HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

17 November 2010

VISANNE 2 mg, tablet
B/28 (CIP code: 347 113-1)
B/84 (CIP code: 576 766-3)
B/168 (CIP code: 576 768-6)

Applicant: BAYER SANTE

dienogest
ATC code: G03D

List I

Date of Marketing Authorisation: 28 January 2010 (decentralised procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Dienogest

1.2. Indication
“Treatment of endometriosis.”

1.3. Dosage and method of administration

“Method of administration:
For oral use.

Dosage:
The dosage of VISANNE is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed. The tablets can be taken with or without food.
Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started directly without interruption.
There is no data available on the use of VISANNE >15 months in patients with endometriosis.
Treatment can be started on any day of the menstrual cycle.
Any hormonal contraception needs to be stopped prior to initiation of VISANNE. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method, such as a condom).

Missed tablets:
The efficacy of VISANNE may be reduced in the event of missed tablets, vomiting and/or diarrhoea (if occurring within 3–4 hours after taking the tablets). In the event of one or more missed tablets, the patient should take one tablet only, as soon as she remembers, and should then continue treatment the next day at her usual time. A tablet not absorbed due to vomiting or diarrhea should likewise be replaced by another tablet.”

Additional information on special populations: see SPC

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

G: Genito-urinary system and sex hormones
G03: Sex hormones and modulators of the genital system
G03D: Progestogens

2.2. Medicines in the same therapeutic category

2.2.1 Strictly comparator medicines

- Other oral progestogens:
  LUTERAN (chlormadinone) 2 mg and 5 mg
  CHLORMADINONE MYLAN, QUALIMED, SANDOZ, TEVA, 5 mg
  CHLORMADINONE TEVA, 2 mg
  DUPHASTON (dydrogesterone) 10 mg
  COLPRONE (medrogestone) 5 mg

2.2.2 Not-strictly-comparator medicines

DEPO-PRODASONE (medroxyprogesterone acetate) 250 mg, suspension for injection

2.3. Medicines with a similar therapeutic aim

- GnRH analogues:
  DECAPEPTYL LP (triptorelin) 3 mg and 11.25 mg, powder and solvent for suspension for injection
  GONAPEPTYL LP (triptorelin) 3.75 mg, powder and solvent for suspension for injection
  ENANTONE LP (leuprorelin) 3.75 mg and 11.25 mg, powder and solvent for suspension for injection
  SYNAREL (nafarelin) 0.2 mg/dose, nasal spray solution

- DANATROL (danazol) 200 mg, for oral use

3. ANALYSIS OF AVAILABLE DATA

The company submitted 4 clinical studies:
- a dose-finding study (without a placebo arm), which will not be described, as a result of which a dose of 2 mg/day was chosen.
- a placebo-controlled study (307041)
- a controlled study versus leuprorelin (97085)
- a non-controlled study (307059), an extension of study 307041, followed by a 6-month observation period after treatment.

3.1. Efficacy

3.1.1 Placebo-controlled study (307041)

Method
Randomised (1:1) placebo-controlled double-blind study with 2 parallel groups.

Inclusion criteria:
- women aged 18 to 45 years;
- pelvic pain associated with histologically confirmed endometriosis (stage I to IV on the rAFS classification[1], diagnosed by laparoscopy or laparotomy in the 12 months preceding the start of treatment); the pain had to be evaluated at at least 30 mm/100 mm at the selection visit and at the inclusion visit 1 cycle later;
- use of a barrier method of contraception, except in cases of tubal sterilisation or where the partner has had a vasectomy.

Main non-inclusion criteria:
- endometriosis requiring surgical treatment;
- failure of previous surgical or medical treatment;
- treatment with a GnRH analogue in the last 6 months, treatment with a progestogen or danazol in the last 3 months, use of an oral contraceptive in the month preceding selection;
- use of an intrauterine device.

Treatment investigated: VISANNE (dienogest), 2 mg once daily for 12 weeks.
Permissible concomitant treatment: ibuprofen, 1 to 3 tablets or 400 to 1200 mg/day in the event of pain, throughout the study.

Twin primary efficacy endpoint: the improvement in pelvic pain, evaluated on a visual analogue scale (VAS), between inclusion and the end of the treatment and also the change in the use of analgesic therapy (ibuprofen) over the same period (a twin endpoint was used because the evaluation of pain can be modified by the use of ibuprofen and because, as this analgesic therapy can mask the effect of the treatment investigated, it cannot be regarded as a covariable in an analysis of covariance). The VAS was a non-graduated 10 cm line running from 0 = no pain to 10 = unbearable pain; the change in the use of analgesic therapy was the change in the number of ibuprofen tablets taken in 28 days between the period preceding inclusion and the period preceding the end of the treatment.

[1] Revised American Fertility Society classification score

Secondary endpoint:

- the change in quality of life between inclusion and the end of the treatment, measured using the SF36 questionnaire.

Statistical analysis:

The comparison of dienogest and placebo was carried out using Röhmel's hierarchical 3-step procedure[2]:

1. testing for non-inferiority compared to placebo for the 2 variables of the primary efficacy endpoint. The non-inferiority margin was set at -15 mm for the VAS and -9 tablets for the analgesic therapy.

If successfully demonstrated:

2. Läuter's test for overall superiority of dienogest compared to placebo for the 2 variables.

If successfully demonstrated:

3. testing for superiority of dienogest compared to placebo for each variable separately using 95% two-sided confidence intervals.

Results

Patients included:

In total, 198 patients were included. Their distribution is shown in *Table 1*.

Table 1: Distribution of the patients investigated

	VISANNE	Placebo
Patients randomised (n)	102	96
Patients treated (FAS) (n)	102	96
Patients who completed the study (n)	98	90
Patients without major protocol deviations (PP) (n)	74	70

FAS: Full Analysis Set: patients who received at least 1 dose of treatment and for whom at least one observation was available after the start of the treatment; PP: per protocol.

The main characteristics of the patients included are shown in *Table 2*.

Table 2: Main characteristics of the patients on inclusion

	VISANNE n = 102	Placebo n = 96
Mean age (years)	31.5 ± 6.7*	31.4 ± 6*
Mean BMI (kg/m^2)	22.7 ± 3.5*	22.5 ± 3.5*
rAFS SCORE		
Stage I - % (n)	12.7% (13)	8.3% (8)
Stage II - % (n)	16.7% (17)	19.8% (19)
Stage III - % (n)	45.1% (46)	44.8% (43)
Stage IV - % (n)	25.5% (26)	26% (25)

*: standard deviation; BMI: Body Mass Index

[2] Röhmel J, Gerlinger C *et al. O*n testing simultaneously non-inferiority in two multiple primary endpoints and superiority in at least one of them. Biom J 2006;48: 916-33

Primary efficacy endpoint:
The results are shown in *Table 3*.

Table 3: Change in pain and in the number of ibuprofen tablets taken:

	VISANNE	Placebo
Pain evaluated with VAS (mm)	n = 74	n = 70
- on inclusion*	57.7 ± 16.4†	56.4 ± 16.7†
- at the end of treatment*	28.5 ±19.8†	40.1 ± 21.4†
- change within the group*	- 29.1 ± 20.6†	- 15.9 ± 14.9†
- difference between groups*	13.2 [7.3;19.2] ‡	
	n = 102	n = 96
- change within the group §	- 27.4 ± 22.9†	- 15.1 ± 16.4†
- difference between groups §	12.3 [6.4; 18.1]	
Mean number of ibuprofen tablets taken:	n = 74	n = 70
- in the 28 days before inclusion*	10.7 ± 7†	9.4 ± 6.8†
- in the 28 days before the end of the treatment*	5.9 ± 5.9†	6.3 ± 6†
- change within the group*	- 4.9 ± 5.6†	-3.3 ± 6.3†
- difference between groups*	1.7 [-0.3; 3.6] ‡	
	n=102	n=96
- change within the group §	4.4 ± 6.4†	3.7 ± 8.2†
- difference between groups §	0.7 [-1.4; 2.9] ‡	

* : analysis of PP population; †: standard deviation; ‡: 95% confidence interval of the difference; §: analysis of FAS population

The non-inferiority of VISANNE compared to placebo was demonstrated for the two components of the primary efficacy endpoint, the lower limit of the confidence interval of the difference between groups being greater than -15 for the VAS and -9 for the number of tablets in the analysis of the per-protocol population and of the FAS population also.

The overall superiority of VISANNE compared to placebo was then demonstrated for the 2 components of the primary efficacy endpoint using Läuter's one-sided two-dimensional test in the per-protocol population ($p = 0.00007$) and in the FAS population ($p = 0.00165$).

In step 3 of Röhmel's procedure (testing for superiority of dienogest compared to placebo for each variable separately using 95% two-sided confidence intervals), the difference between VISANNE and placebo was significant in regard to the change in pain ($p < 0.0001$). For the change in the number of analgesic tablets, the 95% confidence interval of the difference between groups containing zero, the difference between VISANNE and placebo was not significant.

Secondary endpoints:
- Course of the quality-of-life scores for physical and mental health areas on the SF36 questionnaire between inclusion and the end of the study. The results are shown in *Table 4*.

Table 4: Course of the quality-of-life scores (categories of the SF36 questionnaire)*

Area	VISANNE n = 102	Placebo n = 96
Physical health	+ 5.7 ± 6.7	+ 4.7 ± 7.1
Mental health	+ 2.7 ± 8.5	+ 2.3 ± 10.5

*: FAS population

An improvement in the physical and mental health areas of the questionnaire over the course of the study was found in the 2 groups.

3.1.2 Controlled study versus leuprorelin acetate (97085)

Method

Open, controlled, randomised (1:1), non-inferiority study versus leuprorelin acetate with 2 parallel groups.

Inclusion criteria:
- women aged 18 to 45 years;
- with pelvic pain associated with rAFS[1] stage I to IV endometriosis diagnosed by laparoscopy in the 12 months preceding the start of the treatment;
- pain evaluated at at least 30 mm/100 mm at the selection visit and at the inclusion visit 1 cycle later;
- use of a barrier method of contraception (except in cases of tubal sterilisation or where the partner has had a vasectomy).

Main non-inclusion criteria:
- endometriosis requiring surgical treatment;
- failure of previous surgical or medical treatment;
- treatment with a GnRH analogue in the last 6 months, treatment with a progestogen or danazol in the last 3 months, use of an oral contraceptive in the month preceding selection;
- use of an intrauterine device.

Treatments investigated:
- VISANNE (dienogest): 2 mg once daily for 24 weeks;
- Leuprorelin acetate: 3.75 mg by intramuscular injection every 28 days for 24 weeks.

Primary efficacy endpoint: The change in the absolute value for pelvic pain evaluated using a visual analogue scale (VAS), between inclusion and the end of the treatment. The VAS was a non-graduated 10 cm line running from 0 = no pain to 10 = unbearable pain.

Secondary endpoints:
- The change in quality of life between inclusion and the end of the treatment, measured using the SF36 questionnaire.
- The course of lumbar bone mineral density (L1-L4) between inclusion and the end of the treatment in a patient subgroup (3 centres). Patients with a bone mineral density > 2.5 SD below the norm were excluded from this study.

Statistics:

The hypothesis of non-inferiority of VISANNE compared to leuprorelin acetate was analysed using a single-sided test with $\alpha = 2.5\%$.

The non-inferiority limit was 15 mm on the VAS.

Results

Patients included:
In total, 252 patients were included. Their distribution is shown in *Table 5*.

Table 5: Distribution of the patients investigated

	VISANNE	Leuprorelin
Patients randomised (n)	124	128
Patients treated (FAS) (n)	120	128
Patients without major protocol deviations (PP) (n)	90	96

FAS: Full Analysis Set: patients who received at least 1 dose of treatment and for whom at least one observation was available after the start of the treatment; PP: per protocol.

The main characteristics of the patients included are shown in *Table 6*.

Table 6: Main characteristics of the patients on inclusion

	VISANNE n = 120	Leuprorelin n = 128
Mean age (years)	30.6 ± 6.2*	31 ± 5.8*
Mean BMI (kg/m^2)	22.6 ± 3.4*	22.7 ± 3.2*
rAFS SCORE		
Stage I - % (n)	23.3% (28)	30.5% (39)
Stage II - % (n)	29.2% (35)	26.6% (34)
Stage III - % (n)	32.5% (39)	27.3% (35)
Stage IV - % (n)	15% (18)	15.6% (20)

* : standard deviation; BMI: Body Mass Index

Primary efficacy endpoint:
The results are shown in *Table 7*.

Table 7: Change in pain between the start and the end of the study

	VISANNE	Leuprorelin
Pain evaluated with VAS (mm) *	n = 120*	n = 128*
- on inclusion*	53.3	55.4
- at the end of treatment*	12.1	13
- change within the group*	-40.2	-41.8
- difference between groups* [95% CI]	1.58 [-6.4; 9.58].	
- change within the group†	n = 90* -47.51	n = 96* -46.01
- difference between groups† [95% CI]	-1.5 [-9.25; 6.25].	

*: analysis of FAS population; †: per-protocol analysis

As the lower limit of the confidence interval of the difference between groups was greater than -15, the non-inferiority of VISANNE compared to leuprorelin acetate was demonstrated.

Secondary endpoint

- Course of physical and mental health areas on the SF36 questionnaire between inclusion and the end of the study. The results are presented in *Table 8*.

Table 8: Course of physical and mental health areas on the SF36 questionnaire

Area	VISANNE n = 102*	Leuprorelin n = 128*
Physical health	+ 9.6	+ 7.1
Mental health	+ 4	+ 0.9

*: FAS population

An improvement in the physical and mental health areas of the questionnaire over the course of the study was found in the 2 groups.

3.1.3 Non-controlled study (307059), an extension of study 307041

Method

Non-controlled study, an extension of the placebo-controlled study.

Inclusion criteria:
Women who took part in study 307041 wishing to continue or start treatment with VISANNE using effective non-hormonal contraception.

Treatment investigated: VISANNE (dienogest), 2 mg once daily for 36 weeks, duration extended, by amendment, to 52 weeks.

Primary endpoint (tolerance):
Frequency, duration, and intensity of bleeding occurring during the study. Intensity was rated using a 5-level classification: 0 = no bleeding; 2 = spotting (not necessitating protection); 3: light (less than usual menstruation but necessitating protection); 4 normal (bleeding same as in usual menstruation); 5 heavy (bleeding heavier than in usual menstruation).
Secondary endpoint:
Course of pain evaluated with a VAS

Results

Patients included:
In total, 168 patients were included; 81 of them had initially been in the placebo group and 87 in the VISANNE group.

Of these 168 patients:

- all received at least one dose of treatment, and at least one examination after the start of the treatment was available in all cases (FAS population);
- 152 finished the extension phase, 135 of them being treated for 52 weeks and 17 for 36 weeks.

The patients included (FAS population, n = 168) had a mean age of 31.9 ± 6.4 years and a mean BMI of 22.8 ± 3.5 kg/m^2.

Secondary endpoint: Course of pain. The results are presented in *Table 9*.

Table 9: Course of pain during the study

VAS (mm)	VAS at start of study	VAS at end of study
Total population	34.1 ± 21.6* (n = 163)	11.5 ± 11.3* (n = 132)
Placebo in the preceding study	40.7 ± 21.1* (n = 79)	13.5 ± 14.1* (n = 63)
VISANNE in the preceding study	27.9 ± 20.2* (n = 84)	9.7 ± 7.4* (n = 69)

* standard deviation

3.1.4 Post-treatment observation phase

Method:
24-week observation phase after the end of the preceding study, carried out in some of the centres where the latter was performed.

Endpoints:
- bleeding during the observation phase (frequency, duration, intensity)
- endometriosis-associated pain evaluated with a VAS
- need for another treatment for endometriosis
- quality of life evaluated using the SF36 questionnaire

Results
Thirty four patients were followed up, 31 of them for 6 months.

Course of pain:
The pain evaluated on the VAS rose from 10.9 ± 9.7 mm at the start of the observation phase to 14.6 ± 9.5 mm after 6 months.
Need for a treatment for endometriosis: 1 patient needed another treatment for endometriosis.
Course of SF36 questionnaire scores
- the "mental health" area decreased by 0.07 ± 6.3 points
- the "physical health" area decreased by 0.9 ± 7.42 points

The two scores changed very little during the observation period.

3.2. Adverse effects

3.2.1 Placebo-controlled study (307041)

Tolerance was analysed in the patients who received at least 1 dose of treatment (FAS population).
The events

Table 10: Adverse events (% and number of patients who had at least 1 AE):

	VISANNE n = 102	Placebo n = 96
Patients who had at least 1 AE % (n)	33.3% (34)	26% (25)
AEs deemed to be treatment-related	14.7% (15)	7.3% (7)
Intensity of the AEs: - Mild - Moderate - Severe	 17.6% (18) 22.5% (23) 1% (1)	 8.3% (8) 20.8%(20) 5.2% (5)
Dropped out of trial because of an AE	2% (2)*	1% (1)†

*: 1 case of breast pain (probably related to the treatment) and 1 uterine haemorrhage (possibly related to the treatment; †: increase in chorionic gonadotropin, (unlikely to be related to the treatment)

No serious adverse events occurred in this study.

In the VISANNE group, the most frequent adverse events deemed to be treatment-related were: headache (2.9%), nausea, weakness, depression, mastalgia (2% in each case).
In the placebo group, the most frequent adverse events deemed to be treatment-related were headaches (3.1%).
The mean number of days of bleeding was similar in the 2 groups: 20.9 ± 13.8 with dienogest and 20.8 ± 9.2 with placebo.

3.2.2 Controlled study versus leuprorelin acetate (97085)

Tolerance was analysed in the patients who received at least 1 dose of treatment (FAS population).
The adverse events are summarised in *Table 11*.

Table 11: Adverse events (% and number of patients who had at least 1 AE):

	VISANNE n = 120	Leuprorelin n = 128
Patients who had at least 1 AE % (n)	68.3% (82)	74.2% (95)
AEs deemed to be treatment-related	41.6% (50)	47.7% (61)
Intensity of the AEs: - Mild - Moderate - Severe - Serious	 10.8% 40% 14.2% 4.2% (6)*	 10.9% 46.1% 16.4% 0.8% (1)†
Dropped out of trial because of an AE	5% (6) §	3.9% (5)‖

*: 1 hysterectomy for persistent dysmenorrhoea, 1 admission to hospital for severe pelvic pain, 1 depression, 1 case of abdominal pain, 2 cases of urolithiasis with hospitalisation; †: 1 admission to hospital for slipped disc; §: arterial hypertension, tinnitus, ovarian cyst, nausea and depression (2 cases); ‖: hot flushes, arthritis, depression, allergic reaction, sleeping problems

In the VISANNE group, the most frequent adverse events deemed to be treatment-related were: headache (12.5%), weight gain (6.7%), depression (5%), decreased libido (4.2%), and acne (4.1%).
In the leuprorelin group, the most frequent adverse events deemed to be treatment-related were: headache (19.5%), depression (8.6%), sleeping problems (7.8%), vaginal dryness (7%), decreased libido (6.3%), alopecia (5.5%), acne (4.7%), and migraine (4.7%).
The mean number of days of bleeding was higher with dienogest (25.6 ± 18.5 during the first 3 months and 11.8 ± 15.1 during the last 3 months) than with leuprorelin (11.6 ± 7 and 2 ± 4.9 in the same periods).
Bone mineral density (BMD) was measured by dual energy X-ray absorptiometry of the lumbar spine in 21 patients in the VISANNE group and 29 patients in the leuprorelin group. BMD increased on average by 0.25% in the VISANNE subgroup and decreased on average by 4.04% in the leuprorelin subgroup.

The course of lumbar bone mineral density (L1-L4) between inclusion and the end of the treatment measured by DEXA in a patient subgroup (3 centres).
The results for this are shown in *Table 12*.

Table 12: Course of lumbar bone mineral density*

Bone mineral density	VISANNE (n = 21)	Leuprorelin (n = 29)
Change in absolute value (g/cm^2)	+ 0.0022	- 0.0415
Percentage change	+ 0.25	- 4.8

*: in the FAS population.
Lumbar bone mineral density did not change in the VISANNE group; it decreased in the leuprorelin group.

3.2.3 Non-controlled study (307059), an extension of study 307041

Primary endpoint:
The results are presented in *Table 13*.

Table 13: Course of bleeding during treatment

Mean number of days of bleeding/spotting (n patients) - During the first 90 days of the treatment - During the last 90 days of the treatment	 20.2 ± 15.2* (n = 161) 9.7 ± 9* (n = 132)
Mean number of episodes of bleeding/spotting (n patients) - During the first 90 days of the treatment - During the last 90 days of the treatment	 3 ± 1.8* (n = 160) 2 ± 1.6* (n = 132)
% of patients with no or light bleeding (1 to 3) (n patients) - During the first 90 days of the treatment - During the last 90 days of the treatment	 58.6% (n = 164) 88.2% (n = 136)

* standard deviation

Adverse events were analysed in the 168 patients included.
The adverse events are summarised in *Table 14*.

Table 14: Adverse events (% and number of patients who had at least 1 AE):

	n = 168
Patients who had at least 1 AE - % (n)	45.2% (76)
AEs deemed to be treatment-related	16.1% (27)
Intensity of the AEs: - Mild - Moderate - Severe - Serious	 27.4% (46) 26.8% (45) 4.8% (8) 1.8% (3)*
Dropped out of trial because of an AE	2.4% (4)†

*: cholelithiasis, depression (possibly related to the treatment), chronic sinusitis; †: migraine, weight gain, depression (severe), and mastalgia.

The most frequent adverse events deemed to be treatment-related were: “breast discomfort” (4.2%), nausea (3%), and irritability (2.4%).

3.2.4 Post-treatment observation phase

During this phase there was no adverse event considered to be related to the foregoing treatment.

3.3. Conclusion

A randomised study in which VISANNE and placebo were compared on a double-blind basis for 12 weeks in 198 women with histologically confirmed endometriosis showed a greater decrease in endometriosis-related pain in the VISANNE group. The difference between the groups in regard to the intensity of the pain, evaluated on a 100 mm visual analogue scale, was 12.3 mm [6.4; 18.1] ($p < 0.0001$).
A randomised study in which VISANNE and leuprorelin acetate were compared on an open basis for 24 weeks in 252 women with stage I to IV endometriosis showed VISANNE to be non-inferior in regard to reduction of endometriosis-related pain, the difference between the groups being 1.5 mm [-9.25, 6.25].
In these 2 studies, the endometriosis had been diagnosed by laparoscopy or laparotomy.
In an open extension of the placebo-controlled study, 152 patients were treated with VISANNE for 36 to 52 weeks. The mean intensity of the pain measured by VAS was 34.1 mm at the start of the study and 11.5 mm at the end of the study.

In the placebo-controlled study, the most frequent adverse events deemed to be treatment-related were: headache (2.9%), nausea, weakness, depression, mastalgia (2% in each case) in the VISANNE group and headache (3.1%) in the placebo group.
In the study versus leuprorelin acetate, some of the most frequent adverse events deemed to be treatment-related were less frequent with VISANNE than with leuprorelin: headache (12.5% versus 19.5%), depression (5% versus 8.6%), decreased libido (4.2% versus 6.3%), and acne (4.1% versus 4.7%). On the other hand, weight gain (6.7%) and the mean number of days of bleeding (25.6 ± 18.5 versus 11.6 ± 7 during the first 3 months and 11.8 ± 15.1 versus 2 ± 4.9 during the last 3 months) were more frequent with VISANNE than with leuprorelin. In the leuprorelin group, the other most frequent treatment-related adverse events were: sleeping problems (7.8%), vaginal dryness (7%), alopecia (5.5%), and migraine (4.7%).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Pain due to endometriosis can impair quality of life.
The proprietary medicinal product is intended as a symptomatic therapy.
The efficacy/adverse effects ratio is moderate.

Public health benefit

Endometriosis is a common disease, which can impair quality of life. However, the public-health burden of the forms covered by the proprietary medicinal product VISANNE (endometriosis in cases where GnRH analogue therapy has failed) is small, given the limited number of patients concerned.

There is a therapeutic need to improve the management of these patients, but this is not a public-health need.

On the basis of the available data, it is not expected that the proprietary medicinal product VISANNE will have an impact on morbidity/mortality and quality of life in comparison with current management.

Consequently, it is not expected that the proprietary medicinal product VISANNE will benefit public health in this indication.

This proprietary medicinal product is a second-line medicine.
There are treatment alternatives.

The actual benefit of this proprietary medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

In view of:
- the modest size of the effect observed in the clinical studies,
- the longer duration of bleeding with VISANNE than with leuprorelin,
- and the absence of a comparison with a GnRH analogue combined with an “add-back therapy” (hormone replacement therapy intended to compensate for induced hypoestrogenism), particularly in terms of tolerance,

VISANNE does not provide an improvement in actual benefit (IAB V) in the therapeutic strategy for endometriosis.

4.3. Therapeutic use

4.3.1 Therapeutic strategy

Good practice guidelines - Afssaps[3], 2005

Severe forms of endometriosis:

- Endometrioma: endometrioma is treated by surgical means.
- Deep endometriosis with subperitoneal localisation:

Surgical treatment and GnRH analogues are the first-line therapies.
After 3 months' treatment, in cases where it is effective, GnRH agonist therapy can be continued until 6 months or 1 year, depending on the proprietary medicinal product, if combined with an "add-back therapy" (hormone replacement therapy) from the 3rd month of treatment.
In the event of insufficient efficacy after 6 months or 1 year of GnRH agonist therapy, it is recommended that a switch be made to another antigonadotropic treatment (progestogen, oral contraception).
In the event of failure, the treatment is surgical.

Moderate endometriosis:
A 3-month therapeutic trial of a GnRH analogue is recommended. If this fails, therapeutic laparoscopy to remove the endometriotic lesions is indicated.
If it is successful, the GnRH agonist therapy can be continued until 6 months or 1 year, depending on the proprietary medicinal product, in combination with an "add-back therapy" from the 3rd month of treatment.
After 6 months or 1 year, depending on the proprietary medicinal product, it is recommended that a switch be made to another antigonadotropic treatment (progestogen, oral contraception) until the menopause.

Recommendation for clinical practice – CNGOF - 2006[4]
For treating the painful symptoms of endometriosis externa (located outside the uterus), this recommendation mentions progestogens, continuous monophasic oestrogen/progestogen contraceptives, danazol, and GnRH analogues.
"These treatments should be used in accordance with the regimens specified by the Afssaps [French Agency for the Safety of Health Products] in 2005" (see preceding section).
For symptomatic adenomyosis, the standard treatment is a hysterectomy in the case of patients who do not wish to have any more children. Alternative medical treatments are the levonorgestrel IUD, GnRH agonists, and antigonadotropic progestogens.

RCOG guideline - 2006[5]
This guideline relates solely to endometriosis externa.
For treating the pain associated with endometriosis, it mentions oral oestrogen/progestogen contraceptives, danazol, medroxyprogesterone acetate, and GnRH agonists.
It states that these treatments have equivalent efficacy but different adverse effects and costs and that the duration of treatment with danazol and with GnRH agonist therapy is usually limited to 6 months.

[3] Les traitements médicamenteux de l'endométriose génitale (en dehors de l'adénomyose) [Drug therapy of genital endometriosis (apart from adenomyosis)] – Afssaps [French Agency for the Safety of Health Products] – December 2005
[4] Prise en charge de l'endométriose (2006) – CNGOF – recommandations pour la pratique clinique [Management of endometriosis (2006) – National College of French Gynaecologists and Obstetricians – recommendations for clinical practice]– www.cngof.asso.fr
[5] -The investigation and management of endometriosis – Royal College of Obstetricians and Gynaecologists – Green-top Guideline No. 24 – October 2006

4.3.2 Therapeutic use of the proprietary medicinal product

This proprietary medicinal product is a second-line therapy.

4.4. Target population

The target population of VISANNE is the painful forms of endometriosis not dealt with by surgery, in which VISANNE is to be used as follow-on therapy after treatment with a GnRH agonist.
The prevalence of endometriosis (all forms combined) in the female general population is reported to be 5 to 10%[6,7] or 740,000 to 1.5 million women with endometriosis in France[8].
Not all women with endometriosis are candidates for drug therapy with a GnRH analogue. Precise quantification of the target population of VISANNE is not possible on the basis of the epidemiological data available.

As a rough guide, according to IMS-EPPM data (moving annual total to November 2009), the number of patients seeing a doctor who are diagnosed as having endometriosis (code N.80 in the ICD-10 classification) is estimated at 77,000/year.
The number of prescriptions for GnRH analogues in the indication endometriosis is estimated at 15,000/year.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

The transparency Committee wishes to be provided with a post-inclusion study (see annex stating the reasons) concerning:

- the patients treated for endometriosis, no matter what the treatment prescribed:
  - patients' characteristics (sociodemographic data, medical history, history of the disease, particularly previous treatments, etc);
  - description of the disease;
  - prescription details (indications, descriptions of the various lines of treatment used, concomitant prescriptions, contraceptive methods used at the same time, etc.);
- the patients who are prescribed the proprietary product VISANNE:
  - concomitant treatments, particularly analgesics and contraceptives;
  - medium- and long-term tolerance, discontinuation of treatment, and reasons for stopping the treatment;
  - duration of the treatment and resumptions of treatment;
  - pain and quality of life in the medium and long term.

The duration of the clinical follow-up for the data to be collected in the medium and long term, which is to be determined by a scientific committee, should be justified and should be sufficient to answer the Transparency Committee's questions.

Data must be available at the time VISANNE is re-evaluated.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%

[6] Olive, D.L. and L.B. Schwartz, Endometriosis. N Engl J Med, 1993 ; 328 : 1759-69.
[7] Lu, P.Y. and S.J. Ory, Endometriosis: current management. Mayo Clin Proc, 1995; 70 : 453-63.
[8] Number of women between 15 and 49 years of age in France on 1 January 2010: 14,838,802 (source: http://www.insee.fr)

ANNEX

STATING THE REASONS FOR THE REQUEST FOR THE POST-INCLUSION STUDY OF VISANNE (a progestogen used in the treatment of endometriosis)

At its meeting of 17 November 2010 the transparency Committee formulated a request for additional data on the proprietary product VISANNE, a new progestogen indicated in the treatment of endometriosis in cases where GnRH analogue therapy has failed.

This request is justified by the need for additional data on the following points:

- the place of VISANNE in the current strategy for the management of endometriosis;
- the maintenance of the effect of the treatment beyond 24 weeks;
- the duration of treatment and the benefit of re-treatment;
- the medium- and long-term tolerance of VISANNE, particularly with regard to bleeding;
- the effect on quality of life in the medium and long term.

With these data it would be possible to determine whether VISANNE can have medium- and long-term benefit in terms of morbidity and quality of life and to get a better idea of VISANNE's place in the strategy for the management of endometriosis in comparison with GnRH analogues in particular.