HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion
20 November 2013

VOLTAFLEX 625 mg, film-coated tablet
B/60 tablets (CIP: 34009 384 573 2)

Applicant: NOVARTIS SANTÉ FAMILIALE S.A.S.

INN	Glucosamine (hydrochloride)
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)
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 study demonstrating an impact in terms of reduced consumption of NSAIDs on the other hand, VOLTAFLEX has no place in the treatment of mild to moderate osteoarthritis of the knee.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	14 March 2008 (mutual recognition)
Prescribing and dispensing conditions / special status	Not subject to medical prescription
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 VOLTAFLEX, 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 VOLTAFLEX 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 VOLTAFLEX, after the 2-year period set, on the basis of 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

“2 tablets (1250 mg of glucosamine) once daily for relief of symptoms. Glucosamine is not indicted for 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 glucosamine should be re-assessed.
The tablets may be taken with or without food.

Additional information for special populations

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 and/or hepatic impairment

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

Children and adolescents

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

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 have no therapeutic use at this time.

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

6.1 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	
Glucosamine (sulfate)	**OSAFLEXAN 1178 mg**	Rottapharm S.A.R.L.	oral powder for solution in single-dose sachets			10 March 2010	
	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	

6.2 Other health technologies

Not applicable

Conclusion

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

07 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for request)	10 March 2010 (inclusion)
Indication	"Relief of symptoms in mild to moderate osteoarthritis of the knee."
AB (wording)	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, VOLTAFLEX 625 mg is not expected to benefit public health. 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 VOLTAFLEX 625 mg, tablet, is low.
Improvement in Actual Benefit (wording)	VOLTAFLEX 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 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 VOLTAFLEX prescription in terms of reduced NSAID consumption**.

08 ANALYSIS OF AVAILABLE DATA

8.1 Efficacy

The company has not provided any new clinical efficacy data.

8.2 Safety/Adverse effects

The company has not provided any new safety data.

8.3 Usage/prescription data

The company has not provided the results of the study requested by the Transparency Committee that aimed to show that VOLTAFLEX reduced NSAID consumption.

8.4 Summary & discussion

No new efficacy or safety data have been provided.

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 VOLTAFLEX prescription in terms of reducing NSAID consumption.
No data have been provided by the company. As a result, VOLTAFLEX 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 study demonstrating an impact in terms of reduced consumption of NSAIDs on the other hand, VOLTAFLEX 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 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.
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 dated on 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.
No data show such an impact for VOLTAFLEX.
Consequently, VOLTAFLEX 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 VOLTAFLEX, are not very effective on osteoarthritis symptoms and it has not been proven that they reduce NSAID use. Consequently, VOLTAFLEX 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 VOLTAFLEX 625 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 in the indication "Relief of symptoms in mild to moderate osteoarthritis of the knee" and at the dosages in the Marketing Authorisation.