HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

26 November 2008

ART 50 mg, capsule
Pack of 30 capsules (CIP: 335 529-3)

Applicant: NEGMA

Diacerein

ATC Code: M01AX21

Marketing authorisation (MA) date: 12 August 1992, modified 12 October 2007 (modification of indication following the reassessment of the benefit-risk ratio of symptomatic slow-acting drugs for osteoarthritis)

Reason for request: Reassessment of actual benefit according to article R. 163-21 of the Social Insurance Code

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Diacerein

1.2. Indication

Previous indication:
"Symptomatic treatment of functional symptoms and signs of osteoarthritis.
Comments: As action onset is deferred, a period of 30 to 45 days precedes analgesic effect onset. Treatment may therefore have to be initiated with standard immediate action onset analgesic/anti-inflammatory drugs."

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

1.3. Dosage

"2 capsules per day, in two divided doses of 1 capsule, morning and evening."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

M	Muscle and skeleton
M01	Anti-inflammatory and antirheumatic drugs
M01A	Nonsteroidal anti-inflammatory and antirheumatic drugs
M01AX	Other nonsteroidal anti-inflammatory antirheumatic drugs
M01AX21	Diacerein

2.2. Medicines in the same therapeutic category

Other symptomatic slow-acting drugs for osteoarthritis (SYSADOA):

Active ingredient	Proprietary product	Presentation	Indication
Chondroitin (sulphate)	CHONDROSULF 400 mg	Capsule and granules for oral solution in sachets	"Symptomatic slow-acting treatment of osteoarthritis of the hip and knee"
Chondroitin (sodium sulphate)	STRUCTUM 500 mg	Capsule	Second-line treatment of osteoarthritis pain
Diacerein	ZONDAR 50 mg	Capsule	"Symptomatic slow-acting treatment of osteoarthritis of the hip and knee"
Unsaponifiable extracts of avocado and soybean	PIASCLEDINE 300 mg	Capsule	"Symptomatic slow-acting treatment of osteoarthritis of the hip and knee"

2.3. Medicines with a similar therapeutic aim

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

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The dossier submitted by the company includes:

- 7 randomised, double-blind, placebo-controlled studies including one which will not be assessed below as it had a primary radiological endpoint inappropriate for validation of the MA indication of “symptomatic treatment”;
- 2 randomised double-blind studies versus NSAIDs (diclofenac, piroxicam).

3.1.1. Placebo-controlled studies

The protocol of these studies is summarised in table 1 below.

Table 1: Description of placebo-controlled studies

Study	Number of patients Inclusion criteria	Treatment groups and concomitant treatments	Primary endpoints
Amor and Dougados (1994)[1]	N = 288 Hip Osteoarthritis (Lequesne criteria) Radiological stage I, II or III Pain intensity on mobilisation measured with a visual analogue scale (VAS) ≥ 40 mm NSAIDs discontinued for at least 3 days and corticosteroids for at least 1 month	▪ Diacerein (50 mg bid) ▪ Tenoxicam (20 mg qd) ▪ Diacerein (50 mg bid) + tenoxicam (20 mg qd) ▪ Placebo For 2 months	Pain (VAS)
Ascherl (1994)[2]	N = 111 Age: 18 to 70 years Stage I to III unilateral or bilateral osteoarthritis of the knee (EULAR diagnosis), Continuous pain for at least 2 months or Acute pain associated with one pain episode of at least 4 months during last 2 years Lequesne index ≥ 8	▪ Diacerein (50 mg bid) ▪ Placebo For 6 months	Lequesne index
Lequesne (1998)[3]	N = 183 Age: 35 to 80 years Primary hip and/or tibiofemoral osteoarthritis (EULAR criteria) Pain on movement ≥ 33 mm (100 mm VAS) Pain ≥ 2 months Discontinuation of NSAIDs for at least 48 hours, analgesics for at least 8 hours, oral corticosteroids for at least 1 month and local corticosteroid injections for at least 2 months	For 2 months in combination with a NSAID Then 4 months as monotherapy and 2 months of follow-up without treatment 1st period: ▪ Diacerein (50 mg bid) + Voltaren (50 mg bid) ▪ Placebo + Voltaren (50 mg bid) 2nd period: ▪ Diacerein (50 mg bid) ▪ Placebo 3rd period: No treatment	Pain (VAS)
Pelletier (2000)[4]	N = 484 Age: 40 to 80 years Primary knee osteoarthritis according to ACR criteria Pain on mobilisation ≥ 35 mm with a 100-mm visual analogue scale (VAS) after a "wash-out" period Kellgren-Lawrence grade I, II and III, radiological signs of osteoarthritis of tibiofemoral compartment Discontinuation of NSAIDs 7 days before randomisation Discontinuation of corticosteroid injections 3 months before randomisation Discontinuation of oral corticosteroids 1 month before randomisation	▪ Diacerein 50 mg/day ▪ Diacerein 100 mg/day ▪ Diacerein 150 mg/day ▪ Placebo For 4 months	Pain (VAS)

[1] Nguyen M et al. Diacerein in the treatment of osteoarthritis of the hip. *Arthritis & Rheumatism* 1994; 37: 529-536
[2] In-house report
[3] Lequesne M et al. Efficacité et tolérance de la diacerhéine dans le traitement de la gonarthrose et de la coxarthrose. *La revue du praticien* 1998 ; 48 : S31-S35
[4] Pelletier et al. Efficacy and safety of diacerein in osteoarthritis of the knee : a double-blind, placebo-controlled trial. *Arthritis Rheum* 2000; 43: 2339-2348

Table 1: Description of placebo-controlled studies (continued)

Study	Number of patients Inclusion criteria	Treatment groups and concomitant treatments	Primary endpoints
Pham (2004)[5]	N = 301 Primary tibiofemoral osteoarthritis of the knee (ARC and radiological criteria) Pain on movement > 30 mm (100 mm VAS) Joint space > 2 mm	▪ Diacerein: 100 mg/day for 12 months + 3 courses of 3 intra-articular injections/week of physiological saline ▪ Hyaluronic acid NRD 101: 1 diacerein placebo capsule bid for 12 months + 3 courses of 3 intra-articular injections/week of NRD 101 ▪ Placebo group: 1 diacerein placebo capsule bid for 12 months + 3 courses of 3 intra-articular injections/week of physiological saline To maintain the blindness, the intra-articular administration was made by a different physician to the evaluating physician. ▪ Emergency medication: analgesics (2-day wash-out before an evaluation); NSAIDs (7-day wash-out before an evaluation) For 1 year	Pain (VAS)
Pavelka (2007)[6]	N = 168 40-75 years Tibiofemoral knee osteoarthritis (clinical and radiological ARC criteria) Kellgren-Lawrence stage II or III radiological lesions, Pain ≥ 40 mm (100-mm VAS) with at least 2 items of WOMAC A score present for at least 15 days during previous month	▪ Diacerein: 50 mg bid ▪ Placebo: 1 diacerein placebo capsule bid For 3 months Then 3 months of follow-up without treatment Emergency medication: paracetamol (max 3 g/day), except on the night before an evaluation and the day of the evaluation	WOMAC pain score WOMAC total score

Results of placebo-controlled studies:

Amor and Dougados Study (1994)

Enrolled patients had an average age of 63 years and hip osteoarthritis characterised by a mean VAS (100 mm) pain score of 64 mm and a Lequesne[7] index of 10.

Premature trial discontinuations were more frequent in the diacerein and placebo groups than in the tenoxicam and tenoxicam + diacerein groups. The main reasons for discontinuation were the occurrence of adverse events and insufficient efficacy (see table 2).

[5] Pham T et al. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101. in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. *Ann Rheum Dis* 2004; 63: 1611-1617

[6] Pavelka K et al. The efficacy and safety of diacerein in the treatment of painful osteoarthritis of the knee. A randomized, multicenter, double-blind, placebo-controlled study with primary en points at 2 months after the end of a 3-month period. *Arthritis Rheum 2007; 56:* 4055-4064

[7] The Lequesne algofunctional index expressed by the sum of scores for pain, maximum distance walked and difficulties in activities of daily living is used to assess the changes and discomfort experienced by the patient. It is scored from 0 to 24.

Table 2: Premature trial discontinuations – Amor and Dougados study (1994)

	Diacerein	Tenoxicam	Placebo
Number of randomised patients	75	75	71
Premature study discontinuations: n (%)	15 (20)	9 (12)	12 (17)
Reason (n):			
Adverse events	6	2	4
Lack of efficacy	6	5	7
Other reasons	3	2	1

After 2 months of treatment, a statistically significant difference was observed in favour of diacerein and tenoxicam compared to placebo. However, these differences were lower than the threshold of 10 mm considered as clinically relevant (see table 3).

Table 3: Change in pain after 2 months of treatment (ITT population) – Amor and Dougados study (1994)

Pain (100 mm VAS): Mean ± standard deviation	**Diacerein 50 mg bid** N=75	**Tenoxicam 20 mg/day** N=75	**Placebo** N=71
Inclusion (mm)	62.8 ± 1.5	63.9 ± 1.5	63.8 ± 1.4
Change at 2 months (mm)	-22.6 ± 2.9 *	-25.8 ± 3.0 **	-16.2 ± 3.0

* : statistically significant difference versus placebo: p=0.025
** : statistically significant difference versus placebo: p=0.001

Ascherl Study (1994)

The mean age of included patients was of 57 years. The percentage of women was lower in the diacerein group (46%) than in the placebo group (63%). Knee osteoarthritis was bilateral in 71% of patients in the diacerein group and 81% of patients in the placebo group.
The number of premature study discontinuations was 12/59 patients (i.e. 20%) in the diacerein group and 10/52 patients (i.e. 19%) in the placebo group. The main reason for discontinuation in both groups was the occurrence of adverse events.

After 6 months of treatment, the reduction in the Lequesne function index was greater with diacerein than with placebo (- 1.7, statistically significant difference, see table 4).

Table 4: Change in Lequesne index after 6 months of treatment (ITT population with last available value) – Ascherl study (1994)

Lequesne index: Mean ± standard deviation	**Diacerein 50 mg bid**	**Placebo**
Inclusion	(n = 59)	(n = 52)
	12.9 ± 3.7	12.6 ± 3.6
6 months	(n = 51)	(n = 44)
	7.7 ± 5.1	9.9 ± 4.8
Change	-4.5 ± 3.7 *	-2.8 ± 3.6

* : statistically significant difference versus placebo: p=0.01

Lequesne study (1998)

The included patients had a mean age of 62 years and were mainly women (68%). The osteoarthritis was mainly located in the knee: 66% of patients had knee osteoarthritis and 34% hip osteoarthritis in the diacerein group and 58% of patients had knee osteoarthritis and 42% hip osteoarthritis in the placebo group. Pain intensity in the 2 groups was 60 mm on a 100-mm VAS. The Lequesne index was of 10 for the 2 disease sites.

There were many premature study discontinuations in the 2 groups (29/90 patients in the diacerein group i.e. 32%, and 34/93 patients i.e. 37%, in the placebo group). The main reason for discontinuation was the occurrence of an adverse event with diacerein (14 patients) and lack of efficacy in the placebo group (15 patients).

Results for the change in pain intensity evaluated with a 100-mm VAS (see table 5):

- at 6 months (2 months in combination with diclofenac followed by 4 months as monotherapy): there was a significantly greater reduction in pain in the diacerein group than in the placebo group (-20.1 ± 25.3 mm vs -9.0 ± 26.9 mm, p<0.01)
- at 8 months (2 months of follow-up without treatment): there was a significantly greater reduction in pain in the diacerein group than in the placebo group (-22.2 ± 24.1 mm vs -11.6 ± 28.0 mm, p<0.01).

At 6 and 8 months, the observed differences with placebo reached the threshold of 10 mm considered to be clinically relevant.

Table 5: Change in pain measured using a VAS (ITT population with last available value) – Lequesne study (1998)

Pain (100 mm VAS): Mean ± SD	**Diacerein 50 mg bid** (n= 90)	**Placebo** (n=93)
Inclusion	59.0 ± 18.2	60.1 ± 15.6
6 months	38.9 ± 24.4	51.0 ± 25.2
Change (mm)	-20.1 ± 25.3 *	-9.0 ± 26.9
8 months	36.8 ± 25.5	48.5 ± 26.8
Change (mm)	-22.2 ± 24.1 *	11.6 ± 28.0

* : statistically significant difference versus placebo

Pelletier study (2000)

The mean age of included patients was of 64 years. Their knee osteoarthritis was characterised by a mean pain intensity of 70 mm (VAS) and a mean normalised WOMAC score of 177.

There were many premature study discontinuations in the 3 diacerein groups and in the placebo group. The main reasons for discontinuation were adverse events and lack of efficacy (see table 6).

Table 6: Premature study discontinuations – Pelletier study (2000)

	Diacerein 50 mg/day	**Diacerein 100 mg/day**	**Diacerein 150 mg/day**	**Placebo**
Number of randomised patients	126	111	122	125
Premature study discontinuations: n (%)	43 (34)	31 (28)	47 (39)	45 (36)
Reason (n):				
Adverse event	16	11	23	14
Lack of efficacy	21	12	16	23
Other reasons	6	8	8	8

After 4 months of treatment, a statistically significant but non clinically relevant difference was observed between diacerein 100 mg/day (dosage recommended by MA) and placebo in terms of the reduction in pain intensity: difference of -7.5 mm ($CI_{95\%}$ = [-13.4 ; -1.6], p<0.05, see table 7).
No significant difference was observed relative to placebo in the diacerein 50 and 150 mg/day groups.

Table 7: Change in pain intensity after 4 months of treatment (ITT population*) – Pelletier study (2000)

Pain (100 mm VAS):	**Diacerein 50 mg /day** (n = 126)	**Diacerein 100 mg/day** (n = 110)	**Diacerein 150 mg/day** (n = 122)	**Placebo** (n = 124)
Inclusion: Mean ± standard deviation (mm)	67.3 ± 17.7	73.6 ± 16.7	69.9 ± 18.8	70.5 ± 19.1
Change at 4 months (mm)	-16.2	-18.8**	-15.2	-11.4

* : 4 randomised patients were excluded from the ITT population as there was no value after inclusion
** : statistically significant difference versus placebo

Pham study (2004)
The mean age of enrolled patients was of 65 years. Most patients had stage III (74% of patients) and stage II (14% in the diacerein group and 23% in the placebo group) knee osteoarthritis according to the Kellgren-Lawrence staging system. This was characterised by a pain intensity of 60 mm on a 100 mm VAS and a Lequesne index of 10.
After 4 months of treatment, a reduction in pain intensity of about 34 mm (VAS) was observed in the three groups (diacerein, intra-articular hyaluronic acid injection and placebo) but there was no statistically significant difference between them.

Pavelka study (2007)
Enrolled patients had a mean age of 64 years with a large majority of women (80%). Their knee osteoarthritis was characterised by a WOMAC pain score (from 0 to 500) of 239 in the placebo group and 261 in the diacerein group.
The number of premature study discontinuations was of 8/84 patients in both the diacerein and placebo groups. The reason for discontinuation was an adverse event for 3 patients with diacerein and 4 with placebo and lack of efficacy for 3 patients with diacerein and 3 with placebo.

After 3 months of treatment followed by 2 months without treatment, diacerein induced a statistically significant reduction in the WOMAC pain score compared to placebo but this had little clinical relevance (difference of 47 points on a scale from 0 to 500; see table 8).

Table 8: Change in WOMAC A score (ITT population) – Pavelka study (2007)

WOMAC A (score from 0 to 500)	Diacerein 50 mg bid (n = 82)	Placebo (n = 83)
Inclusion	261 ± 87	239 ± 80
Month 3 (end of treatment)	153 ± 104*	191 ± 112
Month 5 (primary endpoint)	144 ± 106*	191 ± 108
Month 6 (end of follow-up)	148 ± 110*	192 ± 113

* : statistically significant difference versus placebo: p<0.001

A similar result was obtained for the total WOMAC score (see table 9)

Table 9: Change in total WOMAC score (ITT population) – Pavelka study (2007)

Total WOMAC score (from 0 to 2400)	Diacerein (n = 82)	Placebo (n = 83)
Inclusion	1251 ± 422	1183 ± 386
Month 3 (end of treatment)	834 ± 508*	982 ± 530
Month 5 (primary endpoint)	733 ± 499*	1011 ± 514
Month 6 (end of follow-up)	759 ± 511*	985 ± 547

* : statistically significant difference versus placebo: p<0.05

3.1.2. Studies versus NSAIDs

Two recent randomised, double-blind studies were submitted, one versus diclofenac (Tang, 2006) and the other versus piroxicam (non-inferiority study: Louthrenoo, 2007). The protocols of these studies are summarised in table 10 below.

Table 10: Description of studies versus NSAIDs

Study	Number of patients Age Diagnosis	Treatment groups and concomitant treatments	Endpoint
Tang (2006)[8]	N = 223 40 to 75 years Tibiofemoral osteoarthritis of the knee (ACR criteria) Kellgren-Lawrence Stage II or III Pain on movement ≥ 40 mm on 100-mm VAS, pain present for at least 15 days during previous month	▪ Diacerein (50 mg bid) ▪ Diclofenac (25 mg tid) For 3 months then 1 month of follow-up without treatment Withdrawal of NSAIDs 1 week before inclusion Emergency medication: paracetamol	Pain on walking for 20 meters (100 mm VAS)
Louthrenoo (2007)[9]	N = 171 40 to 65 years Tibiofemoral osteoarthritis of the knee (ACR criteria) Kellgren-Lawrence Stage II or III, Pain ≥ 40 mm (100-mm VAS) for at least 2 items of WOMAC A (pain) and present for at least 15 days during previous month	▪ Diacerein (50 mg bid) ▪ Piroxicam (10 mg bid) For 4 months then follow-up without treatment for 2 months Withdrawal of NSAIDs 1 week before inclusion Emergency medication: paracetamol	WOMAC A pain score at 5 months Non-inferiority test

Study Results:

Tang study (2006): versus diclofenac

Enrolled patients had a mean age of 59 years and there was a large majority of women (83%). Their knee osteoarthritis was characterised by a pain intensity on walking (20 m) of 63 mm on a 100 mm VAS and a mean WOMAC score of 623 (score from 0 to 2400).

The number of premature study discontinuations was 20/111 (i.e. 18%) in the diacerein group and 19/112 (i.e. 17%) in the placebo group. The main reasons for study discontinuation were the occurrence of adverse events (9 with diacerein and 10 with

[8] Zheng WJ et al. Efficacy and safety of diacerein in osteoarthritis of the knee: a randomized, multicenter, double-dummy, diclofenac-controlled trial in China. APLAR *J Rheumatol* 2006; 9: 64-69

[9] Louthrenoo W et al. The efficacy, safety and carry-over effect of diacerein in the treatment of painful knee osteoarthritis: a randomised, double-blind, NSAID-controlled study. *Osteoarthritis and Cartilage* 2007; 15: 605-614

diclofenac) and loss to follow-up (9 with diacerein and 8 with diclofenac) because of the SARS epidemic as patients were enrolled in China.

After 3 months of treatment, the pain on walking was reduced in the 2 groups but without a statistically significant difference.
Between 3 and 4 months (follow-up without treatment), there was no additional reduction in pain in the 2 groups. Pain intensity remained stable in the diacerein group and there was a very slight increase in the diclofenac group. Although there was a statistically significant difference between the groups in favour of diacerein, it was not clinically relevant as it was < 5 mm (see table 11).

Table 11: Pain on walking for 20 m (ITT population with at least 1 available value after inclusion) – Tang study (2006)

Pain (100 mm VAS): mean ± standard deviation	Diacerein 50 mg bid (n= 106)	Diclofenac 25 mg tid (n= 107)
M0 (Inclusion)	61.5 ± 17.0	63.9 ± 17.8
M3	28.6 ± 19.7	27.3 ± 18.3
Change M3 – M0 (mm)	-32.9 ± 21.6	-36.7 ± 18.7
M4	29.7 ± 19.5	33.0 ± 23.2
Change M4 – M0 (mm)	1.1 ± 14.2*	5.7 ± 17.5

* : statistically significant difference versus diclofenac: p<0.05

NB: There was no sample size calculation or statistical hypothesis testing for superiority.

Louthrenoo study (2007): versus piroxicam

Included patients had a mean age of 54 years with a large majority of women (91%). Their knee osteoarthritis was characterised by a WOMAC pain score of 280 (score of 0 to 500). Both knee joints were affected in 78% of patients in the diacerein group and 90% of patients in the placebo group. There were similar proportions of stage II and III patients in the 2 groups.

The number of study discontinuations was 11/86 patients (i.e. 13%) in the diacerein group and 10/85 patients (i.e. 12%) in the piroxicam group. Six patients discontinued the study for adverse events with piroxicam versus 3 with diacerein. Three patients discontinued the study for lack of efficacy with piroxicam and 4 with diacerein. One hundred and sixty-one of the 171 randomised patients were analysed (exclusion of 10 patients with no value after inclusion).

After 4 months of treatment, the reduction in the WOMAC pain score with diacerein was non-inferior to that obtained with piroxicam (see table 12).

Table 12: Change in the WOMAC pain score (ITT population with at least 1 available value after inclusion) – Louthrenoo study (2007)

WOMAC pain (score from 0 to 500): mean ± standard deviation	Diacerein (50 mg bid) N=82	Piroxicam (10 mg bid) N=79
Inclusion	284 ± 65	275 ± 63
4 months	85 ± 86	71 ± 70
5 months (primary efficacy endpoint)	90 ± 91 *	145 ± 129
6 months	83 ± 88**	201 ± 162

* : statistically significant difference versus piroxicam: p<0.01

** : statistically significant difference versus piroxicam: p<0.0001

At 5 months (4 months of treatment and 1 month of follow-up without treatment), the WOMAC pain score remained lower relative to baseline with diacerein whereas it increased with piroxicam. The difference observed between the 2 treatments was statistically significant.

A similar result was observed at 6 months (4 months of treatment and 2 months of follow-up without treatment).

NB: in the Tang (2006) and Louthrenoo (2006) studies it would have been useful to add a placebo arm to check the efficacy of treatments versus placebo and the remanence of effects versus placebo during the follow-up periods.

3.1.3. Meta-analyses

Fidelix (2006, Cochrane review)[10]

This meta-analysis included 7 randomised, placebo- or active comparator-controlled studies including those described above: N'Guyen, 1994; Lequesne, 1998; Dougados, 2001; Pham, 2004 and Pelletier, 2000. This analysis concerned 2,069 patients with osteoarthritis of the lower limbs (diacerein: 1,089. comparator: 986). One study versus Harpagophytum procubens, a product without MA, was also included (Chantre study, 2000).

Effect on pain (5 studies, n=1,228)

The reduction in pain was greater with diacerein than with placebo with a weighted average difference (on a 100-mm VAS) of 5.16 mm ($CI_{95\%}$ = [- 9.75; -0.57]; statistically significant difference, p not provided), however, the heterogeneity test was significant (p=0.04). When the studies were analysed separately according to the affected joint, no significant difference was demonstrated.

Effect on function (Lequesne index) (4 studies, n=1,006)

No statistically significant difference versus placebo was demonstrated for all patients with a weighted mean difference of -0.29 ($CI_{95\%}$= [- 0.87; 0.28]), or in the knee and hip osteoarthritis sub-groups.

Rintelen (2006)[11]

This meta-analysis included studies published between 1985 and 2005 i.e. 19 comparative, randomised studies that included 2,637 patients (diacerein: 1,328; comparator: 1,309). Eight of these studies were conducted vs placebo and 11 vs active comparator (diclofenac, tenoxicam, piroxicam, naproxen); 8 were performed in patients with osteoarthritis of the knee, 2 in patients with osteoarthritis of the hip, and 8 in patients with knee or hip osteoarthritis (location not specified in one study). A follow-up period without treatment was planned in 11 studies, for 1 month (5 studies), 2 months (4 studies), or 3 months (2 studies).
This meta-analysis also included the Chantre study (2000) vs Harpagophytum procubens.

The analysis was performed by calculating the Glass score. This score expresses the standardised mean difference between the product and its comparator. It ranges from -4 (much worse than comparator) to +4 (much better than comparator). A difference of more than 0.8 points in the Glass score is generally considered to be clinically relevant.

[10] Fidelix TSA, Soares BGDO, Trevisani VF M. Diacerein for osteoarthritis. *The Cochrane Database of Systematic reviews* 2006. Issue 1. Art.No: CD005117.pun2. DOI: 10.102/12651858.CD005117.pub2

[11] Rintelen B et al. A meta-analysis of controlled clinical studies with diacerein in the treatment of osteoarthritis. *Arch Intern Med* 2006; 166: 1899-1906

Effect on pain

In the placebo-controlled studies:

- At the end of the treatment, the Glass score = 1.5 ($CI_{95\%}$= [0.80 ; 2.20]), with a statistically significant difference (p value not provided) in favour of diacerein;
- At the end of the follow-up period without treatment, the Glass score = 2.67 ($CI_{95\%}$= [1.27 ; 4.07]), with a statistically significant difference (p value not provided) in favour of diacerein.

In the active comparator-controlled studies (mainly NSAIDs):

- At the end of treatment, no statistically significant difference between groups
- At the end of the follow-up period without treatment, statistically significant difference (p value not provided) in favour of diacerein (Glass score = 2.13 $CI_{95\%}$= [1.32 ; 2.93]).

Effect on function (WOMAC, Lequesne)

Placebo-controlled studies:

- At the end of treatment, statistically significant difference (p value not provided) on function (Glass score = 1.49 $CI_{95\%}$= [0.78 ; 2.19]).
- There were insufficient data to test the remanence of the effect.

Active comparator-controlled studies:

- Similar effect at the end of treatment, (Glass score = 0.12 $CI_{95\%}$= [-0.68 ; 0.93])
- Diacerein had a greater effect than the comparator at the end of the follow-up period without treatment, (Glass score = 2.58 $CI_{95\%}$= [1.71; 3.45], statistically significant difference, p value not provided).

NB: The results of the Rintelen meta-analysis (2006) must be interpreted with caution considering that the methodological quality of the studies analysed was very variable, from 0 to 5 on a 0-5 scale. In particular, 5 older studies (1985 to 1988) and 1 more recent study (1998) had very low quality scores (0 to 2). These studies included in particular, 1 single-blind study and 1 open-label study (double-blinding was not required for inclusion of the studies). The heterogeneity of the effect was not tested but this heterogeneity is clearly evident on the graphs.

3.2. Adverse events

In the meta-analysis of Fidelix (2006), the results showed that the incidence of diarrhoea with diacerein was 42% (versus 11% with placebo, p = 0.00001). The severity of the diarrhoea was mild to moderate and it occurred during the first 2 weeks of treatment. Diarrhoea was the most frequent reason for premature study discontinuation.

The percentage of study discontinuations for adverse effects was 18% with diacerein and 13% with placebo with no statistically significant difference though the heterogeneity test was statistically significant (p=0.02).

The percentage of study discontinuations for lack of efficacy was 16% with diacerein and 24% with placebo (p = 0.004).

A colouring of the urine frequently occurred with diacerein (25% vs 18% with placebo, p<00001). No significant difference was observed for the other adverse effects: dyspepsia, rash and pruritis.

The SPC mentions the following adverse effects:

- Gastrointestinal effects:

The most frequently reported adverse effects were diarrhoea, soft stools and abdominal pain.
A pigmentation of the colorectal mucosa (Melanosis coli) have rarely been observed.
Dark colouration of the urine due to the structure of the molecule and with no pathological significance may sometimes be observed.

- Cutaneous effects:

Cases of pruritis, rash and eczema have been reported.

A pharmacovigilance survey on the adverse effects observed with proprietary medicines containing diacerein was performed in 2006 following the notification of a case of a hepatic disorder in a patient treated with ART 50 and a paracetamol-dextropropoxiphene combination. At the end of this survey, the French Pharmacovigilance Committee on 16 May confirmed the need to update the SPC by mentioning in particular the possibility of hepatic disorders (the MA is currently being updated).

The changes in the SPC validated by the MA committee are as follows:

“Warnings and special precautions for use:
Taking into account the frequency of diarrhoea, beware of dehydration risk especially in the elderly and subjects receiving ACE inhibitors or diuretics, due to an increase of salt and water depletion risk.
Treatment with ART 50 should be stopped in the case of symptoms suggesting a hepatic disorder.”

"Undesirable effects:
Hepatobiliary disorders:
Unknown incidence: possible abnormal liver function tests and in particular tests for cytolysis"

3.3. Conclusion

The company provided 8 new randomised, double-blind studies evaluating the efficacy of diacerein on symptomatic criteria versus placebo or NSAIDs in patients with knee osteoarthritis (6 studies) or hip osteoarthritis (2 studies).

Placebo-controlled studies:
Patients included in these studies had mainly Kellgren-Lawrence stage I to III knee osteoarthritis or hip osteoarthritis characterised by a pain intensity ≥ 30 or 40 mm on a 100-mm VAS.
In the Amor and Dougados (1994), Lequesne (1998) and Pelletier (2000) studies, the observed reduction in pain was greater with diacerein than with placebo. However, the observed differences of about 10 mm on a 100 mm VAS after 2 to 4 months of treatments were low.
In the Ascherl study (1994), there was a greater reduction in the Lequesne index with diacerein than with placebo (statistically significant difference of -1.7 on a scale between 0 and 24).
In the Pavelka study (2007), after 3 months of treatment and 2 months of follow-up, a statistically significant reduction in the WOMAC pain score with little clinical relevance was observed with diacerein compared to placebo (- 47 on a scale from 0 to 500). A similar result was observed for the total WOMAC score (-278 on a scale from 0 to 2400).

Studies versus NSAIDs:
One of the 2 available studies could be retained (Louthrenoo, 2007). It was performed in patients with Kellgren-Lawrence stage II to III knee osteoarthritis and was characterised by pain ≥ 40 mm on a 100 mm VAS.
Patients were treated for 4 months and then followed up without treatment for 2 additional months.
At the end of the 4-month treatment period, diacerein was non-inferior to piroxicam for the reduction in the WOMAC pain score. After 1 month of post-treatment follow-up, the WOMAC pain score remained at the same level in the diacerein group whereas it increased in the piroxicam group with a statistically significant difference of little clinical relevance of 55 points (on a scale from 0 to 500) between treatments.

Two meta-analyses were also provided including one with a better methodological quality (Fidelix 2006. Cochrane review). This meta-analysis which included only recent studies (1994 to 2004) showed that diacerein had a clinically irrelevant effect compared to placebo on pain (- 5.16 mm on a 100 mm VAS, 5 studies, with a significant heterogeneity test) and that there was no statistically significant difference for the reduction in the Lequesne index compared to placebo (4 studies).

From the safety point of view, the clinical studies demonstrated, as expected, a high incidence of diarrhoea (up to 42%).
Study withdrawals were more frequent than with placebo and were mainly due to the adverse effects (diarrhoea). Study discontinuations for lack of efficacy were more frequent in the placebo group.
Pharmacovigilance data underlined a risk of hepatic disorders (unknown incidence).

Overall, diacerein had a low efficacy in relieving the symptoms of pain and improving joint function compared to placebo. The efficacy compared to NSAIDs and the possibility of a persistent effect after treatment discontinuation compared to these NSAIDs are poorly established.
A high incidence of diarrhoea was observed with diacerein.

4 MEDICINE USE DATA

4.1. Observational study

Fagnani Study (1998)[12]: "Health economic assessment of ART 50 mg in routine practice"
The purpose of this study was to compare the efficacy of ART 50 treatment combined with usual treatment with that of usual therapy alone in patients with knee and/or hip osteoarthritis.
This was a pragmatic, open-label, prospective, randomised study in 2 parallel groups, with 9 months follow-up.

Inclusion criteria:
- Outpatients,
- Age ≥ 50 years,
- Tibiofemoral osteoarthritis of the knee and/or osteoarthritis of the hip for at least 3 months,
- Pain for at least 3 months,
- Requiring treatment by NSAIDs and/or analgesics or slow-acting drugs for osteoarthritis.

Two treatment groups were formed:

- ART 50 mg: ART 50 mg, 2 capsules per day for 6 months + usual therapy used by the investigator for 9 months (except slow-acting drugs for osteoarthritis).
- Usual treatment: usual therapy used by the investigator for 9 months (NSAIDs, analgesics, slow-acting drugs for osteoarthritis, physiotherapy).

In the 2 groups, the investigator had to try and withdraw the NSAIDs after week 6. NSAIDs had to be stopped at 6 months, except if the patient had a painful exacerbation.

[12] Fagnani F et al. Medico-economic analysis of diacerein with or without standard therapy in the treatment of osteoarthritis. Pharmacoeconomics 1998; 13: 135-146

Endpoints:

- Pain assessment (100 mm VAS),
- Lequesne index,
- AIMS quality-of-life (Arthritis Impact Measurement Scales) Nottingham Health Profile (NHP),
- Resources consumed in terms of
    - Medications (analgesics, NSAIDs, antacids),
    - Medical interventions (visits, surgical procedures),
    - Ancillary medical procedures (physiotherapy, nursing care),
    - Spa treatment.
- Hospital stays.

Results:

1) Study sample size

One hundred and nine patients were included in the ART 50 + usual therapy (UT) group and 98 in the UT alone group.

In the ART 50 + UT group, 24 patients prematurely stopped the study, including 13 for adverse events and 1 for lack of efficacy.

In the UT alone group, 15 patients prematurely stopped the study, including 8 for lack of efficacy (no patient stopped treatment for AEs).

2) Characteristics of included patients

Patients had an average age of 66.5 years and were suffering from knee or hip osteoarthritis characterised by a Lequesne index of 9.2, pain measured on a 100-mm VAS of 59.8 mm in the ART 50 + UT group and 57.3 mm in the UT alone group.

3) Results for the clinical endpoints

During the first 6-month period, when patients could be treated by NSAIDs, treatment by ART 50 mg + UT was superior to UT alone in terms of a reduction in the Lequesne index and pain (100 mm VAS). However, the observed differences (1.3 point for the Lequesne index and 7 mm on the VAS) had little clinical relevance (see table 12).

During the following 3 months (discontinuation of NSAIDs), no significant difference was observed between the two groups either for the Lequesne index or pain.

Table 12: Results for the Lequesne index and pain (VAS) – ITT analysis study

Change (mean ± standard deviation)	ART 50 mg + usual therapy (n = 109)	Usual therapy (n = 98)
Lequesne index		
D0-M6	-2.5 ± 3.5**	-1.2 ± 3.8
M6-M9	-0.5 ± 3.5	-0.1 ± 3.6
Pain (100-mm VAS)		
D0-M6	-16.27 ± 23.4**	-9.37 ± 23.3
M6-M9	-3.25 ± 25.3*	-0.26 ± 25.3

* p<0.05 ; ** p<0.01 ; *** p<0.001

4) Results for analgesic and NSAID consumption (see table 13).

No statistically significant difference was observed between the ART 50 mg + UT and UT alone groups for NSAID consumption.

A statistically significant difference in analgesic consumption, with little clinical relevance, was observed in favour of treatment by ART 50 mg + UT compared to UT alone for the first 6-month period but not during the following 3 months (discontinuation of NSAIDs).

Table 13: Results for analgesic and NSAID consumption – ITT analysis.

Change in consumption (mean in DDD* units ± standard deviation)	ART 50 mg + usual therapy (n = 109)	Usual therapy (n = 98)
NSAIDS		
D0-M6	-1.7 ± 6.3	-1.1 ± 5.7
M6-M9	-1.6 ± 4.6	-1.4 ± 5.1
Analgesics		
D0-M6	-0.7 ± 2.9**	-0.4 ± 4.3
M6-M9	+0.9 ± 3.8	-0.3 ± 3.8

* DDD : Daily Defined Dose
** p<0.005

Conclusion:
In this relatively old, real-life practice study in patients with knee or hip osteoarthritis, ART 50 mg in combination with usual therapy (excluding slow-acting drugs for osteoarthritis) had no statistically significant or clinically relevant advantage compared to the usual therapy (that may have included a slow-acting drug for osteoarthritis) on the Lequesne index, pain or NSAID and analgesic consumption.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Symptomatic osteoarthritis of the hip and knee is characterised by pain and a functional incapacity which may progress to chronic disease. Patients may subsequently require joint replacement surgery.

This proprietary drug provides slow-acting symptomatic treatment.

Public health benefit:

Knee osteoarthritis and hip osteoarthritis represent a considerable public health burden.

A reduction in the functional limitations and incapacities induced by osteoarthritis, as well as an improvement in the quality of life of affected individuals is a public health need. The response to this need is not only pharmacological.

The available data for pain and algofunctional indexes do not conclusively demonstrate that diacerein has an impact on the improvement in quality of life and reduction of functional limitations: no quality of life data and small effect on symptoms.

The theoretical value of slow-acting drugs for osteoarthritis, in terms of public health, is a reduction in NSAID consumption, which may help reduce the incidence of gastrointestinal side effects that are particularly harmful in elderly patients. For diacerein, no convincing data were submitted to show such a reduction.
Moreover, the gastrointestinal safety of diacerein may compromise compliance and continuation of treatment.

Consequently, ART 50 mg does not benefit public health.

This proprietary drug is not very effective for relieving osteoarthritis symptoms. Diarrhoea frequently occurs in patients treated by diacerein (up to 42% of patients in the studies). The efficacy/safety ratio is low.

Osteoarthritis management is based above all on diet and lifestyle changes (weight loss, regular physical exercise) and non-pharmacological measures (physiotherapy, wearing of biomechanical corrective aids, walking-sticks etc). Symptomatic treatment mainly involves analgesics and oral NSAIDs. This proprietary medicine only has a limited therapeutic usefulness.

The actual benefit of ART 50 mg, capsule is low.

5.2. Therapeutic use

The first measures to be implemented for symptomatic treatment of osteoarthritis of the lower limbs are diet and lifestyle changes (reduction in excess body weight, regular physical activity outside exacerbations of pain or congestion when a reduction in activity is necessary) and non-pharmacological measures (physiotherapy, wearing of biomechanical corrective aids, walking-sticks etc).

During symptomatic phases, treatment mainly comprises analgesics, starting with paracetamol, and during acute exacerbations, short courses of oral NSAIDs at minimum effective doses.

Local treatments may also be used such as topical NSAIDs, intra-articular corticosteroid injections, in particular during inflammatory episodes, or hyaluronic acid.

Slow-acting drugs for osteoarthritis (chondroitin sulphate, CHONDROSULF, unsaponifiable extracts of avocado and soybean, diacerein and glucosamine) have a low efficacy against both pain and functional incapacity and it has not been clearly shown if they substantially decrease NSAID consumption. They therefore only have limited therapeutic use.

Surgery (arthroplasty, joint replacement) is reserved for radiologically advanced, painful and disabling forms of osteoarthritis refractory to the usual therapeutic measures.

5.3. Transparency Committee recommendations

The Transparency Committee recommends to maintain 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 favourable opinion is subject to the setting up and conduction of a study within a timeframe of 2 years aiming to show the benefit of ART 50 prescription in terms of a reduction in NSAID consumption.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 35 %