TRANSPARENCY COMMITTEE
Opinion
20 November 2013

DOLENIO 1178 mg, film-coated tablets
Box of 30 tablets (CIP: 34009 393 133 1)

DOLENIO 1178 mg, tablets in blister pack
Box of 30 tablets (CIP: 34009 496 655 0)

Applicant: BIOCODEX

<table>
<thead>
<tr>
<th>INN</th>
<th>Glucosamine (sulfate)</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 13 January 2010.</td>
</tr>
<tr>
<td>List(s) concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
</tr>
<tr>
<td></td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indication(s) concerned</td>
<td>&quot;Relief of symptoms in mild to moderate osteoarthritis of the knee. &quot;</td>
</tr>
<tr>
<td>Actual Benefit</td>
<td>Insufficient Actual Benefit</td>
</tr>
<tr>
<td>----------------</td>
<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, DOLENIO 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>19 March 2009 (mutual recognition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing and dispensing conditions / special status</td>
<td>List II</td>
</tr>
<tr>
<td>ATC Classification</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td>M Musculo-skeletal system</td>
</tr>
<tr>
<td></td>
<td>M01 Anti-inflammatory and anti-rheumatic drugs</td>
</tr>
<tr>
<td></td>
<td>M01A Non-steroidal anti-inflammatory and anti-rheumatic drugs</td>
</tr>
<tr>
<td></td>
<td>M01AX Other non-steroidal anti-rheumatic and anti-inflammatory drugs</td>
</tr>
<tr>
<td></td>
<td>M01AX05 glucosamine</td>
</tr>
</tbody>
</table>

02 BACKGROUND

During the application for inclusion on the national health insurance and hospital use lists for DOLENIO, 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 DOLENIO prescription in terms of reducing NSAID consumption (opinion of 13 January 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 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 DOLENIO, after the 2-year period set, on the basis of the results from a 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

"Dosage: 1 tablet daily. 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."
**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. The risk/benefit ratio for diacerein was deemed unfavourable by the MA Committee (July 2012). 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 currently 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>
</tr>
</thead>
<tbody>
<tr>
<td>Glucosamine (hydrochloride)</td>
<td>FLEXEA 625 mg</td>
<td>Expanscience</td>
<td>tablet</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>22 July 2009</td>
<td></td>
</tr>
<tr>
<td></td>
<td>STRUCTOFLEX 625 mg</td>
<td>Pierre Fabre Medicament</td>
<td>hard capsule</td>
<td></td>
<td></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>yes</td>
</tr>
<tr>
<td>CHONDROSULF 400 mg</td>
<td>Genévrier</td>
<td>hard capsule and oral granulate for solution in sachet</td>
<td></td>
<td></td>
<td></td>
<td>09 January 2013</td>
<td></td>
</tr>
<tr>
<td>Diacerein</td>
<td>ART 50 mg</td>
<td>Negma-Lerads</td>
<td>hard capsule</td>
<td>Delayed-effect symptomatic treatment of hip and knee osteoarthritis.</td>
<td>Insufficient</td>
<td>09 January 2013</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ZONDAR 50 mg</td>
<td>Pharma 2000</td>
<td>hard capsule</td>
<td></td>
<td></td>
<td>09 January 2013</td>
<td></td>
</tr>
<tr>
<td>PIASCLEDINE 300 mg</td>
<td>Expanscience</td>
<td>hard capsule</td>
<td></td>
<td></td>
<td></td>
<td>09 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.
DOLENIO has a marketing authorisation in the following European countries: Belgium, Denmark, Germany, Spain, Ireland, Italy, Netherlands, Portugal, Bulgaria, Iceland, Romania, Estonia, Latvia, Cyprus, Czech Republic, Hungary and Austria. The status for reimbursement by national insurance systems for DOLENIO in these countries was not provided.

**Summary of Previous Assessments**

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th>13 January 2010 (inclusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>&quot;Relief of symptoms in mild to moderate osteoarthritis of the knee.&quot;</td>
</tr>
</tbody>
</table>
| **AB**          | 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 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, DOLENIO 1178 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 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 DOLENIO 1178 mg, film-coated tablet, is low. |
| Improvement in Actual Benefit | DOLENIO 1178 mg, film-coated 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 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 DOLENIO 1178 mg 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 not provided any new safety data.

09.3 Usage/prescription data

Observational study: INDIGO Observational 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, 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 VOLTALEX. 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 this Transparency Committee request dated on 13 January 2010, BIOCODEX presented interim results of an observational study (INDIGO) conducted from October 2012 and still underway at the time of this opinion. The interim report of this observational study focuses on data collected and analysed between 17/10/2012 and 30/04/2013. The final results of this study should be available in June 2014.

INDIGO is a prospective observational study whose primary objective is to measure the impact of initiating treatment with DOLENIO on NSAID consumption in osteoarthritis patients. The secondary objectives of the study are to describe the conditions for using DOLENIO, evaluate the impact of treatment on analgesic and PPI consumption and the impact of treatment on pain and functional impairment of treated patients during follow-up.

This study, which started enrolling in February 2013, was conducted with a sample of community pharmacists in metropolitan France interested and trained to participate in pharmaco-epidemiological studies and members of the In fine PHARMA network as well as those identified by BIOCODEX from sales files.

This cohort is made up of all patients regularly frequenting the pharmacy (with their treatment prescription history available for the past 6 months) and coming to the pharmacy with a first prescription for DOLENIO for their own use and who received at least one NSAID prescription within 6 months prior to their inclusion. They were included after receiving a first DOLENIO prescription.
Patients on delayed-effect symptomatic treatment for osteoarthritis or who received an intra-articular injection of corticosteroid or hyaluronic acid within the previous 3 months, or who had had joint surgery which has been affected by osteoarthritis within the previous 6 months were not included.

The follow-up period was conducted for 6 months after inclusion or until loss to follow-up, death or withdrawal from the study.

Data were collected from pharmacists as soon as the patient came to the pharmacy to fill a prescription for medicines indicated in the symptomatic treatment of arthritis, analgesics or PPIs, as well as from patients interviewed by telephone in the week following inclusion, then every month during the follow-up period.

The history of filled prescriptions for osteoarthritis medicines is collected by the pharmacist for a period of 6 months and for other treatments for a period of 3 months from the participating pharmacy's prescription software and a case report form given to the pharmacist (collecting information on medicines dispensed over-the-counter or from another pharmacy). Furthermore, after being given a diary for recording consumption, patients were asked about their drug consumption, especially NSAIDS, analgesics, other osteoarthritis drugs and PPIs as well as glucosamine-based dietary supplements.

Analysis was done on all the data meeting the inclusion and non-inclusion criteria and for which the participating pharmacist had filled out an inclusion case report form.

The main analysis sought to compare the mean quantity of NSAIDS dispensed expressed as the defined daily dose (DDD) between a period of 3 months prior to inclusion and the period comprised between the third and sixth month after starting DOLENIO. This analysis is based on data from the prescription history printed out by the pharmacist.

The mean patient-reported NSAID quantity consumed was also analysed.

Analyses of sensitivity comparing different periods were conducted in order to consider the cyclic progression of the disease.

Secondary analyses compared the impact of DOLENIO treatment on pain (measured by a simple numerical scale from 0 to 10) and on the extent of impairment during activities of daily living (measured by the Lickert scale) and compared the mean quantities of analgesic and PPIs dispensed in the 3 months prior to inclusion and between the third and sixth month after starting DOLENIO.

In all, 650 patients were planned to detect a 15% difference in NSAID quantity dispensed (or an RR = 0.85, power 80%, 95% confidence and expected loss to follow-up of 15% in the six-month follow-up).

Description of the INDIGO observational study:

On 30 April 2013 (date the database was frozen), of the 2023 pharmacists contacted, 349 had agreed to participate in the study, 196 received a set-up visit and 43 included at least one patient.

The number of active pharmacists on the date of this report is low because of the still recent set up in community pharmacies and difficulties in recruiting explained by the low sales volume of DOLENIO.

Out of the 86 patients identified by the pharmacists who came to the participating community pharmacies to fill a first DOLENIO prescription, a total of 35 patients were considered to be eligible.

---

1 Unit of measurement defined by WHO, as the assumed average maintenance dose, per day, for a medicinal product, used in its main indication in adults. [http://www.whocc.no/atc_ddd_index/](http://www.whocc.no/atc_ddd_index/)
However, among them, only 24 patients strictly meeting the inclusion and non-inclusion criteria were included. Reasons for non-inclusion were the following: no NSAID prescription filled in the 3 months prior to inclusion (n=4 patients), treatment by another medicine with an indication similar to DOLENIO within 3 months prior to inclusion (n=5) and infiltration within the previous 6 months (n=2) and no history of prescriptions filled in the pharmacy (n=1).

The main characteristics of patients at inclusion (N=24) were the following:
- the patients were predominantly women (19/24);
- the median age on inclusion was 60.00 years [extremes: 46 - 82];
- the majority of them were either retired (8/24) or active (5/24) at inclusion in the study;
- the median body mass index was 24.35 [extremes: 19 - 36];
- among the 15 patients who provided information on the location of the arthritis, the majority reported the knee as the main joint affected by arthritis (11/15) and also reported at least one other secondary arthritis location;
- the median delay between the onset of osteoarthritis reported by the patient and prescription of DOLENIO was 21 months [extremes: 2 - 343];
- the median pain score reported by the patient for the month of inclusion (score from 0 to 10) was 6.5 [extremes: 0 - 9];
- discomfort in activities of daily living due to osteoarthritis was expressed by 16 patients, 7 of whom reported it to be "extremely uncomfortable" or "very uncomfortable", 5 "moderately uncomfortable" and 4 "a little uncomfortable" or "not at all uncomfortable";

The main co-morbidities of patients at inclusion were not described.

On the date of the interim report, four patients had conducted one follow-up visit, one patient had conducted two follow-up visits and one patient had conducted three follow-up visits. The cohort follow-up is therefore too limited to allow analysing the follow-up data.

RESULTS

At this stage of the interim report, only inclusion data could be described, since no patient had reached the end of the planned six-month follow-up period.

Results regarding NSAID consumption:

- Main analysis and sensitivity

On 30 April 2013, the results on changes in NSAID consumption during the follow-up were not available.
Secondary analyses

Description of the conditions for prescribing DOLENIO at inclusion:
Out of the 23 DOLENIO prescriptions analysed, the prescribing physician was a general practitioner in 15 cases, a rheumatologist in 7 cases and a general homeopath in one case. The dosage prescribed was 1 tablet per day. The median duration of treatment prescribed, including any refills, was 2.96 months [extremes 1-6 months]. For 12 patients, DOLENIO was prescribed in combination with other osteoarthritis treatments: NSAID (n=9 patients), PPI (n=5), analgesics (n=5) and one other delayed-action symptomatic treatment (n=1).

Results regarding pain and functional status:
On 30 April 2013, the results of the secondary analysis on pain progression (simple numerical scale with a score of 0 to 10) and extent of discomfort in activities of daily living (measured by the Lickert Scale: "extremely uncomfortable", "very uncomfortable", "moderately uncomfortable", "a little uncomfortable" or "not at all uncomfortable") reported by patients were not available.

Results regarding analgesic and PPI consumption:
On 30 April 2013, the results of the secondary analyses on the changes in analgesic and PPI consumption were not available.

CONCLUSION
The Committee made inclusion of DOLENIO on the list of reimbursed products dependent on conducting a study within two years showing the impact of DOLENIO in terms of reducing NSAID consumption. At the deadline, the company had not submitted the requested data. Furthermore, the Committee has serious doubts regarding the possibility that this observational study would reach its goal of including 650 patients in six months as only 24 patients could be included during a three-month inclusion period. Pharmacy participation is also far below the target set.

As a result, at this time, DOLENIO has not been proven to contribute to reducing NSAID consumption in osteoarthritis patients.

09.4 Summary & discussion
No new clinical data were provided regarding the safety and efficacy of DOLENIO. In its opinion of 13 January 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 DOLENIO prescription in terms of reducing NSAID consumption.

At the interim report stage for the INDIGO observational study, only 24 patients have been included. The feasibility of the study is very uncertain at this stage in view of the actual inclusions over a three month period.

The cohort follow-up is therefore too limited at this stage of the interim report to allow analysing the follow-up data.

The results on changes in NSAID consumption are not available.

As a result, DOLENIO 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, DOLENIO 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 knee arthritis 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 interim results of the INDIGO study still do not confirm the impact of DOLENIO on reducing NSAID consumption.
    - Consequently, DOLENIO 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 DOLENIO, are not very effective on pain and functional disability and it has not been proven that they reduce NSAID use. Consequently, DOLENIO 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 DOLENIO 1178 mg, tablet, 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 and on the list of medicines approved for hospital use in the indication "Relief of symptoms in mild to moderate osteoarthritis of the knee" and at the dosages in the Marketing Authorisation.