HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

26 November 2008

PIASCLEDINE 300 mg capsules
Pack of 15 capsules (CIP: 321 495-4)

Applicant : EXPANSCIENCE

Avocado oil unsaponifiables, soya-bean oil unsaponifiables

Date of MA: September 1, 1977 validated May 20, 1992
Amended: December 13, 2007 (wording of indication modified following a review of the benefit/risk ratio of symptomatic slow-acting drugs in osteoarthritis)

Medicinal product reimbursed by National Insurance (35%) - Approved for use by hospital

Reason for request: Review of the actual benefit in osteoarthritis in accordance with art. R.163-21 of the French Social Security Code.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Avocado oil unsaponifiables, soya-bean oil unsaponifiables

1.2. Indication

Former indication:
"In rheumatology: adjuvant treatment of osteoarthritis pain."

New indication:
"In rheumatology: Symptomatic slow-acting treatment of hip and knee osteoarthritis."

1.3. Dosage

Method of administration: For oral use.

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

Dosage:
1 capsule per day during a meal
PIASCLEDINE 300 mg is contraindicated in patients with a history of allergic reactions to any of the product's ingredients.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

No ATC classification for rheumatology.

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

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

Active ingredient	Proprietary product	Presentation	Indication
Chondroitin (sulphate)	CHONDROSULF 400 mg	capsule and granules for oral solution in sachet	Symptomatic slow-acting treatment of hip and knee osteoarthritis
Chondroitin (sodium sulphate)	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

2.3. Medicines with a similar therapeutic aim

Other medications for osteoarthritis: analgesics, oral and topical NSAID, corticosteroids by intraarticular injection, hyaluronic acid (as a medicinal product or medical device) by intraarticular injection.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The company submitted 6 randomised, double-blind studies on efficacy over a duration of 3 and 6 months, of which 5 were placebo-controlled and 1 in comparison to diacerein (see description of trials in table 1).

Table 1: Description of clinical studies

Study	No. of patients Inclusion criteria	Groups of treatment and concomitant treatments	Main endpoints
PR193 (Blotman, 1997[1]) Phase III	N = 164 Age: 45-80 **Femorotibial osteoarthritis** **Osteoarthritis of the hip** Since > 6 months ACR criteria Kellgren IB, II or III NSAID before D0: stable > 1 month Concomitant paracetamol: ≤ 3 g/day Lequesne[2] > 4 Spontaneous pain (VAS) ≥ 25 mm NSAID not withdrawn before inclusion Other OA long-term treatments not authorised	▪ PIASCLEDINE 300 mg/day ▪ Placebo For 3 months Concomitant treatments: NSAID continued from D0 to D45 then acute withdrawal. Corticosteroid, analgesics and other long-term osteoarthritis treatments not authorised Paracetamol authorised between D0 and D45 for conditions other than osteoarthritis if essential (max 3 g/day)	% of patients with reintroduction NSAID within 45 days of total cessation and resumption time (Kaplan-Meier curve)
PR292 (Mazières, 1998[3]) Phase III	N = 164 Age: 45-75 **Femorotibial osteoarthritis** **Osteoarthritis of the hip** Since > 6 months ACR criteria Kellgren IB, II or III NSAID/analgesics before D0: ≥ 3 months Lequesne: 4 – 14 (≥ 3 months) Spontaneous pain (VAS): ≥ 30 mm NSAID and analgesics withdrawal 2 weeks before inclusion	▪ PIASCLEDINE 300 mg/day ▪ Placebo For 6 months then 2 months' follow-up Concomitant treatments: NSAID other constitutional osteoarthritis treatments, corticosteroids not authorised (except where absolutely necessary: 1 IA injection in the knee authorised).	Change in Lequesne index between D0 and M6

1 Blotman F. et al. Efficacité et tolérance des insaponifiables d'avocat/soja dans le traitement de la gonarthrose et de la coxarthrose symptomatiques. Rev Rhum 1997;64(12):944-54

2 The Lequesne algofunctional index, expressed as the sum of the scores related to pain, maximum distance walked and difficulty in daily life, allows for assessing changes and discomfort experienced by the patient. It is scored on a 0 to 24 scale

3 Mazières B and al. Symptomatic efficacy of avocado/soybean unsaponifiables in the treatment of osteoarthritis of the knee and hip. Arthritis and Rheumatism 1998;41:81-91

Table 1: Description of studies (continued)

Study	No. of patients Inclusion criteria	Groups of treatment and concomitant treatments	Main endpoints
PR594 Appelboom, 2001[4]) Phase III	N = 260 Age: 45-80 **Uni or bicompartmental, uni or bilateral femorotibial osteoarthritis** Since > 6 months ACR criteria Kellgren IB, II or III NSAID before D0: between 90 and 100 mg diclofenac-equivalent 2 weeks before D0 Lequesne: 4 - 12 Spontaneous pain (VAS): ≥ 30 mm No NSAID withdrawal before inclusion	▪ PIASCLEDINE 300 mg/day ▪ PIASCLEDINE 600 mg/day ▪ Placebo For 3 months Concomitant NSAID and analgesic treatments	Average daily consumption of NSAID and analgesics between D30 and D90 in mg diclofenac equivalent
PR1399 (Kahan)	N = 182 Age > 45 **Femorotibial osteoarthritis** Since > 6 months ACR criteria Kellgren IB, II or III Concomitant paracetamol ≤ 3 g/day Spontaneous pain (VAS): ≥ 40 mm Pain + functional difficulties: > 1 month / last 3 Pre-inclusion cessation of NSAID: 5 days Analgesics withdrawal: 2 days	▪ PIASCLEDINE ▪ Placebo For 6 months (concomitant NSAID)	Motion pain (VAS)
PR1600 (Berenbaum)	N = 187 Age > 45 **Upper polar osteoarthritis of the hip** Since > 6 months ACR criteria Narrowing + osteophytosis Lequesne: 4 - 12 Concomitant paracetamol ≤ 4 g/day Spontaneous pain (VAS): ≥ 40 mm Pain + functional difficulties: > 1 month / last 3 Pre-inclusion NSAID withdrawal: 3 days Analgesics withdrawal: 3 days	▪ PIASCLEDINE ▪ Placebo For 6 months (concomitant NSAID)	Lequesne index
PR194 (Blotman) Non-inferiority	N = 128 Age: 45 – 80 **Femorotibial osteoarthritis** Since > 6 months ACR criteria Kellgren IB, II or III Lequesne: 4 – 12 (on NSAID) NSAID before D0: stable >1 month Concomitant paracetamol Spontaneous pain (VAS): ≥ 30 mm on NSAID Pain + functional difficulties No pre-inclusion NSAID and analgesics withdrawal.	▪ PIASCLEDINE ▪ Diacerein For 3 months	Consumption of NSAID and/or analgesics

4 Appelboom T and al. Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. A double-blind, prospective, placebo-controlled study. Scand J Rheumatol 2001;30(4):242-7

Study results:

Blotman study (1997) – PR193

The patients included (n=164) were, on average, 63 years old, and the majority were women (63.8% in the PIASCLEDINE group and 68.7% in the placebo group).
38.0% suffered from osteoarthritis of the hip and 62.0% from osteoarthritis of the knee.
The osteoarthritis was unilateral in 53.1%.

After 3 months' treatment including a period of 45 days with a concomitant NSAID followed by complete withdrawal of the latter, the percentage of patients having restarted NSAID was lower with PIASCLEDINE than with the placebo, as was the daily and total consumption of NSAID and the number of days on NSAID between D45 and D90 (statistically significant differences, see table 2).

Table 2: consumption of NSAID between D45 and D90 (ITT population*) – Blotman study (1997)

Endpoint	**PIASCLEDINE** (n = 77)	**Placebo** (n = 16)	**p (PIASCLEDINE – placebo)**
% NSAID reintroduction from D45 to D90 (%)	43.4	69.7	p<0.001
Daily consumption of NSAID D45-D90 (average in mg/day diclofenac equivalent)	26 ± 38	50 ± 48	p=0.001
Total NSAID consumption between D45 and D90 (in mg diclofenac equivalent)	372	814	p<0.01
Number of days on NSAID	6.3 ± 10.7	11.0 ± 10.2	p<0.01

*: patients undergoing at least one evaluation

Mazières study (1998) – PR292

The patients included (n=164) were 64 years old on average, and the majority were women (74.1% in the PIASCLEDINE group and 69.6% in the placebo group).
30.5% suffered from osteoarthritis of the hip and 69.5% from osteoarthritis of the knee. According to the Kellgren-Lawrence classification, the osteoarthritis was stage IB for 25.6% of patients, stage II for 54.3%, stage III for 17.7%, and stage IV for 2.4% of patients.
A deviation from protocol was observed in 27 patients (11 with PIASCLEDINE and 16 with the placebo). In 20 cases (6 with PIASCLEDINE and 14 with the placebo), this deviation was considered major (at least one corticosteroid infiltration in a joint studied).
11.8% of the patients on PIASCLEDINE and 19.0% of patients on placebo dropped out of the study early. Of the 164 randomised patients, 162 patients with at least 1 evaluation after D0 were included in the ITT analysis.
The investigator deemed patient compliance to be satisfactory for over 95% of patients.

After 6 months' treatment, the improvement in the Lequesne index was greater with PIASCLEDINE than with the placebo (statistically significant difference, see table 3), albeit slight (2.1 point change difference on a 24-point scale).

Table 3: difference in Lequesne index after 6 months' treatment (ITT population with at least 1 evaluation after inclusion) - Mazières study (1998)

Lequesne index	**PIASCLEDINE** (n = 84)	**Placebo** (n = 78)	**Difference PIASCLEDINE - placebo**	**95% CI of difference**
Baseline	9.7 ± 0.3	9.4 ± 0.3	-	-
Month 6	6.8 ± 0.4	8.9 ± 0.4	-2.1 ± 0.5 (p=0.01)	[-3.2; -1]

Appelboom study (2001) – PR594
The patients included (n=260) were 64.9 years old on average, and the vast majority were women (79%). In 60% of cases, their osteoarthritis of the knee was stage II or stage III according to the Kellgren-Lawrence classification, with developing pain symptoms for the past 7.2 years on average. The baseline Lequesne index was 9.7 on average.
During the study there were 54 major deviations from protocol out of the 260 patients included and 35 patients dropped out of the study early (12 in the PIASCLEDINE 300 mg group, 11 in the PIASCLEDINE 600 mg group and 12 in the placebo group), of which 9 due to adverse events, 8 lost to follow-up, 6 due to a concomitant disease, 5 due to a worsening of their symptoms or inefficacy, 3 for personal reasons, 2 for taking an unauthorised treatment, 1 with a Lequesne index of 12 on D15 and one patient who died from a stroke unrelated to treatment.

The patients were treated with PIASCLEDINE or were given the placebo for 3 months. Between months 1 and 2 and between months 2 and 3 (end of the study), the daily consumption of NSAID and analgesics was lower in the PIASCLEDINE 300 mg group than in the placebo group (statistically significant differences, see table 4).
A decrease in the consumption of NSAID and analgesics of at least 50% was observed in 36% of patients in the placebo group versus 71% in the PIASCLEDINE 300 mg group between the M2 - M3 period and the D15 - D0 period ($p<0.01$).

Table 4: Consumption of NSAID and analgesics (diclofenac equivalent) between D30 and D90 (ITT population, comparison to placebo) - Appelboom study (2001)

Consumption of NSAID in mg/day diclofenac equivalent	**PIASCLEDINE 300 mg** (n = 82)	**Placebo** (n = 82)	**p (PIASCLEDINE – placebo)**
D-15 to D0	142.9 ± 47.8	135.9 ± 54.7	
D0 to M1	133.8 ± 53.8	130.0 ± 45.1	
M1 to M2	63.1 ± 48.3	99.0 ± 57.0	p<0.01
M2 to M3	45.2 ± 51.7	81.0 ± 63.4	p<0.01

Kahan study – PR1399
The patients included (n=182) were 66.2 years old on average, and the majority were women (74%). Most patient characteristics were comparable. However, differences between the groups were observed for weight, duration of pain, functional difficulties, number of previous surgeries, number of anomalies in the musculoskeletal system and the proportion of patients given previous treatment for osteoarthritis of the knee over the 30 days prior to inclusion (79% in the placebo group and 61.5% in the PIASCLEDINE group).
According to the Kellgren-Lawrence classification, the osteoarthritis of the knee was stage IB for 40.1% of patients, stage II for 34.6% of patients, and stage III for 25.6% of patients.

In the ITT population (with documented values, without extrapolation), after 6 months' treatment, the pain, measured on a 100mm VAS, was lower with PIASCLEDINE than with the placebo (difference of -7.00 ± 3.13 mm, 95% CI = [-13.13; +0.87], p=0.027). However, this effect is not reaching the 10 mm threshold, considered as clinically relevant.

Berenbaum study – PR1600
The patients included (n=187) were aged 69.2 on average. Patient characteristics were comparable in the two groups.

No statistically significant difference of change in the Lequesne index was evidenced between PIASCLEDINE and placebo after 6 months' treatment, in these patients suffering from upper polar osteoarthritis of the hip.

Blotman study – PR194

This was a non-inferiority study. The patients included (n=128) were aged 65.9 on average. The osteoarthritis of the knee was bilateral in 73.4% of cases and stage II or III in 66.4% of cases. The patient characteristics were comparable in the two groups, except for the higher proportion of women in the PIASCLEDINE group.

After 3 months' treatment, the results demonstrated the non-inferiority of PIASCLEDINE compared to diacerein in the ability to decrease consumption of NSAID or analgesics and in the proportion of patients having reduced consumption by at least 50% (see table 5).

Table 5: Consumption of NSAID and analgesics (diclofenac equivalent) between D0 and D90 (ITT population) - Blotman study PR194

Consumption of NSAID / analgesics	**PIASCLEDINE** (n = 64)	**Diacerein** (n = 64)	**Difference PIASCLEDINE - diacerein**	**90% CI of difference**
mg/day diclofenac equivalent	1185 (-659)	1044 (-864)		
% difference between D0 and D90 (median)	38.4	43.8	-2.2	[-13.4; 5.4]*
% patients ≥ 50% decrease	42.2	46.9	-4.7	[-19.1; 9.7]*

*: PIASCLEDINE was considered non-inferior to diacerein if the lower limit of the 90% confidence interval for the difference between the treatments was less than -20%

NB: the criteria chosen to accept the non-inferiority are not highly restrictive: 90% confidence interval and -20% non-inferiority limit in terms of percentage difference between D0 and D90 and percentage of patients with a decrease in NSAID consumption greater than or equal to 50%.

Specific analysis of results regarding the NSAID sparing effet

This analysis is based on the results of the Blotman (1997 – PR193), Mazières (1998 – RP292), Appelboom (2001 – PR594) and Blotman (PR194) studies during which the patients were given a concomitant NSAID treatment, while their NSAID consumption was recorded.

Reminder of prescription conditions in those studies:

PR193: The patients were to be treated with NSAID in a stable and regular manner for at least 1 month before inclusion. From D0 to D45, the patients had to be given their usual NSAID treatment. On D45, the NSAID treatment was stopped. Patients could then resume their usual treatment between D45 and D90 if this was considered necessary.
The sparing effect was calculated by comparing consumption between D45 and D90 to the consumption defined as "stable" before inclusion and from D0 to D45.

PR292: Patients had to withdraw from any NSAID treatment over the 2 weeks preceding inclusion. As of inclusion, patients were allowed to resume an NSAID and/or analgesics treatment.
The sparing effect was evaluated by comparing consumption with PIASCLEDINE to consumption with the placebo.

PR594: The NSAID consumption was quantified over the 2 weeks preceding the inclusion then over the 3 months' PIASCLEDINE or placebo treatment.
The sparing effect was evaluated, firstly by calculating the change in consumption for each group between the 2 periods, and secondly by calculating the difference in the change in consumption between PIASCLEDINE and placebo.

PR194: In this study, the patients were also treated over 3 months with PIASCLEDINE or placebo. Only the intrinsic variation in NSAID consumption was calculated for each group.

The results in terms of intrinsic variation compared to D0 and in terms of relative variation compared to placebo are expressed as diclofenac equivalent and in numbers of diclofenac 25 mg tablet packs spared (see tables 6 and 7).

Table 6: Intrinsic variation compared to D0 in NSAID consumption expressed as mg diclofenac equivalent / day

	Study PR193	**Study PR194**	**Study PR594**	
	PIASCLEDINE 300	PIASCLEDINE 300	PIASCLEDINE 300	PIASCLEDINE 600
D0 (mg/day)	75.00	143.75	142.90	130.70
Mean with treatment (mg/day)	26.00	78.31	80.70	84.37
Difference (mg/day)	**49.00**	**65.44**	**62.20**	**46.33**
No. of packs of 30 tabs of diclofenac 25 mg spared compared to D0	**1.96**	**2.62**	**2.49**	**1.85**

Table 7: Relative variation in NSAID consumption compared to placebo expressed as mg diclofenac equivalent / day

	Study 193		**Study 292**		**Study 594**		
	PIAS 300	PLACEBO	PIAS 300	PLACEBO	PIAS 300	PIAS 600	PLACEBO
D0	75.00	78.00	-	-	142.90	130.70	135.90
Mean with treatment	26.00	50.00	13.10	23.78	80.70	84.37	103.33
Difference	49.00	28.00	13.10	23.78	62.20	46.33	32.57
Difference vs. placebo	21.00	-	10.68	-	29.63	13.77	-
No. of packs of 30 tabs of diclofenac 25 mg compared to D0 vs. placebo	**0.84**	**-**	**0.43**	**-**	**1.19**	**0.55**	**-**

In patients treated with PIASCLEDINE, 1.85 to 2.62 packs of NSAID were spared per month in the form of diclofenac 25 mg compared to the baseline and 0.43 to 1.19 packs compared to placebo.

3.2. Safety

The adverse events referred to in the SmPC (December 13, 2007) are as follows:

- rare regurgitations with a fatty odour that can be avoided by taking the capsule during meals
- rare cases of hypersensitivity[5]
- exceptional cases of liver disorders with elevated transaminases, alkaline phosphatases, bilirubin or gamma GT[5]
- gastrointestinal disorders: diarrhoea and epigastric pain (frequency unknown).

In the study comparing PIASCLEDINE to diacerein (Blotman – PR194), the incidence of adverse events was 42.2% with diacerein and 25.0% with PIASCLEDINE. Diarrhoea was very frequent with diacerein (35.9% versus 12.5% with PIASCLEDINE).

[5] Pharmacovigilance data

3.3. Conclusion

The efficacy of PIASCLEDINE was evaluated in 6 randomised, double-blind studies lasting 3 and 6 months, of which 5 were placebo-controlled and 1 in comparison to diacerein. The patients included in these studies had osteoarthritis of the knee (5 studies) or of the hip (1 study) meeting ACR criteria, stage IB, II or III according to the Kellgren-Lawrence classification, with a Lequesne index greater than 4. The patients had to have VAS (100 mm) spontaneous pain ≥ 25, 30 or 40 mm depending on the study.

During the placebo-controlled studies, PIASCLEDINE was superior to placebo, in statistically significant terms, in decreasing the consumption of NSAID evaluated in 2 studies (Blotman-PR193 and Appelboom-PR594). This effect can be considered as moderate.

The effect of PIASCLEDINE on the Lequesne index was evaluated in 2 studies (Mazières-PR292 and Berenbaum-PR1600). A slight statistically significant decrease in the Lequesne index (2.1 points on a 24-point scale) was observed compared to the placebo in the Mazières-PR292 study only.

In one study (Kahan-PR1399), a statistically significant decrease in pain, but inferior to the 10 mm threshold considered as clinically relevant, was observed for PIASCLEDINE (-7.00 ± 3.13 mm on VAS).

In the study in comparison to diacerein (Blotman-PR194) lasting 3 months, the results demonstrated the non-inferiority of PIASCLEDINE compared to diacerein in terms of decreased consumption of NSAID or analgesics.

The main adverse events observed with PIASCLEDINE were gastrointestinal effects. In the Blotman study (PR194), diarrhoea was observed in 12.5% of the patients treated with PIASCLEDINE and 35.9% of those treated with diacerein.

All studies included, the NSAID sparing effect, in terms of packs per month of 30 tablets of diclofenac 25 mg, in patients treated with PIASCLEDINE was 1.85 to 2.62 packs when compared to baseline and 0.43 to 1.19 packs when compared to placebo. The clinical relevance of this decrease in NSAID consumption in terms of decreased digestive complications is not known.

To conclude, PIASCLEDINE showed little efficacy in improving pain symptoms and articular function in osteoarthritis patients and had a moderate effect on the decrease in consumption of NSAID, with a positive safety profile.

4 DRUG USAGE DATA

4.1. Observational study

The aim of this study was to evidence and quantify a NSAID sparing effect, as well as other concomitant drugs (analgesics, anti-ulcer drugs, gastric demulcents and topical NSAID) under real conditions of PIASCLEDINE use.

This is a retrospective study based on Thales-Herakles network data relating to the monitoring of osteoarthritis patients.
The study plan included:

1) the comparison of patients treated with PIASCLEDINE to control patients with the same characteristics;
2) the comparison, within the PIASCLEDINE group, of the different variables studied, before and after treatment.

The patients included had been diagnosed with osteoarthritis and had had at least one consultation and/or prescription for this reason over the 24 months prior to inclusion. They must not have been treated with a slow-acting osteoarthritis drug during the 12 months prior to the study. The inclusion period was between 01/03/2006 and 31/12/2006. The patients had to be monitored for more than 12 months before and after inclusion.

In practice, initially, 13,916 observations were identified, of which 780 met the inclusion criteria for the PIASCLEDINE group. The control group of 780 patients was formed from the remaining 13,136 observations.
Secondly, the population included was limited to patients with osteoarthritis of the hip and knee, in accordance with the wording of the MA's indication. Hence, the study's final population was 621 patients, 314 in the PIASCLEDINE group and 307 in the control group.

The endpoints were:
- NSAID consumption:
  - number of patients receiving a prescription for NSAID at least once
  - number of days' treatment per year
  - number of prescriptions per patient
  - number of courses of treatment
- Consumption of other drugs and other care related to osteoarthritis

Results:

1) Characteristics of patients included (see table 8)

Table 8: Main characteristics of patients included (results expressed as n/N (%) or mean ± standard deviation)

	CONTROL	PIASCLEDINE 300
Gender: Male	108 (34.4%)	92 (30%)
Female	206 (65.6%)	215 (70%)
Age (years)	73.2 ± 10.4	68.7 ± 10.4
Age of record (years)	6.4 ± 1.3	6.4 ± 1.5
Age of diagnosis (years)	5.4 ± 1.8	4.8 ± 2.2
Diagnosis: Osteoarthritis of the knee	230 (73.2%)	248 (80.8%)
Osteoarthritis of the hip	113 (36%)	85 (27.7%)
Diffuse or exacerbations OA	145 (46.2%)	145 (47.2%)
Other osteoarthritis location	130 (41.4%)	133 (43.3%)
Number of prior digestive problems	18.1 ± 30.2	11.4 ± 21.9
SySADOA* prescribed before the study	108/314 (34.4%)	177/307 (57.7%)

* SySADOA: symptomatic slow-acting drug in osteoarthritis

Due to a lack of homogeneity in certain characteristics, the analysis of the results was completed by an adjusted-model analysis (logistic regression model).

1) Consumption of NSAID compared to control group
14.0% of patients in the PIASCLEDINE group and 19.7% of the placebo group received at least 1 NSAID prescription. The adjusted difference is statistically significant (see table 9).

A statistically significant difference in favour of PIASCLEDINE was observed for the criteria "number of prescriptions per patient", "number of courses of treatment" and "number of DDD units", but no statistically significant difference was evidenced for the "number of days' treatment" criterion (see table 9).

Table 9: Results for NSAID consumption compared to control group (results expressed as n/N (%) or mean ± standard deviation [N])

	CONTROL	PIASCLEDINE 300	p
No. of patients having at least 1 NSAID prescription	62/314 (19.7%)	43/307 (14%)	0.01*
No. of days' treatment / year	19.1 ± 59.8 [313]	11.3 ± 40.7 [306]	0.06
No. of prescriptions / patient	0.5 ± 1.5 [314]	0.2 ± 0.8 [307]	0.005
No. of courses of treatment	0.3 ± 0.7 [314]	0.2 ± 0.6 [307]	0.02

* probability associated with "treatment with PIASCLEDINE 300" factor (Yes/no) of logistical regression model. The probability associated with the Chi2 test (non-adjusted model) is not significant (p=0.056).

3) Consumption of other drugs and other care related to osteoarthritis compared to control group

A statistically significant difference in favour of PIASCLEDINE was observed for a percentage of patients being treated with topical NSAID, analgesics, anti-spasmodic drugs, or anti-diarrhoeal drugs, in terms of number of days of anti-ulcer drugs and number of consultations (see table 10).

No statistically significant difference was observed in the administration of corticosteroids and muscle relaxants (see table 10).

Table 10: Results for the consumption of other drugs and other care related to osteoarthritis compared to control group (results expressed as n/N (%) or mean ± standard deviation [N])

	CONTROL	PIASCLEDINE 300	p
Topical NSAID application	141/314 (44.9%)	113/307 (36.8%)	0.04
Analgesics intake	288/314 (91.7%)	226/307 (73.6%)	<0.001
Corticosteroids intake	33/314 (10.5%)	35/317 (11.4%)	NS
Muscle relaxants intake	27/314 (8.6%)	18/307 (5.9%)	NS
Antispasmodic drugs intake	25/314 (8%)	41/307 (13.4%)	0.03
Anti-ulcer drugs intake	162/314 (51.6%)	86/307 (28%)	<0.001
No. days on anti-ulcer drugs	122.5 ± 164.9 [62]	48.8 ± 99.5 [43]	< 0.01
Anti-diarrhoeal drugs intake	39/314 (12.4%)	15/307 (4.9%)	0.001
No. of consultations	8.7 ± 5 [314]	7.1 ± 3.6 [307]	< 0.001

4) Pre- and post-treatment comparison of NSAID consumption in PIASCLEDINE group

This data cannot be used as very few patients were treated with NSAID at the time of inclusion (14.7%) and a large number of patients had taken symptomatic slow-acting drugs in osteoarthritis over the 12 months prior to inclusion (57.7%) while, according to protocol, these patients should not have been included.

Conclusion:

Statistically significant differences in favour of PIASCLEDINE were observed compared to the untreated group in terms of NSAID consumption and concomitant prescriptions, particularly of analgesics (92% of patients vs. 74%) and anti-ulcer drugs (52% vs. 28%), however, the study's retrospective method limits the impact of these results.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Reassessment of the actual benefit

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

This product is a symptomatic treatment with delayed effect.

Public health benefit:

Osteoarthritis of the hip and osteoarthritis of the knee are a substantial 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. The solution to this need does not stem solely from drugs.

The data available on pain and algofunctional indexes does not lead to the conclusion that soya-bean oil and avocado oil unsaponifiables help to improve quality of life and reduce functional limitations: absence of quality of life data, little effect on symptoms.

The hypothetical benefit of symptomatic slow-acting drugs in osteoarthritis, in terms of public health, lies in the decrease in NSAID consumption, which can help reduce the frequency of adverse digestive effects that are particularly deleterious among the elderly. For soya-bean and avocado oil unsaponifiables, the data available shows an ability to decrease NSAID consumption. However, the clinical relevance of this decrease in NSAID consumption, in terms of decreased morbidity and mortality related to digestive haemorrhages, is unknown.

Consequently, PIASCLEDINE does not provide a public health benefit.

This product has little efficacy in improving the symptoms of osteoarthritis. The efficacy/adverse effects ratio is moderate.

The management of osteoarthritis depends first and foremost on diet and lifestyle changes (weight loss, regular exercise) rather than pharmacological measures (physiotherapy, orthoses, cane, etc.). Symptomatic treatment mainly involves oral NSAID and analgesics. This product has limited therapeutic relevance.

The actual benefit of PIASCLEDINE 300 mg capsules is low.

5.2. Therapeutic use

The first measures to take for the treatment of symptomatic osteoarthritis of the lower limbs are dietary and lifestyle-related (decrease in excess weight, regular exercise when no exacerbation of pain or congestion when exercise should be reduced) rather than pharmacological (physiotherapy, orthosis, walking stick, etc.).

During the symptomatic phases, the treatment mainly comprises analgesics, starting with paracetamol, and in the event of acute exacerbation, short-term oral NSAID at a minimal effective dose.

Local treatments can also be used, such as topical NSAID, intra-articular corticosteroid injections, especially during congestive phases, or hyaluronic acid injections.

Symptomatic slow-acting drugs in osteoarthritis (chondroitin sulphate CHONDROSULF, avocado and soya-bean oil unsaponifiables, diacerein and glucosamine) have moderate efficacy on both pain and functional impairment and it has not been demonstrated that they substantially reduce NSAID consumption. Their therapeutic relevance is therefore limited.

Surgery (arthroplasty, fitting of prosthesis) is limited to cases of osteoarthritis that have progressed according to X-ray, and that are painful, incapacitating, and refractory to usual treatments.

5.3. 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 hospital and various public services.

This recommendation is subject to the creation and completion of a study within 2 years to demonstrate the effect of prescribing PIASCLEDINE 300 mg on the reduction of NSAID consumption.

Packaging: Appropriate for prescription requirements.

Rate: 35%