HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

22 July 2009

ENDOSTA 625 mg, tablet
Box of 60 (CIP: 380 534-2)
Box of 180 (CIP: 380 535-9)

Applicant: EXPANSCIENCE

Glucosamine (hydrochloride)

ATC Code: M01AX05

List I

Date of Marketing Authorisation: 12 July 2007 (mutual recognition)
Amendment to marketing authorisation: prescription conditions in list II (date awaited)

Reason for request: Inclusion on the list of medicinal products reimbursed by National Insurance and approved for use in hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Glucosamine (hydrochloride)

1.2. Indication

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

1.3. Dosage

"1250 mg 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-evaluated.

Tablets can be taken with or without food.

Additional information on special populations

Children and adolescents

ENDOSTA is not recommended for use in children and adolescents below the age of 18, due to lack of data on safety and efficacy.

Elderly

No specific studies have been performed in the elderly, but according to clinical experience dosage adjustment is not required when treating otherwise healthy, elderly patients.

Impaired renal and/or liver function

In patients with impaired renal and/or liver function no dose recommendations can be given, since no studies have been performed."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

M	Musculo-skeletal system
M01	Antiinflammatory and antirheumatic products
M01A	Antiinflammatory and antirheumatic products, non-steroids
M01AX	Other antiinflammatory and antirheumatic products, non-steroids
M01AX05	Glucosamine

2.2. Medicines in the same therapeutic category

Other symptomatic slow-acting drugs in osteoarthritis (SySADOA):

Active substance	Proprietary product	Presentation	Indication
Chondroitin (sulfate)	CHONDROSULF 400 mg	capsules and granules for oral solution in sachet:	Symptomatic slow-acting treatment of hip and knee osteoarthritis
Chondroitin (sodium sulfate)	STRUCTUM 500 mg	capsule	Adjuvant treatment of arthritic pain
Diacerein	ART 50 mg	capsule	Symptomatic slow-acting treatment of hip and knee osteoarthritis
Diacerein	ZONDAR 50 mg	capsule	Symptomatic slow-acting treatment of hip and knee osteoarthritis
Avocado oil and soya bean oil unsaponifiables	PIASCLEDINE 300 mg	capsule	Symptomatic slow-acting treatment of hip and knee osteoarthritis

2.3. Medicines with a similar therapeutic aim

Other drug treatments for osteoarthritis: analgesics, oral and topical NSAIDs, intra-articular corticosteroids, hyaluronic acid (as a medicinal product or medical device) by intra-articular injection.

3 ANALYSIS OF AVAILABLE DATA

The applicant has provided clinical data concerning the efficacy and safety of glucosamine, which were selected from a literature review. A total of 39 studies were selected, including:

- 15 placebo-controlled clinical studies, one of which also including a comparison vs paracetamol.
- 2 open-label clinical studies
- 6 meta-analyses
- 8 publications relating other clinical data
- 4 publications relating to post-marketing experience

The selected studies, with the exception of the meta-analyses, only involved pharmaceutical-grade glucosamine as sulfate or hydrochloride salts. The equivalence between the sulfate and hydrochloride salts has been evidenced in pharmacokinetic studies and in one open-label clinical study (Qiu 2005; see CHMP conclusions in response to submissions concerning the risk/benefit ratio of glucosamine)

3.1. Efficacy

3.1.1. Efficacy versus placebo

The following will be described below:

- the most recent studies (randomised, double-blind, 6 months treatment duration), which were not included in the marketing authorisation dossier: Herrero-Beaumont (2005) and Clegg (2006)
- the most relevant older studies, owing to their methodology quality and to their duration (6 months and 3 years): Pavelka (2002) and Reginster (2001)
- the meta-analysis by Towheed (2005) which is the most recent and the most comprehensive.

The other studies are summarised in appended tables (annex 1)

Herrero-Beaumont (2007)[1] study:
Randomised double-blind 6-month study using the double dummy technique, comparing glucosamine (sulfate, 1 x 1500 mg/day) with placebo and paracetamol (3 x 1 g/day) in 318 patients with primary symptomatic osteoarthritis of one or both knees, meeting the ACR criteria and with grade II or III disease severity according to the Kellgren/Lawrence classification.

The primary endpoint was the change in the Lequesne algofunctional index[2] (score range between 0 and 24) after 6 months of treatment.

Results:
The patients included had a mean age of 64 years. The vast majority were women (over 85%). Knee osteoarthritis was grade II in 52% of cases, grade III in 37% of cases and of unspecified grade in 11% of cases.

[1] Herrero-Beaumont *et al*. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. Arthritis Rheum. 2007 Feb;56(2):555-67.

[2] The Lequesne algofunctional index is expressed as a sum of scores relating to pain, maximum walking distance and activities of daily living, which allows for assessing disease progression and discomfort suffered by the patient. It is a scale from 0 to 24.

The mean intensity of Lequesne index was around 11 at the time of inclusion, and the intensity of pain, evaluated following a 0-100 standardisation of the WOMAC pain subscale was around 40. The treatment groups were comparable.

After 6 months of treatment, glucosamine was superior to placebo in terms of reduction in Lequesne index, with a statistically significant difference of -1.2 (p=0.032). No statistically significant difference was observed between paracetamol and placebo (see table 1).

Table 1: Change in Lequesne index (ITT population) - Herrero-Beaumont (2007):

	Glucosamine	**Placebo**	**Paracetamol**
n	106	104	108
Change at 6 months 95% CI	-3.1 [-3.8; -2.3]	-1.9 [-2.6; -1.2]	-2.7 [-3.3; -2.1]
p (difference versus placebo)	0.032	-	0.18

The effect size associated with these changes in Lequesne index was evaluated according to the Cohen method[3]

The effect size was: d = 0.32 (95% CI = [0.05; 0.57]) for glucosamine (ITT population)
d = 0.23 (95% CI = [0.04; 0.50]) for paracetamol (ITT population)

These effects can be considered to be small.

Clegg (2006)[4] study: GAIT (glucosamine/chondroitin Arthritis Intervention Trial)

Randomised double-blind 6-month study, controlled by placebo and celecoxib (200 mg/day), comparing glucosamine (hydrochloride, 1500 mg/day) with chondroitin (sulfate, 1200 mg/day) and with a combination of glucosamine + chondroitin in 1583 patients with symptomatic osteoarthritis of the knee.

Patients had to have osteoarthritis grade II or III on the Kellgren-Lawrence classification, American Rheumatism Association functional class I, II or III and a score between 125 and 400 on the WOMAC pain subscale.

The primary endpoint was the percentage of patients with a 20% reduction in WOMAC pain score after 24 weeks of treatment.

Results:

The patients included had a mean age of 58.6 years. The majority were women (64.1%).

58% of patients were in ARA functional class II, with 25% being in class I and 17% in class III.

55% of patients had osteoarthritis grade II on the Kellgren/Lawrence classification. Mean WOMAC pain score on inclusion was 236.

The treatment groups were comparable.

After 24 weeks of treatment, no statistically significant difference vs placebo was observed in the glucosamine, chondroitin or glucosamine/chondroitin combination arms. Celecoxib, the active comparator arm, was superior to placebo (see table 2). Comparisons were only made with placebo.

[3] Cohen J (1988). Statistical power analysis for behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

"Effect size" (d)	**Interpretation**
0.2 – 0.5	Small effect
0.5 – 0.8	Medium effect
> 0.8	Large effect

[4] Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, *et al.* Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006;354(8):795-808.

Table 2: Percentage of patients with a 20% reduction in WOMAC pain score after 24 weeks (responders, ITT analysis) - study by Clegg (2006)

	Placebo	Glucosamine	Chondroitin	Glucosamine + chondroitin	Celecoxib
n	313	317	318	317	318
% responders	60.1	64.0	65.4	66.6	70.1
p		0.30	0.17	0.09	0.008

The authors note that the absence of difference between placebo and glucosamine, chondroitin and a combination of both active substances could be explained by the significant treatment effect in the placebo arm (60.1% responded) which could be linked to the inclusion of a large number of patients who had few symptoms.

Pavelka (2002)[5] study:
Randomised double-blind 3-year study, comparing glucosamine (sulfate, 1 x 1500 mg/day) with placebo in 202 patients with symptomatic primary uni- or bilateral femorotibial osteoarthritis of the medial compartment, meeting the ACR criteria, with grade II or III disease severity according to the Kellgren/Lawrence classification, and with Lequesne index between 4 and 12. Rescue analgesic treatment (paracetamol) was allowed if required, and had to be recorded.

Only outcomes in terms of change in clinical symptoms will be presented below, of indicative value (secondary endpoint), as the study's primary endpoint (measurement of joint space) does not correspond to a valid indication in the marketing authorisation. The effect on symptoms was evaluated using change in Lequesne index and total WOMAC score.

Results:
The patients included had a mean age of 62 years. The vast majority were women (77.5%). Knee osteoarthritis was grade II in 53.5% of cases and grade III in 46.5% of cases.
At the time of inclusion, the mean Lequesne index was 8.95 for the whole study patients, and the intensity of pain, evaluated after a 0 to 100 standardisation of WOMAC pain subscale, was around 30. The treatment groups were comparable.

After 3 years of treatment, in the ITT population, glucosamine was superior to placebo with respect to the Lequesne index and total WOMAC index (the difference was statistically significant, see table 3). A statistically significant difference, favouring glucosamine, was also observed for the WOMAC pain, functional and stiffness subscores.

The effect size associated with changes in Lequesne index and WOMAC score in glucosamine-treated patients was evaluated using the Cohen method:
The effect size was: d = 0.37 for Lequesne index (ITT population)
d = 0.20 for WOMAC index (ITT population)
These effects can be considered to be small.

[5]Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2002;162(18):2113-23.

Table 3: Changes in Lequesne index and WOMAC score after 3 years of treatment (ITT) - Pavelka (2002):

	Glucosamine	Placebo	Difference	p
n	101	101		
Change.* Lequesne index	-1.7	-0.82	-0.91	0.002
95% CI	[-2.2; -1.2]	[-1.1; -0.51]	[-1.5; -0.34]	
Change.* standardised total WOMAC	-8.0	-4.9	-3.1	0.01
95% CI	[-9.8; -6.3]	[-6.5; -3.2]	[-5.5; -0.77]	

*: change expressed as number of points

Reginster (2001)[6] study:

Randomised double-blind 3-year study, comparing glucosamine (sulfate, 1 x 1500 mg/day) with placebo in 212 patients with symptomatic primary medial femorotibial osteoarthritis of one or both knees, meeting the ACR criteria and with grade II or III disease according to the Kellgren/Lawrence classification. Rescue analgesic (paracetamol) or NSAID (diclofenac, piroxicam or proglumetacin) treatment was allowed if required, and had to be recorded.

Outcomes in terms of change in clinical symptoms will be presented below of indicative value only (secondary endpoint), as the study's primary endpoint (measurement of joint space) does not correspond to a valid indication in the marketing authorisation. The efficacy in relief of symptoms was evaluated using % change in total WOMAC index, as well as the pain, functional and stiffness subscores.

Results:

The patients included had a mean age of 65 years. The vast majority were women (76.5%). Knee osteoarthritis was grade II in 70% of cases and grade III in 30% of cases.

Pain intensity, evaluated using the WOMAC pain score, was 939.7 in the placebo arm and 1030.2 in the glucosamine arm. The characteristics of each arm were comparable.

After 3 years of treatment, in the ITT population, total WOMAC index worsened in the placebo arm, while it improved in the glucosamine arm (see table 4). The difference observed between glucosamine and placebo was statistically significant. The effect was also statistically significant when considering the population of patients still present in the study after 3 years (PP population).

With regard to the WOMAC index subscales, glucosamine was superior to placebo in relieving pain and function but not stiffness.

No between-group statistically significant difference was observed in terms of consumption of rescue analgesics and NSAIDs.

Table 4: Change in total WOMAC index after 3 years of treatment - Reginster (2001):

	Glucosamine	Placebo	Difference	p
ITT Population				
n	106	104		
total WOMAC Change (%)	-11.70	+9.80	-21.60	0.020
95% CI	[-20.30; -3.20]	[-6.20; +25.80]	[-39.60; -3.50]	
PP population (population present at 3 years)				
n	68	71		
total WOMAC Change (%)	-24.30	+9.80	-34.10	0.016
95% CI	[-37.00; -11.60]	[-14.60; +34.30]	[-61.80; -6.40]	

[6] Reginster *et al*. Long-tem effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001;357(9252):251-6.

The effect size associated with the change in Lequesne index was evaluated according to the Cohen method. It was 0.25 for glucosamine in the ITT population, i.e. an effect that can be considered of slight clinical relevance.

Meta-analysis by Towheed (2005)[7]:

The aim of this meta-analysis was to analyse all randomised, controlled, blinded (single and double blind were accepted) studies versus placebo or an active comparator, that have evaluated the efficacy and toxicity of glucosamine (of pharmaceutical or food grade) in the treatment of osteoarthritis.

Twenty randomised double-blind studies, published between 1980 and 2004 (including 8 published between 2000 and 2004) were included in the meta-analysis.

Patients included:

These studies included a total of 2596 patients with a mean age of 61.1 years, the majority of whom were women (67%).

Patients had osteoarthritis in various sites (knee, hip, other), in single or multiple locations.

Duration of studies:

The duration of studies was variable (3 to 24 weeks, and 2 3-year studies) and many were short (13/20 studies lasted ≤ 8 weeks).

Comparators:

Of the 20 studies that were included, 17 compared glucosamine, given as the sulfate salt (16 studies) or as the hydrochloride salt (1 study) with placebo and 4 with an NSAID (ibuprofen or piroxicam).

One study compared glucosamine with both placebo and a NSAID.

A total of 1182 patients were treated with glucosamine and 1414 took a placebo or were treated with an active comparator.

Route of administration and dosage of glucosamine:

The glucosamine route of administration varied greatly between studies:

- oral treatment only in 16 studies
- intra-articular administration (IA) in 2 studies
- intra-muscular administration (IM) in 3 studies
- intravenous administration (IV) in 1 study
- multiple routes (IM or IA and IM or IV) in 2 studies

For oral treatment, the dosage was 1500 mg once daily (4 studies) or 500 mg 3 times daily (12 studies).

For parenteral treatment, the dosage was 400 mg given once daily (2 studies) or twice weekly (1 study).

Assessment endpoints:

Evaluation criteria also varied according to the study:

- pain
- mobility
- functional status
- overall condition evaluated by the patient
- overall condition evaluated by the investigator

No study evaluated quality of life.

Evaluations were done using WOMAC and Lequesne indices or scoring scales (0-3 or 0-4).

[7]Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Well G. Glucosamine therapy for treating osteoarthritis. (Update of: Cochrane Database Syst Rev. 2001;(1):CD002946). Cochrane Database Syst Rev. 2005;(2):CD002946.

Main results relating to the glucosamine vs placebo comparison:
Glucosamine (pharmaceutical and food grade) was noted to be superior to placebo, with the difference being statistically significant, on the pain criterion (all evaluation methods combined) and on Lequesne index (see table 5). However, it should be noted that the heterogeneity test was significant for both comparisons.

No statistically significant difference was observed between glucosamine and placebo in terms of total WOMAC index as well as the pain, function and stiffness subscales in the whole randomised studies or in those studies with adequate allocation concealment.

When the analysis was carried out on studies using pharmaceutical grade glucosamine (see table 6), glucosamine was superior to placebo in terms of pain (all evaluation methods combined), Lequesne index and total WOMAC score. The heterogeneity test was statistically significant for the first two criteria.
No statistically significant difference was demonstrated for the WOMAC pain, stiffness and function subscores.

Table 5: Comparison of glucosamine (pharmaceutical and food grade) versus placebo - Towheed (2005)

	Glucosamine versus placebo					
Endpoint	**Number of studies**	**Statistical method**	**Effect size**	95% CI	**P****	**Heterogeneity test**
Pain*	15	SMD	-0.61	[-0.95; -0.28]	0.0003	<0.0001
Lequesne index: score	4	SMD	-0.51	[-0.96; -0.05]	0.03	<0.0001
Total WOMAC score	5	SMD	-0.15	[-0.30; 0.00]	NS	NS
WOMAC pain	7	SMD	- 0.04	[-0.17; 0.20]	NS	NS
WOMAC stiffness	5	SMD	-0.06	[-0.23; 0.11]	NS	NS
WOMAC function	6	SMD	-0.07	[-0.21; 0.08]	NS	NS

*: all evaluation methods combined
**: overall effect
SMD: standardised mean difference

Table 6: Comparison of glucosamine (pharmaceutical grade) versus placebo - Towheed (2005)

	Glucosamine versus placebo					
Endpoint	**Number of studies**	**Statistical method**	**Effect size**	95% CI	**P****	**Heterogeneity test**
Pain*	7	SMD	-1.31	[-1.99; -0.64]	0.0001	<0.0001
Lequesne index: score	4	SMD	-0.51	[-0.96; -0.05]	0.030	<0.0001
Total WOMAC score	2	SMD	-0.23	[-0.42; -0.03]	0.020	NS
WOMAC pain	2	SMD	- 0.10	[-0.29; 0.09]	NS	NS
WOMAC stiffness	1	SMD	-0.22	[-0.50; 0.06]	NS	-
WOMAC function	2	SMD	-0.14	[-0.21; 0.08]	NS	NS

*: all evaluation methods combined

**: overall effect

SMD: standardised mean difference

Conclusion of the meta-analysis:
Glucosamine was observed to have an effect in comparison to placebo, on pain and Lequesne index. However, these results must be interpreted with care, given the lack of homogeneity of these studies, particularly in terms of:

- criteria and scoring scales used, with a small number of studies analysed for each criterion, particularly when looking at studies involving pharmaceutical-grade glucosamine;
- inclusion criteria varying according to the study: diagnostic criteria, severity and location of the osteoarthritis;
- use of glucosamine of food or pharmaceutical grade ; results relating to pharmaceutical-grade glucosamine provide only a small number of studies for each criterion being examined;
- the varied routes of administration (PO, IM, IV, IA);
- the variable treatment duration (3 - 24 weeks and 3 years) and many were short (13/20 studies lasted ≤ 8 weeks).

No significant and clinically relevant difference was observed in terms of total WOMAC index or the pain, function or stiffness subscales

3.1.2. Efficacy versus other slow acting drugs in osteoarthritis

Clegg (2006) study: GAIT (glucosamine/chondroitin Arthritis Intervention Trial)
See study outlined in § 3.1.1.

3.1.3. Efficacy versus paracetamol

In the study by Herrero-Beaumont (2007), which was described above, glucosamine was compared with placebo. The study also included a paracetamol control arm; however, no significant difference was observed between paracetamol and placebo in terms of change in Lequesne index after 6 months of treatment. Statistical analysis comparing glucosamine with paracetamol was not planned in the protocol.

3.1.4. Efficacy versus NSAID

Efficacy of glucosamine versus NSAID was evaluated in 4 studies (see table 7), which were included in the meta-analysis by Towheed (2005).

Table 7: Description of studies comparing glucosamine with NSAIDs

Study	No. of patients: Inclusion criteria	Duration of treatment	Glucosamine	Comparator	Endpoints
Qiu (1998) China	N = 178 28 - 78 years symptomatic osteoarthritis	4 weeks	1500 mg/day, 3 doses/day Oral route	Ibuprofen: 1200 mg/day, 3 doses/day Oral route double dummy	Composite pain score: sum of scores at rest, on movement and with pressure, each scored 0 - 3. Joint swelling, rate of improvement/failure
Lopes Vaz (1982) Portugal	N = 40 48 - 68 years symptomatic osteoarthritis of one knee, uncomplicated	8 weeks	1500 mg/day, 3 doses/day Oral route	Ibuprofen: 1200 mg/day, 3 doses/day Oral route	Pain (score from 0 to 3) Joint swelling Overall assessment
Muller-Fassbender (1994) Germany	n = 200 > 18 years symptomatic osteoarthritis of the knee (Lequesne signs)	4 weeks	1500 mg/day, 3 doses/day Oral route	Ibuprofen: 1200 mg/day, 3 doses/day Oral route	% responders: reduction of 1 or 2 points in Lequesne index Change in Lequesne index

Rovati (1997) Unpublished	N = 319 45-85 years Primary osteoarthritis of the knee	12 weeks	1500 mg/day Oral route	Piroxicam: 20 mg/day Combination of glucosamine/piroxicam	Lequesne index Pain (VAS)

Results of the meta-analysis:

For the pain criterion (all evaluation methods combined), glucosamine was superior to NSAIDs with an effect size of 0.40 ($_{95\%}$CI = [-0.60; -0.19]), which can be considered to be " small" according to the Cohen method (see table 8).

No significant difference in Lequesne index was observed. However, in this analysis which involved 2 of the 4 studies, the heterogeneity test was significant (see table 9).

Table 8: Results of studies comparing glucosamine to NSAIDs in the treatment of pain (all evaluation methods combined)

Study	Pain criterion	Glucosamine		NSAID		Height effect	95% CI
		N	Mean (SD)	N	Mean (SD)		
Qiu 1998	Score between 0 and 9	87	3.60 (3.09)	81	4.18 (2.76)	-0.20	[-0.50; 0.11]
Rovati 1997	VAS	79	24.30 (19.30)	77	35.70 (22.40)	-0.54	[-0.86; -0.20]
Lopes Vaz 1982	Score between 0 and 3	18	0.80 (0.50)	20	1.20 (0.60)	-0.71	[-1.36; -0.5]
Total		**184**		**178**		**-0.40**	**[-0.60; -0.19]**
Heterogeneity: NS							
Overall effect: 0.0002							

Note: Results in terms of pain do not appear to be very reliable, in that 3 different scales were used to evaluate pain intensity in the 3 studies. The 100 mm VAS that is usually used in studies of osteoarthritis drugs was used in just one study.

Table 9: Results of studies comparing glucosamine to NSAIDs in terms of Lequesne index

Study	Glucosamine		NSAID		Effect size	95% CI
	N	Mean (SD)	N	Mean (SD)		
Muller-Fassbender 1994	94	9.60 (5.80)	95	9.60 (5.80)	0.00	[-0.29; 0.29]
Rovati 1997	79	5.50 (2.80)	77	7.90 (3.70)	-0.73	[-1.05; -0.40]
Total	**173**		**172**		**-0.36**	**[-1.07; 0.35]**
Heterogeneity: 0.0009						
Overall effect: NS						

3.2. Adverse effects

3.2.1. Data from clinical studies

In the studies by Herrero-Beaumont (2007), Clegg (2006) and Pavelka (2002), the safety of glucosamine was no different to that of placebo.
Glucid metabolism was not significantly modified.

Likewise, in the meta-analysis by Towheed (2005), no difference was demonstrated between glucosamine and placebo in terms of safety. Only 4% of patients on glucosamine and 5% of patients on placebo left the study because of toxicity.

3.2.2. Pharmacovigilance data

Glucosamine is widely used, either as a pharmaceutical-grade medicinal product or in the form of food supplements. The number of prescriptions is estimated at around 10 million per year. In the period 4 August 2005 to 4 August 2007, glucosamine was not subject to any specific alerts, according to pharmacovigilance data from Sweden, Denmark and Iceland.

However, the Medicines and Healthcare products Regulatory Agency (MHRA, the British pharmacovigilance body) has recorded, among 55 cases of adverse effects observed over a 10-year period, 2 cases of hepatitis and 1 case of abnormal liver function tests involving glucosamine and 2 cases of abnormal liver function tests involving a combination of chondroitin and glucosamine. Five other cases, 3 in Britain and 1 in France, have been published, and 1 British case has been reported by the Food Standard Agency. All of these 11 cases, one of which had a fatal outcome, were examined by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (United Kingdom). This body concluded that "Current evidence does not suggest that glucosamine is likely to be a cause of hepatitis although a causal link cannot be completely excluded. It should be noted, however, that the likelihood of an individual user of glucosamine experiencing adverse effects is, at most, very low."

3.2.3. SmPC:

The most common adverse events associated with glucosamine treatment are nausea, abdominal pain, indigestion, constipation, and diarrhoea. In addition, headache, tiredness, rash, itching, and flushing have been reported. Those effects are usually mild and transitory.

3.3. Conclusion

In the recent studies, lasting 6 months and involving patients with symptomatic osteoarthritis of the knee (grade II-III on the Kellgren/Lawrence classification), glucosamine caused a modest improvement in Lequesne index and total WOMAC score in comparison with placebo in the study by Herrero-Beaumont (2007), while no statistically significant difference vs placebo was observed in the study by Clegg (2006) with respect to the proportion of patients with a 20% reduction in WOMAC pain score.

In older studies, which were selected for their methodological quality and involved a 3-year treatment period (studies by Pavelka, 2002, and Reginster, 2001), glucosamine was superior to placebo in terms of Lequesne index and total WOMAC score in patients with symptomatic osteoarthritis of the knee (grade II-III on Kellgren/Lawrence classification). These results should be interpreted with care, however, as these were secondary criteria in these studies.

The GAIT study (Clegg 2006) showed no statistically significant difference between chondroitin, glucosamine and placebo in patients with low pain intensity on inclusion.

In the meta-analysis by Towheed (2005), involving studies that included patients with all types of osteoarthritis, glucosamine was superior to placebo mainly in terms of pain and Lequesne index, but these effects were of slight clinical relevance. In addition, a glucosamine effect of similar low clinical relevance was observed, better than that of NSAIDs as regards pain, but not Lequesne index.
However, the results of this meta-analysis must be interpreted with care, given the lack of homogeneity of these studies in terms of methods.

In these studies, the safety profile of glucosamine was no different from that of placebo. The most frequent adverse effects involved the digestive system. Cases of hepatitis have been observed with glucosamine; however, the relationship with glucosamine does not appear to be proven and, while it cannot be ruled out, it should be extremely weak.

In conclusion, glucosamine had low efficacy in the improvement of pain and joint function in patients with osteoarthritis, particularly of the knee, and was well tolerated.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual medical benefit

Symptomatic osteoarthritis of the knee is characterised by pain and functional impairment, that is likely to become chronic. In the long term, this disease can require surgery and an articular prosthesis implant..

This proprietary drug provides symptomatic treatment.

Public health benefit:

Osteoarthritis of the knee is a moderate public health burden.

The decrease in functional limitations and impairment caused by osteoarthritis, and the improvement in the quality of life of patients, are a public health need. Responses to this need do not consist only of drug treatments.

The data available on pain and algofunctional indexes does not lead to the conclusion that glucosamine help to improve quality of life and reduce functional limitations: absence of quality of life data, slight symptomatic effect.

The theoretical benefit of symptomatic slow-acting drugs in osteoarthritis, in terms of public health, lies in the decrease in NSAID consumption, which can reduce the frequency of adverse digestive effects that are particularly deleterious among the elderly. As regards glucosamine, there was no definite proof to demonstrate such a benefit.

Accordingly, no public health benefit can be expected with ENDOSTA.

This proprietary product is not very effective in improving the symptoms of knee osteoarthritis. The efficacy/adverse effect ratio is modest.

The management of osteoarthritis depends first and foremost on diet and lifestyle changes (weight loss, regular physical exercise) and non-pharmacological methods (e.g. physiotherapy, orthotics, walking sticks). Symptomatic treatment mainly involves analgesics and oral NSAIDs. This product has a limited role to play in symptomatic treatment of mild to moderate osteoarthritis of the knee.

Because of its modest efficacy levels and its limited role in therapeutic strategy, the actual benefit provided by ENDOSTA 625 mg tablets is low.

4.2. Improvement in actual benefit

ENDOSTA 625 mg, tablet, does not provide an improvement in actual benefit (IACB V) in comparison with other slow-acting osteoarthritis drugs.

4.3. Therapeutic use

The first measures to take when treating symptomatic osteoarthritis of the lower limbs are diet and lifestyle measures (losing weight, regular physical activity except during painful or inflammatory flare-ups during which reduction in activity is necessary) and non-pharmacological methods (e.g. physiotherapy, orthotics, walking sticks).

During the symptomatic phases, treatment consists mainly of analgesics, starting with paracetamol, and during acute flare-ups, oral NSAIDs in short courses at the minimal effective dose.

Local treatments can also be used, such as topical NSAIDS, intra-articular injections of corticosteroids, particularly during inflammatory phases, or hyaluronic acid.

Symptomatic slow-acting drugs in osteoarthritis (chondroitin sulfate CHONDROSULF, avocado and soya unsaponifiables, diacerhein and glucosamine) have modest efficacy in terms of pain and functional disability. It is not shown that these agents can lead to a substantial reduction in the consumption of NSAIDs. For this reason, they have a limited role to play in the therapeutic strategy. Glucosamine is only indicated for the symptomatic treatment of mild to moderate osteoarthritis of the knee.

Surgery (arthroplasty, insertion of prosthesis) is reserved for cases of osteoarthritis with X-ray signs development, that cause pain and disability, and that do not respond to the usual therapeutic methods.

4.4. Target Population

The target population for ENDOSTA is defined as the population of patients with symptomatic osteoarthritis of the knee.

According to data from a pilot epidemiological study[8] carried out in France in 1380 people aged between 40 and 75, the prevalence of symptomatic osteoarthritis of the knee was estimated at 7.6%, which, when extrapolated to the general French population aged between 40 and 75 (data from INED, 2008), corresponds to a total population of around 2 million patients.

4.5. Transparency Committee recommendations

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

This approval is subject to the implementation and performance, within 2 years, of a study designed to show the impact of the prescription of ENDOSTA 625 mg on NSAIDs consumption decrease.

4.5.1. Packaging:

Appropriate for the prescription conditions

4.5.2. Rate:

35%

[8] Roux CH *et al*. Screening for hip and knee osteoarthritis in the general population: predictive value of a questionnaire and prevalence estimates. Ann Rheum Dis. 2008 Oct;67(10):1406-11.

APPENDICES

Appendix 1: Other studies versus placebo

Study: **- Investigator** **- Country** **- Year**	**Methodology**	**No. of subjects, Age, Sex**	**Diagnosis and Inclusion criteria**	**Duration of treatment**	**Glucosamine:** **- Dosage** **- Route of administration**	**- Comparator(s)** **- Dosage** **- Route of administration**	**Evaluation criteria**	**Results (Efficacy)**
- Braham *et al.* - Australia - 2003	Double-blind, randomised, parallel-group. Placebo-controlled	50 patients included, 20 - 70 years Men and women	Volunteer subjects suffering from regular knee pain of undetermined origin.	12 weeks	- 2000 mg/day - 1 dose in the morning - Oral	- Placebo, identical to glucosamine - 1 dose in the morning - Oral	Efficacy: pain and functional symptoms (several tests) Safety: - Adverse effects - Overall assessment	GLU > PLA ($p < 0.05$) for all tests apart from joint line palpation
- Rindone *et al.* - USA - 2000	Double-blind, randomised, parallel-group. Placebo-controlled	114 patients included, 34 - 81 years Men and women	Patients with osteoarthritis of the knee with signs on X-ray, Kellgren > 0	8 weeks	- 1500 mg/day - 3 doses per day - Oral Other analgesics permitted (not quantified)	- Placebo, identical to glucosamine - 3 doses per day - Oral Other analgesics permitted (not quantified)	Efficacy: Pain (VAS) at rest and on walking. Safety: - Adverse effects - Overall assessment	No significant difference in terms of pain
- Houpt *et al.* - Canada - 1999	Double-blind, randomised, parallel-group. Placebo-controlled	118 patients included, 40 - 85 years Men and women	Patients with osteoarthritis of the knee with signs on X-ray (recruited by advertising + telephone)	8 weeks	- 1500 mg/day - 3 doses per day - Oral Other analgesics permitted (not quantified)	- Placebo, identical to glucosamine - 3 doses per day - Oral Other analgesics permitted (not quantified)	Efficacy: - WOMAC index pain subscore - Total WOMAC Safety: - Adverse effects - Overall assessment	No difference on primary criterion. GLU > PLA on pain as evaluated by the patient ($p < 0.05$)
- Noack *et al.* - Italy - 1994	Double-blind, randomised, parallel-group. Placebo-controlled	252 patients included, > 18 years Men and women	Patients with osteoarthritis of the knee according to Lequesne criteria with signs on X-ray, stage I-III	4 weeks	- 1500 mg/day - 3 doses per day - Oral Other analgesics permitted	- Placebo, identical to glucosamine - 3 doses per day - Oral Other analgesics permitted	Efficacy: Lequesne score = rate of responders (↓ Lequesne ≥ 3) Safety: - Adverse effects - Overall assessment	GLU > PLA ITT: $p = 0.016$ PP: $p = 0.014$

Annex 1: Other studies versus placebo (continued)

Study: **- Investigator** **- Country** **- Year** **- Biblio ref no.**	**Methodology**	**No. of subjects, Age, Sex**	**Diagnosis and Inclusion criteria**	**Duration of treatment**	**Glucosamine:** **- Dosage** **- Route of administration**	**- Comparator(s)** **- Dosage** **- Route of administration**	**Evaluation criteria**	**Results (Efficacy)**
- Drovanti *et al.* - Italy - 1980	Double-blind, randomised, parallel-group. Placebo-controlled	80 patients included, m = 60 years Men and women	Patients in hospital setting, with symptomatic osteoarthritis	4 weeks	- 1500 mg/day - 3 doses per day - Oral	- Placebo, identical to glucosamine - 3 doses per day - Oral	Efficacy: - joint pain, - other functional and physical signs, - Overall assessment Safety: - Adverse effects - Laboratory tests.	GLU > PLA ($p < 0.01$) for all evaluation criteria.
- Pujalte *et al.* - Philippines - 1980	Double-blind, randomised, parallel-group. Placebo-controlled	24 patients included, 45 - 73 years Men and women	Patients with symptomatic osteoarthritis	6 - 8 weeks	- 1500 mg/day - 3 doses per day - Oral Other analgesics permitted (not quantified)	- Placebo, identical to glucosamine - 3 doses per day - Oral Other analgesics permitted (not quantified)	Efficacy: joint pain, other functional and physical signs, overall assessment Safety: Adverse effects.	GLU > PLA ($p < 0.01$) for all evaluation criteria apart from restriction of movement
- Hughes *et al.* - United Kingdom - 2002	Double-blind, randomised, parallel-group. Placebo-controlled	80 patients included, > 40 years Men and women	Patients with symptomatic osteoarthritis of the knee with signs on X-ray (Kellgren I-IV)	26 weeks	- 1500 mg/day - 3 doses per day - Oral Other analgesics and NSAIDS permitted (quantities recorded)	- Placebo, identical to glucosamine - 3 doses per day - Oral Other analgesics and NSAIDS permitted (quantities recorded)	Efficacy: pain (VAS), WOMAC, McGill pain questionnaire, knee flexion. Safety: Adverse effects.	GLU>PLA in terms of knee flexion ($p < 0.05$), no difference on other criteria.