



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

9 January 2013

The opinion adopted by the Transparency Committee on 4 July 2012
was given a hearing on 5 December 2012 and
observations were examined on 9 January 2013

Examination of the dossier for a proprietary medicinal product included for a 5-year period
starting on 31 December 2005 (Official Gazette of 29 December 2006)

PIASCLEDINE 300 mg, hard capsule
B/15 (CIP code: 321 495-4)

Applicant: EXPANSCIENCE

Avocado oil unsaponifiable, soybean oil unsaponifiable

Date of Marketing Authorisation: 1st September 1977, validated on 20 May 1992

Amendment: 13 December 2007 (modification of the wording of the indication following the
re- assessment of the benefit/risk ratio of slow action symptomatic anti-arthritics (SASAAs))

Reasons for request:

Renewal of inclusion on the list of medicines refundable by National Health Insurance.

Re-assessment of the actual benefit following the Transparency Committee conclusions in its
opinions of 26 November 2008 and reiterated in its opinion of 21 September 2011.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Avocado oil unsaponifiable, soybean oil unsaponifiable

1.2. Indication

“Rheumatology:
Symptomatic treatment with delayed effect for osteoarthritis of the hip and knee.”

Stomatology:
Adjuvant treatment for periodontal diseases.”

1.3. Dosage

“Method of administration: Oral route.

The capsule is to be swallowed whole, with a large glass of water.

Dosage:

1 capsule per day, taken with food

PIASCLEDINE 300 mg is contraindicated in patients with a history of allergic reactions to one of the components of the product.”

2 REMINDER OF THE COMMITTEE'S OPINIONS AND CONDITIONS OF INCLUSION

Committee Opinion of 21 February 2001

Re-assessment of actual benefit:

Osteoarthritis

"This proprietary medicinal product concerns a condition which is characterised by a progression towards a disability and/or a marked deterioration in quality of life.

This proprietary medicinal product is intended as symptomatic treatment.

The efficacy of this proprietary medicinal product in this indication is modest.

This proprietary medicinal product is an adjuvant medication.

There are medicinal and non-medicinal treatment alternatives to this proprietary medicinal product.

The actual benefit is low in the adjuvant treatment of osteoarthritic pain."

Periodontal diseases

The condition treated with this proprietary medicinal product is not life-threatening, nor does it cause serious complications, or any disability, or a marked deterioration in quality of life.

This proprietary medicinal product is intended as symptomatic and preventive treatment.

The efficacy/safety ratio for this medicinal product in this indication is low.

There are medicinal and non-medicinal treatment alternatives to this proprietary medicinal product.

The actual benefit is insufficient in the adjuvant treatment of periodontal diseases."

Committee Opinion of 15 February 2006

Renewal of inclusion:

Actual benefit:

Osteoarthritis:

"Osteoarthritis is a condition that affects the joints with a prevalence that increases with age. It may lead to pain and varying levels of functional disability. Debilitating forms, especially of the hip and knee, may require surgery.

This proprietary medicinal product is intended as symptomatic treatment.

Paracetamol is the first-line analgesic treatment. Due to their gastrointestinal and renovascular adverse effects, NSAIDs are indicated at a minimum effective dose and for the shortest time necessary in cases where the use of paracetamol has failed. Slow action symptomatic anti-arthritics (SASAAs) may be considered for long-term pain, with the aim of reducing the use of analgesics and non-steroidal anti-inflammatory drugs.¹

Given the modest efficacy of PIASCLEDINE in terms of reducing pain and functional disability and in demonstrating a decrease in the use of NSAIDs, this proprietary medicinal product is an adjuvant treatment for osteoarthritic pain.

The actual benefit of this proprietary medicinal product is low."

Adjuvant treatment of periodontal diseases:

"Periodontal diseases are defined as multifactor infectious diseases. They are characterised by clinical signs and symptoms that may include inflammation, provoked or spontaneous bleeding of the gums, the formation of pockets alongside loosening and loss of socket bone, dental movement which may result in the loss of teeth.

These conditions may result in a decreased quality of life.

¹ Xavier Chevalier. Les médicaments de l'arthrose ; Médecine thérapeutique Volume 5, Numéro 8, 651-3, Oct.99

This proprietary medicinal product is intended as a symptomatic treatment.

The aim of this treatment is to prevent and manage periodontal disease and to repair and/or regenerate damaged periodontal tissue. In all cases, education in oral and dental hygiene is an essential part of treatment. Therapeutic methods available are mechanical, non-surgical treatments (supragingival scaling and scale and polish), medicinal treatments and surgical procedures. There are no guidelines that state the use of this medicinal product in the aforementioned indication.

Available data in this indication is unsatisfactory to properly determine its efficacy and the degree of effect observed.

The efficacy of this proprietary medicinal product has not been clearly established.

The administration of this proprietary medicinal product may lead to rare adverse effects, such as hypersensitivity reactions or in exceptional circumstances affect the liver.

The efficacy/adverse effects ratio for PIASCLEDINE has not been clearly established.

The actual benefit in this indication is insufficient.”

Conclusions:

“The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Insurance in the indication: “adjuvant treatment of osteoarthritic pain.”
Reimbursement rate: 35%”

Committee Opinion of 26 November 2008

Re-assessment of the actual benefit at the request of the Committee following the re-assessment of the benefit/risk ratio by the Marketing Authorisation Committee:

Actual benefit:

“Symptomatic osteoarthritis of the hip and knee is characterised by pain and functional incapacity that are likely to progress into a chronic condition. Eventually surgical intervention may be required, with the fitting of a prosthesis.

This proprietary medicinal product provides symptomatic treatment with a delayed effect.

Public health benefit:

Osteoarthritis of the knee and hip are a substantial public health burden.

The reduction in functional limitations and incapacities brought about by osteoarthritis, as well as the improvement in the quality of life of those affected is a public health need. The response to this need is not purely medicinal.

Available data on pain and also functional indices does not enable conclusions to be drawn on the existence of an impact of avocado and soybean oil unsaponifiables on the improvement in quality of life and on the reduction in functional limitations: absence of quality of life data and small effect on symptoms.

The theoretical benefit of (SASAAs), in terms of public health, lies in the reduction in the use of NSAIDs, which may enable a reduction in the frequency of intestinal adverse effects, especially those that are life-threatening in elderly patients. For avocado and soybean oil unsaponifiables, the available data shows an impact in the reduction in the use of NSAIDs. However, the clinical relevance of this reduction in use of NSAIDs, in terms of a reduction in morbidity and mortality linked to gastrointestinal bleeding, is not known.

Consequently, PIASCLEDINE is not expected to benefit public health.

This proprietary medicinal product has little effect in improving the symptoms of osteoarthritis. The efficacy/adverse effects ratio is modest.

Above all, the management of osteoarthritis is based on making lifestyle and dietary adjustments (losing weight, taking regular physical exercise) and not pharmacological changes (physiotherapy, wearing orthotics, using walking sticks etc.). Symptomatic treatment

mainly comprises the use of analgesics and oral NSAIDs. This proprietary medicinal product is of limited therapeutic benefit.

The actual benefit of PIASCLEDINE 300 mg capsules is low.”

Conclusions:

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

This favourable opinion is under the condition that a study is carried out within two years with the aim of demonstrating the impact of prescribing PIASCLEDINE 300 mg in reducing the use of NSAIDs.

Reimbursement rate: 35%.”

Committee Opinion of 21 September 2011

Re-assessment of the actual benefit following referral to from the Director of Social Security:

“Due to its modest level of efficacy and limited therapeutic use, the actual benefit of PIASCLEDINE 300 mg capsules remains low in the Marketing Authorisation indications.

The Transparency Committee recommends 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.

Reimbursement rate: 15%.”

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2012)

Rheumatology:

M Musculo-skeletal system
 M01 Antiinflammatory and antirheumatic products
 M01A Antiinflammatory and antirheumatic products, non-steroids
 M01AX Antiinflammatory and antirheumatic agents, non-steroids
 M01AX26 Avocado and soybean oil, unsaponifiables

Stomatology:

A Alimentary tract and metabolism
 A01 Stomatological preparations
 A01A Stomatological preparations
 A01AD Other agents for local oral treatment

3.2. Medicines in the same therapeutic category

These are other slow action symptomatic anti-arthritis (SASAAs):

Active ingredient	Proprietary medicinal product	Form	Indication
Chondroitin (sulfate)	CHONDROSULF 400 mg	hard capsule and granule for oral solution in sachets	Symptomatic treatment with delayed effect for osteoarthritis of the hip or knee.
Diacerein	ART 50 mg	hard capsule	Symptomatic treatment with delayed effect for osteoarthritis of the hip or knee
Diacerein	ZONDAR 50 mg	hard capsule	Symptomatic treatment with delayed effect for osteoarthritis of the hip or knee
Glucosamine	FLEXEA 625 mg	tablet	Relief of symptoms in mild to moderate osteoarthritis of the knee
Glucosamine	DOLENIO 1178 mg	tablet	Relief of symptoms in mild to moderate osteoarthritis of the knee
Glucosamine	OSAFLEXAN 1178 mg	powder for oral solution in single-dose sachets	Relief of symptoms in mild to moderate osteoarthritis of the knee
Glucosamine	STRUCTOFLEX 625 mg	hard capsule	Relief of symptoms in mild to moderate osteoarthritis of the knee
Glucosamine	VOLTAFLEX 625 mg	film-coated tablet	Relief of symptoms in mild to moderate osteoarthritis of the knee

For all these proprietary medicinal products, the actual benefit is low while waiting for the results from the observational study (PEGASE), the aim of which is to show that these medicinal products enable savings to be made in terms of NSAID use.

3.3. Medicines with a similar therapeutic aim

Other medicinal treatments for osteoarthritis of the hip or knee: analgesics, oral and topical NSAIDs, intra-articular corticosteroid injections and intra-articular hyaluronic acid injections (medicinal product or medical device).

4 UPDATE ON THE DATA AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Efficacy

The applicant has not provided any new clinical data.

4.2. Adverse effects

New safety data (PSUR covering the period 01/06/2007 to 31/05/2010) did not highlight any particular concerns.

4.3. Conclusion

No new efficacy data have been provided. Updated pharmacovigilance data did not highlight any new issues.

5 MEDICINAL PRODUCT USAGE DATA

5.1. Observational study: PEGASE study

AIM and METHOD

In 2008, the Transparency Committee began the re-assessment of all slow action symptomatic anti-arthritics (SASAAs); they considered that, in light of their low efficacy, the potential benefit of SASAAs lies in a possible reduction in the use of NSAIDs. This is why their favourable opinion regarding their continued reimbursement was on the condition that “a study was implemented and carried out within two years, with the aim of showing the impact of the prescription of ART 50 mg/ ZONDAR 50 mg, CHONDROSULF and PIASCLEDINE in terms of the reduction in the use of NSAIDs.”

In response to the request by the Transparency Committee for the study, the companies marketing ART 50 mg/ZONDAR 50 mg, CHONDROSULF and PIASCLEDINE initially presented results from an interim analysis, then secondly, the final results from a combined observational study (the “PEGASE” study).

The results from the final analysis were submitted by the company marketing PIASCLEDINE on 19 November 2012 and have been included in this opinion.

The aim of this cohort study of patients with osteoarthritis of the knee or hip, whether they were being treated with SASAAs or not, was to measure the impact of the use of SASAAs on the use of NSAIDs and to describe the usage profile for SASAAs during the follow-up period.

The PEGASE study, which started including patients in March 2010, was conducted on a sample of GPs or private rheumatologists practising in mainland France identified randomly 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.^{2,3} They were included consecutively, during a consultation for a pain episode of their osteoarthritis, from when new treatment with a SASAA or any other new osteoarthritis treatment (control) regardless of the type - pharmacological (NSAID or analgesics, infiltration) or non-pharmacological (health/dietary measures, physiotherapy, orthotics, other forms of physical therapy) - was started.

Patients on SASAAs or hyaluronic acid for more than 3 months, with arthritis, tendinitis of the lower limbs or radicular pain were specifically not included.

The follow-up period lasted up to 16 months after inclusion, until lost to follow-up, death, withdrawal from the study or up to the end of the study (number achieved or major event concerning the life of the product).

Data were collected by doctors at inclusion and during an annual follow-up consultation appointment carried out between 12 and 16 months after inclusion and for certain patients by standard telephone follow-up in the month following inclusion, then at 4, 8, 12 and 16 months.

Patients were questioned about their consumption of SASAAs and NSAIDs over the two-month period by indicating the number of days on which treatment was taken in these two months (more or less every day, for 31 to 60 days in total, for 17 to 30 days, for 6 to 16 days, for 1 to 7 days, never).

In order to take into account the treatment dynamics during the follow-up period (discontinuation of treatment, potential substitutions, etc.), a treatment time-population analysis was conducted. Thus, the periods of exposure to SASAAs were subdivided across the whole follow-up period into two-month analysis time units (ATU).

All exposure was considered as binary (exposed/not exposed) for each SASAA in the two-month unit (independent of any combination). The risk of presenting the event of interest was considered as constant within each ATU.

The event of interest was the use of systemic NSAIDs,⁴ which was considered as binary (taken: yes/no) within each ATU.

The aim of the primary analysis was to compare the use of NSAIDs in the two-month periods of exposure to a SASAAs with the two-month periods of no SASAAs exposure, on the understanding that during the previous two-month period there was no exposure to any SASAAs.

In total, 3,000 person-months of exposure and 4,500 person-months of non-exposure were initially planned to enable the difference in risk of the use of NSAIDs of 15% to be detected (which is an RR = 0.85, 80% power, 95% confidence). The mean anticipated follow-up period was 9 months.

² Altman, R et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. [Arthritis Rheum.](#) 1986 Aug; 29 (8): 1039-49.

³ Altman, R et al : The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. [Arthritis Rheum.](#) 1991 May; 34 (5): 505-14.

⁴ NSAIDs used in the analysis: diclofenac, diclofenac + misoprostol, aceclofenac, etodolac, ibuprofen, nabumeton, flurbiprofen, ketoprofen, alminoprofen, fenoprofen, naproxen, nimesulide, celecoxib, etoricoxib, meloxicam, piroxicam, tenoxicam, indometacin, sulindac.

Description of the PEGASE cohort:

Of the 24,107 GPs and 1,236 private rheumatologists contacted to participate in the study, 2,860 agreed to participate and 617 (521 GPs and 96 rheumatologists) included at least one patient.

On the 8 March 2012, 3,803 patients meeting the inclusion and non-inclusion criteria were included in the interim analysis.

On 4 October 2012, a total of 5,485 patients meeting the inclusion and non-inclusion criteria were included. Only the sub-population of patients included outside the competitive recruitment for those taking glucosamine were considered in the analysis, i.e. 4,555 patients.

The main patient characteristics at inclusion were:

- 63.8% of patients were female;
- the mean age at inclusion was 66.8 years;
- in the majority of cases, the level of education of the patients was below the baccalaureate (2,279/3,521 i.e. 64.7%) and a large proportion of them (2,819 /3,525 i.e. 80.0%) were retired or with no professional activity at inclusion in the study;
- the mean BMI was 28.0 [standard deviation: 5.0];
- of the 4,539 patients with a diagnosis, the majority of patients presented with osteoarthritis of the knee (78.9%), of the hip (16.2%) or both (4.6%);
- osteoarthritis had been present for less than a year for 26.0% of patients, for 1 to 5 years for 41.2% and for more than 5 years for 32.3% of patients;
- the median number of pain flare-ups over the last 6 months was 2.0 [range: 0.0 - 12.0];
- the mean pain score (measured from 0 to 10 on a VAS) was 5.5 [standard deviation 1.8];
- disability at inclusion (Lequesne algo-functional index) was significant to very significant (46.4%) or even unbearable (19.0%);
- the main co-morbidities presented were cardiovascular disease (61.0%), musculo-skeletal disorders (60.7%), endocrine (33.4%) and intestinal disorders (24.8%) and osteoarthritis in other parts of the body (41.9%);
- a limited number of patients (2.6%) declared that they were allergic to NSAIDs;
- more than one in ten patients declared having had physiotherapy (11.6%) or orthotics (12.6%);
- 6.1% of patients declared that they had a prosthesis.

The characteristics of the population presented at the interim report stage were similar to those of the final report population described below.

Status of progress of the cohort at the interim report stage:

On the cut-off date (8 March 2012), the mean cohort follow-up period was 7.2 months (n = 2,907), with 2,907, 2,239, 1,417 and 636 patients having a follow-up period of 4, 8, 12 and 16 months respectively.

A total of 1,258/3,803 (33%) patients were never exposed to any SASAAs during the follow-up period.

Table 1: Summary of the level of progress of the cohort on 8 March 2012 (interim report):

	ART 50 mg/ ZONDAR 50 mg/ generics	CHONDROSULF	PIASCLEDINE	Not exposed to any SASAA
Number of patients participating on the date of interim report	424	580	723	1,258
Mean follow-up time on the date of the interim report (months)	9.0	9.6	8.7	ND
Mean duration of exposure (months)	6.3	6.5	6.9	ND
"Approximate" time-population on the date of the interim report (patient-months)	2,671	3,770	4,988	ND
Expected time-population according to protocol (patient-months)	3,000	3,000	3,000	4,500

On the date of the final report, the mean follow-up time of the cohort was 9.71 months. A total of 4,223, 3,523, 2,752, 1,770, 931 and 426 patients had a follow-up period of 4, 8, 12, 16, 20 and 24 months respectively.

A total of 1,288/4,555 (28.3%) patients were never exposed to any SASAAs during the follow-up period.

RESULTS

The results presented below only concern PIASCLEDINE.

On the date of the interim report, among the 791 patients who received a prescription for PIASCLEDINE, 68 (8.6%) eventually refused follow-up and the 589 patients who agreed to participate had data from at least one follow-up on the date of the interim report.

Nevertheless, among these patients, 429 patients (i.e. 72.8%) reported taking PIASCLEDINE during the follow-up period and were considered in the interim analysis.

On the date of this analysis, the mean exposure to PIASCLEDINE for these patients was 6.9 months, corresponding to 2,940 patient-months of accumulated exposure (i.e. 1,470 ATU).

On the date of the final report, among the 930 patients who received a prescription for PIASCLEDINE, 92 (9.8%) eventually refused follow-up and the 832 patients who had agreed to participate had data from at least one follow-up on the date of this report.

Nonetheless, only 602 patients (i.e. 72.4%) reported taking PIASCLEDINE during follow-up and accumulated 4,526 patient-months of exposure in the study (i.e. 2,263 ATUs).

Characteristics of patients exposed to PIASCLEDINE differed to those of patients who were never exposed to any SASAAs during follow-up. On the whole patients were younger (66.3 years versus 69.4 years on average), commonly had a higher level of education (37.9% versus 30.2%), reported fewer cardiovascular (58.9% versus 67.2%) and endocrine co-morbidities (33.7% versus 36.3%), used orthotics less frequently (11.1% versus 15.8%) and had fewer prostheses (4.6% versus 9.1%).

A history of osteoarthritis >5 years was more common in the non-exposed patients (38.2% versus 31.8%), while the number of pain flare-ups in the 6 months prior to inclusion, the pain scale and the Lequesne index were similar in both groups.

The differences seen at the stage of the final report between the characteristics of patients exposed to PIASCLEDINE and those of patients who had never been exposed to any SASAAs during the follow-up period have already been stated in the interim analysis.

Results for the use of NSAIDs

➤ Primary analysis

- Results from the interim report:

On 8 March 2012, the analysis units were divided as follows: 1,470 were for two months exposure to PIASCLEDINE, 5,550 were for two months of non-exposure to any SASAA and 526 were not documented. Accumulative total of 1,788 ATUs for the use of NSAIDs were counted.

Table 2: Association between all the ATUs for incident exposure to PIASCLEDINE and the ATUs for the use of NSAIDs during the follow-up period (n=6,678)

	No. of ATUs for PIASCLEDINE	% use of NSAIDs within ATUs	OR* (95% CI)
No SASAA (reference**)	5,244	25.4	1
All exposure durations ***	1,434	25.8	0.92 [0.74-1.15]
• Exposure from 0 to 4 months after starting	375	28.3	0.92 [0.66-1.29]
• Exposure from 4 to 8 months after starting	460	27.4	0.99 [0.72-1.36]
• Exposure of + 8 months after starting	599	23.0	0.83 [0.52-1.32]

* 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 (continuous), the number of osteoarthritis pain flare-ups (binary), 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, risk factors for not taking NSAIDs and in the treatment arm in the previous two months, defined according to a variable classification (1st treatment with SASAA considered, already used in the past, not known).

**Two-month periods of non-exposure to any SASAA, on the understanding that during the previous two months there was no SASAA exposure (n=5,244/5,550).

*** 13 two-month periods for which it was not possible to determine the precise duration of exposure after starting treatment.

Thus, during the study, the frequency of use of NSAIDs was 25.8% for the two months of exposure to PIASCLEDINE and 25.4% for the two month period of non-exposure to any SASAAs respectively.

The two-month period of NSAID exposure indicates that patients using NSAIDs have a different profile compared with non-users: on average they are younger (65.6 years versus 68.1 years), are more often female (68.7% versus 64.2%), with a history of osteoarthritis of more than 1 year (77.9% versus 72.3%), a higher mean pain score (5.3 versus 4.7), a higher algo-functional score (63.6% versus 51.9% highlighting a significant to very significant disability). These patients are also more likely to be treated with physiotherapy, use orthotics or have prostheses (26.3% versus 23.8%).

The overall results, which lack detail, are also presented and compare the two-month exposure to three anti-osteoarthritis (n = 3,265) to the two-month periods of non-exposure.

These results are similar to those presented for each individual proprietary medicinal product (OR = 0.99 [0.85-1.15]).

- Results from the final report:

On the 4 October 2012, the analysis units were divided as follows: 2,212 were for two months exposure to PIASCLEDINE and 9,240 were for two months of non-exposure to any SASAAs. Accumulative total of 2,910 ATUs for the use of NSAIDs were counted.

Table 3: Association between all the ATUs for exposure to PIASCLEDINE and the ATUs for the use of NSAIDs during the follow-up period (n=11,452)

	No. of ATUs for PIASCLEDINE	% use of NSAIDs within ATUs	OR* (95% CI)
No SASAA (reference**)	9,240	24.2	1
All durations of exposure	2,212	25.3	0.98 [0.82-1.17]
• Exposure from 0 to 4 months after starting	1,137	25.9	0.97 [0.81-1.17]
• Exposure from 4 to 8 months after starting	558	25.8	1.09 [0.84-1.41]
• Exposure of + 8 months after starting	517	23.4	1.01 [0.72-1.43]

* 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 (continuous), the number of osteoarthritis pain flare-ups (binary), 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) and the existence of a morbidity risk factor for not taking NSAIDs.

**Two-month periods of non-exposure to any SASAAs.

Thus, during the study, the frequency of use of NSAIDs was 25.3% for the two-month exposure to PIASCLEDINE and 24.2% for the two-month period of non-exposure to any SASAAs respectively.

The definitive results from the primary analysis thus confirm the results from the interim analysis and the absence of a difference in NSAID use between the two groups, whether SASAAs were taken or not.

The sensitivity analysis, taking into account the period of 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, gave similar results.

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

The patient profiles of NSAID users were different to those of non-users. The differences noted in the interim report are still present in the final report.

➤ **Secondary analyses**

In the final report, the secondary analyses are presented by the applicant.

A secondary analysis was carried out on the sub-group of patients who started treatment with PIASCLEDINE on inclusion in the study and had not used a SASAA in the three months prior to the inclusion date.⁵

This analysis was combined with a sensitivity analysis, taking or not taking the carry-over effect into account, and a stratified analysis taking into account the duration of exposure to PIASCLEDINE.

Table 4: Association between all the ATUs for exposure to PIASCLEDINE and the ATUs for the use of NSAIDs during the follow-up period only for patients who started PIASCLEDINE treatment on inclusion in the study:

		No. of ATUs for PIASCLEDINE	% use of NSAIDs within ATUs	OR* (95% CI)
Analysis not taking carry-over effect into account	No SYSADOA (reference**)	9,240	24.2	1
	All durations of exposure	1,340	22.7	0.95 [0.77-1.17]
	• 0 to 4 months after starting	658	25.8	1.01 [0.81-1.26]
	• 4 to 8 months after starting	351	23.9	0.98 [0.71-1.37]
	• More than 8 months after starting	331	15.1	0.62 [0.38-1.0]
Analysis taking into account carry-over effect***	No SYSADOA (reference**)	9,240	24.2	1
	All durations of exposure	1,452	22.4	0.89 [0.74-1.07]
	• 0 to 4 months after starting	646	26.3	1.01 [0.81-1.27]
	• 4 to 8 months after starting	417	24.5	0.94 [0.72-1.23]
	• More than 8 months after starting	389	13.6	0.55 [0.38-0.82]

** 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 (continuous), the number of osteoarthritis pain flare-ups (binary), 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 a morbidity factor for not taking NSAIDs and in the treatment arm in the previous two months, defined according to a variable classification (1st treatment with SYSADOA considered, already used in the past, not known).

**Two-month periods of non-exposure to any SYSADOAs.

*** The carry-over effect was considered as a period of two months following the discontinuation of treatment when treatment was taken for at least two consecutive two-month periods.

Since inclusion of patients with a prescription for less than three months of symptomatic slow acting drugs in osteoarthritis 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.

The analysis presented in the final report is only based on the sub-group of patients who started PIASCLEDINE treatment on inclusion in the study. Analysis of prevalent patients, i.e. those who started during the three months prior to inclusion, is not presented, although initially planned for in the protocol.

⁵ The study protocol was amended on 23/09/2010 to change the exclusion criteria including patients taking SYSADOA or who had received a hyaluronic acid injection **more than 3 months previously**.

In addition, this stratified sub-group analysis was carried out despite the non-significance of the results from the primary analysis on the total study population, and can therefore only be considered as exploratory.

The various analyses taking into account both the carry-over effect and the duration of exposure per four-month period led to a number of statistical tests being carried out and resulted in an alpha risk control that was not corrected.

Furthermore, statistically significant results were only reported for durations of exposure over eight months and only concern a limited number of ATUs (around 25%).

This limited number of ATUs suggests a low duration of exposure to SASAAs in the cohort, especially beyond 8 months, which could be explained either by interrupted follow-up of patients in the cohort or by discontinuation of treatment. No information on the potential losses to follow-up was presented.

The absence of informative elements regarding these different points also limits the interpretation of these results.

Consequently, and given the limitations stated previously, the Committee cannot take these new analyses into consideration.

Results for pain and functional state:

The results from the *post hoc* secondary analysis carried out for pain (VAS score from 0 to 10, categorised as 0-4 / 5-10) and functional impact (modified Lequesne algo-functional index – telephone version - categorised by the median of the observed distribution in modest or average disability / significant, very significant or unbearable disability) are presented below:

Table 5: Association between all the ATUs for exposure to PIASCLEDINE and the ATUs for pain (VAS \geq 5) during the follow-up period (n=11,041)

		No. of ATUs for PIASCLEDINE	% two-month period of pain within ATUs	OR* (95% CI)
Analysis with carry-over effect***	No SASAA (reference**)	8,831	60.8	1
	All durations of exposure	2,210	61.9	1.06 [0.93-1.21]
	• 0 to 4 months after starting	1,101	71.7	1.41 [1.15-1.73]
	• 4 to 8 months after starting	583	54.4	0.77 [0.65-0.91]
	• More than 8 months after starting	526	49.6	0.65 [0.52-0.81]

* 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 physiotherapy/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 risk factor for not taking NSAIDs.

** Two-month periods of non-exposure to any SASAAs.

*** The carry-over effect was considered as a period of two months following the discontinuation of treatment when treatment was taken for at least two consecutive two-month periods.

Table 6: Association between all the ATUs for exposure to PIASCLEDINE and the ATUs with significant disability or more during the follow-up period (n=11,193)

	No. of ATUs for PIASCLEDINE	% two-month periods with significant disability or more within ATUs	OR* (95% CI)	
Analysis with carry-over effect***	No SASAA (reference**)	8,946	58.3	1
	All durations of exposure	2,247	58.6	0.98 [0.87-1.1]
	• 0 to 4 months after starting	689	62.5	1.04 [0.88-1.24]
	• 4 to 8 months after starting	332	55.1	0.82 [0.7-0.97]
	• More than 8 months after starting	295	54.4	0.8 [0.66-0.96]

* 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 physiotherapy/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 risk factor for not taking NSAIDs.

**Two-month periods of non-exposure to any SASAAs.

*** The carry-over effect was considered as a period of two months following the discontinuation of treatment when treatment was taken for at least two consecutive two-month periods.

These analyses, carried out on a *post-hoc* basis, could not be used by the Committee. Furthermore, they did not enable the clinical relevance of these results to be determined.

CONCLUSION

In its Opinion of 26 November 2008, within the context of a low Actual Benefit (AB), there was a condition to the Transparency Committee's recommendation of maintaining reimbursement, the implementation which was performance of a study with the aim of demonstrating the impact of prescribing PIASCLEDINE on the reduction in the use of NSAIDs.

The interim results from the PEGASE study, despite being from a secondary interim analysis not initially stated in the protocol, were confirmed in the final analysis.

The primary results observed were:

- an absence of taking PIASCLEDINE treatment, even though it was prescribed, in nearly 30% of patients at the time of the interim report and in 27.6% of patients at the time of the final report,
- an approximate rate of 25% for the use of NSAIDs across the whole population with osteoarthritis of the knee or hip,
- a similar frequency of use of NSAIDs in the ATUs with exposure to PIASCLEDINE (25.3%) versus the ATUs without exposure (24.2%).

These results enable the absence of an impact of SYSADOAs, and PIASCLEDINE in particular, on the use of NSAIDs to be highlighted.

Secondary sub-group and stratified analyses provided within the context of the definitive report cannot be taken into account due to the fact that they are only exploratory.

5.2. Prescribing data

According to IMS prescription data (moving annual total November 2011), 1.2 million prescriptions were issued for PIASCLEDINE. This proprietary medicinal product was mainly prescribed for osteoarthritis in 84% of cases (8% for osteoarthritis of the knee and 1% for osteoarthritis of the hip).

Considering previous Committee conclusions, the low AB, and analysis of data from the PEGASE study that demonstrated an absence of a difference in the use of NSAIDs based on the intake of SYSADOAs or not, the Committee has concluded:

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual clinical benefit

Symptomatic osteoarthritis of the hip and knee is characterised by pain and functional incapacity that are likely to progress into a chronic condition. Eventually surgical intervention may be required, with the introduction of a prosthesis.

This proprietary medicinal product provides symptomatic treatment with a delayed effect.

Public health benefit:

Osteoarthritis of the knee and hip represent a substantial public health burden.

The reduction in functional limitations and incapacities due to osteoarthritis, as well as the improvement in quality of life of those affected, represent a public health need that is already an established priority in the Law of 9 August 2004 on public health policy (Objective 85). However, the response to this need is not limited to treatment with medication.

Available data on pain and algo-functional indices do not enable conclusions to be drawn on the existence of an impact of avocado and soybean oil unsaponifiables on the improvement in quality of life and on the reduction in functional limitations: absence of quality of life data and minimal effect on functional incapacity.

The theoretical benefit, in terms of public health, of slow action anti-inflammatories may lie in the reduction in the use of NSAIDs, which is likely to reduce the frequency of intestinal adverse effects, which are particularly harmful in elderly patients.

Both the interim and definitive results from the PEGASE study show a limited use of NSAIDs in the population with osteoarthritis of the knee or hip and a very similar use of NSAIDs regardless of the exposure to slow-action anti-arthritis.

Thus, the theoretical benefit in terms of public health of treatment with slow action anti-arthritis on the use of NSAIDs is not confirmed in current medical practice.

Consequently, this proprietary medicinal product is not expected to benefit public health.

The effects of avocado and soybean oil unsaponifiables on pain and functional incapacity linked to osteoarthritis are minimal. It has not been shown whether avocado and soybean oil unsaponifiables will enable savings to be made in the use of NSAIDs. The efficacy/adverse effects ratio for PIASCLEDINE is low.

Above all, the management of osteoarthritis is based on making health and dietary adjustments (losing weight, taking regular physical exercise) and non-pharmacological modalities (physiotherapy, wearing orthotics, using walking sticks etc.). Symptomatic treatment mainly comprises the use of analgesics and oral NSAIDs. Symptomatic slow acting drugs in osteoarthritis, especially avocado and soybean oil unsaponifiables, have minimal effect on the symptoms of osteoarthritis and it has not been demonstrated that they enable a reduction the use of NSAIDs.

As with other symptomatic slow acting drugs in osteoarthritis , this proprietary medicinal product is of no therapeutic benefit.

The actual benefit of PIASCLEDINE 300 mg capsules is insufficient to justify reimbursement by National Insurance.

6.2. Therapeutic use

The initial measures implemented in the treatment of symptomatic osteoarthritis of the lower limbs are health- and diet-based (losing excess weight, participating in regular physical activity when not suffering with pain flare-ups or stiffness, when reduction in activity is needed) and non-pharmacological (physiotherapy, wearing of orthotics, using walking sticks etc.).

Treatment should be targeted to the individual, taking into account the risk factors associated with the knee (obesity, restricted mobility, physical activity) and general risk factors (age, combination of medication, etc.), the intensity of the pain and the resulting disability, the presence of signs of inflammation (effusions), and the extent of joint damage.

During symptomatic phases, treatment mainly comprises taking analgesics, starting with paracetamol, and during acute episodes, short periods with oral NSAIDs at the minimum effective dose in patients who are not responding to paracetamol. Due to the gastrointestinal risk, coxibs are preferred.

Localised treatment may also be used, such as topical NSAIDs, intra-articular corticosteroid injections, especially during phases of stiffness, or hyaluronic acid.

Symptomatic slow acting drugs in osteoarthritis (chondroitin sulfate, avocado and soybean oil unsaponifiables, diacerein and glucosamine) have a minimal effect on both pain and functional incapacity. They did not demonstrate that they were able to reduce the use of NSAIDs, which are the cause of very notable and often serious adverse effects, especially in the elderly. In addition, the benefit/risk ratio for diacerein was considered as unfavourable in a recent assessment by the Marketing Authorisation Committee (July 2012). Consequently, these proprietary medicinal products are of no therapeutic benefit.

The place of glucosamines in the therapeutic strategy for the symptomatic treatment of mild to moderate osteoarthritis of the knee will only be determined following the results of the PEGASE observational study, which aims to demonstrate their impact on the use of NSAIDs.

Surgery (arthroplasty, introduction of a prosthesis) is only for cases of painful and debilitating osteoarthritis, with radiological progression, and which is unresponsive to other usual treatment measures.

6.3. Transparency Committee recommendations

The Transparency Committee does not recommend continued inclusion on the list of medicines refundable by National Health Insurance.