning were considered as exposures to delayed effect osteoarthritis medicines. Doctors’ prescriptions without reported consumption in the interview were not considered to be exposures.

The event of interest was systemic NSAID 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 combination with another compound) to 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, patient inclusion 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 with delayed-effect symptomatic osteoarthritis treatment to favour patients on glucosamines. Thus, patients taking glucosamines were recruited in several waves from the beginning 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 up 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;

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.
3) the control time for new patients, recruited and followed up 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 cut off 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 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 specified to detect an 18% difference in NSAID use risk (or an RR = 0.82), power 80%, confidence 95%).

**Description of the PEGASE cohort:**

Out of 38,014 general practitioners and 1236 private rheumatologists contacted to participate in the study, 4052 agreed to participate in the study and 745 (642 general practitioners 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 cohort follow-up period 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 FLEXEA.

Among the 940 patients who received a FLEXEA prescription at inclusion or during the follow-up (i.e., 14.6% of the Pegase cohort), 181 (19.3%) eventually refused follow-up and 163 (17.3%) reported not taking or immediately discontinuing the prescribed treatment. Furthermore, 759 patients who agreed to participate had at least one follow-up visit. On the date of the final report, the mean duration of FLEXEA exposure for these patients was 12.3 months, corresponding to 9318 patient-months of cumulative exposure.

The characteristics of patients exposed to FLEXEA differed from those of patients who were never exposed to any slow-acting osteoarthritis medicine during follow-up. The exposed patients
- were younger on average (65.1 versus 69.1 years old);
- more commonly had a higher education level (45.2% versus 30.7%);
- were more often retired or had no occupation (24.1% versus 14.8%);
- had fewer cardiovascular (54.8% versus 63.6%) and endocrine (31.0% versus 35.6%) co-morbidities;
- had fewer prostheses (3.8% versus 8.7%);
- Fewer of them had a history of osteoarthritis of more than 5 years (28.8% vs. 37.7%)
- the mean number of pain flare-ups in the 6 months before inclusion, the pain scale and the Lequesne index were similar in both groups.

Results regarding NSAID use:

- ➢ Primary analysis and sensitivity (see Table 2)

On 22 April 2013, the date the PEGASE database was frozen for glucosamine-based proprietary medicinal products, the analysis units were divided as follows: 2319 were for two-month periods of FLEXEA exposure, the number of two-month periods of non-exposure to any medication with indications similar to FLEXEA varied depending on the control time considered. The number of non-documented ATUs was not specified. A cumulative total of 566 NSAID-use ATUs were counted.

The two-month periods of NSAID exposure indicate that the patients using NSAIDs had a different profile compared to non-users:
- younger on average (65.1 versus 67.0 years old);
- more often women (67.0% versus 61.9%);
- more common history of osteoarthritis > 1 year (78.7% versus 71.9%);
- higher mean pain score (5.3 versus 4.5);
- higher algofunctional index 66.1% versus 52.5% expressing a very significant disability).
- more frequent use of physical therapy, orthotics or prostheses (26.4% versus 23.4%).

Global results comparing two-month periods exposed to all glucosamines to two-month periods of non-exposure were not presented.
Thus, during the study, the frequency of NSAID use was, respectively, 21.6% for the two months of exposure to FLEXEA and 24.4% for the 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 FLEXEA and not exposed to any delayed-effect osteoarthritis medicine (OR = 1.09 [0.91-1.29]) (see Table 1). Sensitivity analyses B and C led to results similar to those of the primary analysis. 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 FLEXEA ATUs and the NSAID use ATUs during the follow-up period.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Exposure to FLEXEA ATUs</th>
<th>% NSAID use within ATUs</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: all control two-month periods included (primary analysis not specified in the protocol)</td>
<td>No delayed-effect symptomatic osteoarthritis treatment (reference**)</td>
<td>15529</td>
<td>21.6</td>
</tr>
<tr>
<td></td>
<td>All exposure durations ***</td>
<td>2319</td>
<td>24.4</td>
</tr>
<tr>
<td></td>
<td>• Exposure from 0 to 4 months after starting</td>
<td>1107</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>• Exposure from 5 to 8 months after starting</td>
<td>628</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td>• Exposure from over 8 months after starting</td>
<td>584</td>
<td>22.9</td>
</tr>
<tr>
<td>B: all control two-month periods included with cutoff at 4/10/2012 (not specified in the protocol)</td>
<td>No delayed-effect symptomatic osteoarthritis treatment (reference**)</td>
<td>13651</td>
<td>22.1</td>
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<tr>
<td></td>
<td>All exposure durations ***</td>
<td>2319</td>
<td>24.4</td>
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<tr>
<td></td>
<td>• Exposure from 0 to 4 months after starting</td>
<td>1107</td>
<td>26.0</td>
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<td></td>
<td>• Exposure from 5 to 8 months after starting</td>
<td>628</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td>• Exposure from over 8 months after starting</td>
<td>584</td>
<td>22.9</td>
</tr>
<tr>
<td>C: only control two-month periods included before 4/10/2012 (specified in the protocol)</td>
<td>No delayed-effect symptomatic osteoarthritis treatment (reference**)</td>
<td>9135</td>
<td>23.8</td>
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<td></td>
<td>All exposure durations ***</td>
<td>2319</td>
<td>24.4</td>
</tr>
<tr>
<td></td>
<td>• Exposure from 0 to 4 months after starting</td>
<td>1107</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>• Exposure from 5 to 8 months after starting</td>
<td>628</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td>• Exposure from over 8 months after starting</td>
<td>584</td>
<td>22.9</td>
</tr>
</tbody>
</table>

* 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 (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 co-morbidities 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, leading to non-significant results concordant with those of primary analysis A and sensitivity analyses B and C:
- 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 = 1.03, 95% CI = [0.89-1.2]. 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 sub-group of patients who started treatment with FLEXEA 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:\textsuperscript{4}: OR = 0.93, 95% CI = [0.75-1.17]. 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), a secondary 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 3 two-month periods of FLEXEA exposure compared to the incident analysis: OR = 1.13, 95% CI = [0.96-1.33].

Furthermore, 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 use, without carry-over effect, of 1.8 (95% CI = [1.28-2.53]) in the case of prior NSAID consumption to the detriment of the group exposed to FLEXEA and 0.83 (95% CI = [0.61-1.13] 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 categorized by 0-4 / 5-10) and functional impairment (modified Lequesne algofunctional index - telephone version - categorized by the median of the observed distribution of modest or medium disability / significant, very significant or unbearable disability) are presented below:

\textsuperscript{4} The study protocol was amended on 23/09/2010 in order to change the exclusion criterion relating to patients taking slow-acting osteoarthritis medicines or who received a hyaluronic acid injection more than 3 months earlier.
Table 2: Association between all the exposure to FLEXEA ATUs and the pain ATUs (VAS ≥ 5) during follow-up

<table>
<thead>
<tr>
<th>Analysis A: control two-month periods included</th>
<th>Number of FLEXEA ATUs</th>
<th>% two-month period of pain (5-10) within ATUs.</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All exposure durations ***</td>
<td>2271</td>
<td>64.1</td>
<td>1.36 [1.16-1.58]</td>
</tr>
<tr>
<td>• 0 to 4 months after starting</td>
<td>1104</td>
<td>73.9</td>
<td>1.66 [1.37-2.01]</td>
</tr>
<tr>
<td>• 4 to 8 months after starting</td>
<td>610</td>
<td>58.2</td>
<td>0.96 [0.76-1.21]</td>
</tr>
<tr>
<td>• More than 8 months after starting</td>
<td>557</td>
<td>52.5</td>
<td>0.81 [0.61-1.07]</td>
</tr>
</tbody>
</table>

* 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 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 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 FLEXEA and the non-exposed groups.

CONCLUSION

The results of the PEGASE study presented, regardless of the choice of non-exposed group, are concordant and confirm that FLEXEA has no impact on 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.
- Analysis C, although specified in the protocol, is not the most relevant and the least biased methodological choice given the time lag between the non-exposed and exposed recruitment. 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 depending on 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 glucosamine 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 FLEXEA, like those of other delayed-effect osteoarthritis 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.

08.4 Summary & discussion

No new clinical data were provided regarding the safety and efficacy of FLEXEA.

In its opinion of 22 July 2009, 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 FLEXEA prescription in terms of reducing NSAID consumption.

The main results of the PEGASE study observed are:
- not taking prescribed FLEXEA by 17.3% of patients;
- an NSAID use rate of around 22% in the entire population with knee or hip osteoarthritis;
- no difference in terms of NSAID use frequency in the analysis time units (ATUs) for FLEXEA exposure and non-exposure to any delayed-effect symptomatic osteoarthritis treatment (24.4% versus 21.6%, OR = 1.09, 95% CI = [0.91-1.29] in analysis A, results reinforced in sensitivity analyses B and C).

These results lead to the conclusion that that there is no impact of medicinal products indicated in the symptomatic treatment of osteoarthritis, FLEXEA in particular, on NSAID use. Secondary analyses by subgroup and stratified analyses cannot be taken into consideration because of their exploratory nature.

As a result, FLEXEA has not been proven to contribute to reducing NSAID consumption in osteoarthritis patients.
09  **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, FLEXEA has no place in the treatment of mild to moderate osteoarthritis of the knee.

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 osteoarthritis of the knee is characterized by pain and functional disability that can become chronic. It may eventually require surgical treatment with a prosthesis implant.
- This proprietary 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 FLEXEA on reducing NSAID consumption. Consequently, the proprietary medicinal product FLEXEA 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 FLEXEA, are not very effective on pain and functional disability and it has not been proven that they reduce NSAID use. Consequently, FLEXEA has no role in the treatment of mild to moderate osteoarthritis of the knee.

*Taking account of these points, the Committee finds that the actual benefit of FLEXEA 625 mg, tablets 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 60) and on the list of medicines approved for hospital use (for the box of 60 and 180) in the indication "Relief of symptoms in mild to moderate osteoarthritis of the knee" and at the dosages in the marketing authorisation.