HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 February 2010

LEELOO 0.1 mg/0.02 mg, coated tablet
Strip of 21, B/1 (CIP: 384 792-6)
Strip of 21, B/3 (CIP: 384 793-2)

Applicant: THERAMEX

Levonorgestrel 0.1 mg / ethinylestradiol 0.02 mg

List I

ATC code (2009): G03AA07

Date of Marketing Authorisation: 31 March 2008 (decentralised procedure – rapporteur member state: Germany)

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

Medical, Economic, and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Levonorgestrel 0.1 mg / Ethinylestradiol 0.02 mg

1.2. Indication

"Oral contraception"

1.3. Dosage and method of administration

"Posology and method of administration

The tablets must be taken in the order given on the blister pack, at approximately the same time each day and, if necessary, with some water. One tablet is taken daily for 21 consecutive days. Every subsequent blister pack is started after a 7 day tablet-free interval during which time a withdrawal bleed usually occurs. This bleeding will usually start on the 2nd or 3rd day after the last tablet has been taken and it may not have stopped, before the next pack is started.

How to start Levonorgestrel/Ethinylestradiol

No preceding hormonal contraceptive use (in the past month)

The tablets should be started on day 1 of the woman's natural cycle (i.e. on the first day her menstrual bleed). It is acceptable to start the tablets on day 2-5, but during the first cycle the concomitant use of a barrier method for the first 7 days of administration of the tablets is recommended.

Changing from another combined hormonal contraceptive (combined oral contraceptive, vaginal ring or transdermal patch)

The woman should start with Levonorgestrel/Ethinylestradiol on the day after the usual tablet-free interval (or the day after removal of the vaginal ring or transdermal patch) or the day after the last placebo tablet of the previous oral contraceptive.

Changing from a progestogen-based products (progestogen-only pill or mini-pill, injection, implant) or an intrauterine device (IUD)

The woman may switch from progestogen-only pills on any day (from an implant or intrauterine device on the day it is removed; from injection when the next injection should have been given). However, simultaneous use of a non-hormonal method of contraception (mechanical barrier) for the first 7 days of administration of Levonorgestrel/Ethinylestradiol is recommended.

After abortion/miscarriage in 1st trimester

The woman may start taking the Levonorgestrel/Ethinylestradiol tablets immediately. In this case, it is not necessary to take additional contraceptive precautions.

After delivery or abortion/miscarriage in 2nd trimester

The woman should be advised to start on day 21-28 after delivery or abortion in the 2nd trimester. If she starts later than this, she should be advised to use a concomitant barrier method during the first 7 days of tablet intake. However, if she already has had intercourse, pregnancy must be excluded, before she starts the tablets, or she should wait for her first menstrual bleed.

Missed tablets

Levonorgestrel/Ethinylestradiol contains a very low dose of two hormones. Consequently, the contraceptive efficacy margin is lower if a woman forgets to take a tablet.

If the woman is less than 12 hours late in taking the forgotten tablet, the contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers, and the remaining tablets should be taken as usual.

If the delay exceeds 12 hours, the contraceptive protection may be reduced. The closer the omission to the usual tablet-free interval, the higher the probability of pregnancy.
Handling of missed tablets may be managed by the following two basic rules:

1. Tablets should never be delayed for longer than 7 days.
2. 7 days of uninterrupted tablet taking is required to maintain adequate suppression of the hypothalamus-pituitary-ovarian-axis.

Thus, the following advice may be given in daily practice:

Week 1

The woman should take the last missed tablet as soon as she remembers this, even if this means that she has to take 2 tablets at the same time. Hereafter, she continues taking the tablets at the usual time point. She should use a barrier method concomitantly (e.g. a condom) for the next 7 days. If intercourse has taken place during the previous 7 days, the possibility of pregnancy must be considered. The more forgotten tablets, and the closer to the usual tablet-free interval this takes place, the greater the risk of pregnancy.

Week 2

The woman should take the last missed tablet as soon as she remembers, even if this means that she has to take 2 tablets at the same time. Hereafter, she continues taking the tablets at the usual time point. Provided that the tablets have been taken correctly during the 7 days preceding the forgotten tablet, it is not necessary to take additional contraceptive precautions. However, if this is not the case, or if more than 1 tablet has been forgotten, the woman should be advised to use another contraceptive method for 7 days.

Week 3

The risk of reduced efficacy is imminent because of the ensuing 7-day tablet-free interval. Reduction of contraceptive efficacy may, however, be prevented by adjusting the tablet intake. Therefore, by following one of the following two alternatives, it is not necessary to take additional contraceptive precautions, provided that all tablets have been taken correctly during the 7 days preceding the forgotten tablet. However, if this is not the case, the woman should be advised to follow the first of these two alternatives and use another contraceptive method concomitantly for the next 7 days.

1. The woman should take the last missed tablet as soon as she remembers, even if this means that she has to take 2 tablets at the same time. Thereafter, she should continue to take the tablets at the usual time point. She should start on the next blister pack immediately after taking the last tablet in the current blister pack, i.e. there will be no tablet-free interval between the blister packs. A withdrawal bleed is unlikely to occur before the end of the second blister pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The woman may also be advised to stop taking tablets from the current blister pack. In this case, she should keep a tablet-free interval of up to 7 days, including the days she forgot to take her tablets, and thereafter continue with the next blister pack.

If the woman has missed several tablets, a non-hormonal method of contraception should be used until the next withdrawal bleed.
If the woman has missed tablets and does not get a withdrawal bleed during the first, normal tablet-free interval, the possibility of pregnancy must be considered. This possibility must be excluded before a new blister strip is started.

Advice in the case of vomiting/diarrhoea

If severe diarrhoea or vomiting occurs within 3-4 hours after taking a tablet of Levonorgestrel/Ethinylestradiol, absorption of the active substances may not be complete. In this case, other methods of contraception should be used in addition. The advice concerning missed tablets should also be followed. If the woman does not want to change her usual tablet intake, she should take the required extra tablet(s) from another blister pack. In the event of persistent or recurrent gastrointestinal problems, other, non-hormonal methods of contraception should be used.

How to delay or shift a period

In order to delay a period, the woman should continue the next blister pack of Levonorgestrel/Ethinylestradiol, after taking the last tablet in the current pack, without a tablet-free interval. The extension can be carried on for as long as desired until the end of the second blister pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Levonorgestrel/Ethinylestradiol 0.1mg/0.02 mg is resumed after the usual 7 days tablet-free interval.

To shift her period to another day of the week than the woman is used to with the present tablet intake, she may be advised to shorten the forthcoming tablet-free interval by as many days as she likes. The shorter the interval, the greater the risk that she will not have a withdrawal bleed and she may have break throughbleeding or spotting during the second blister pack (just as when delaying a period)."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

G	: Genito-urinary system and sex hormones
G03	: Sex hormones and modulators of the genital system
G03A	: Hormonal contraceptive for systemic use
G03AA	: Progestogens and estrogens, fixed combinations
G03AA07	: Levonorgestrel and estrogen

2.2. Medicines in the same therapeutic category

2.2.1 Strictly comparable products

Oral estrogen-progestogen contraceptives:

INN	Dose of ethinylestradiol	Proprietary product
1st generation estrogen-progestogen contraceptives		
Norethisterone acetate/ethinylestradiol	Biphasic: 30 and 40 µg (reimbursable)	MINIPHASE
Norethisterone/ethinylestradiol	Monophasic: 35 µg (non-reimbursable)	ORHO-NOVUM
	Triphasic (progestogen): 35 µg (reimbursable)	TRIELLA
2nd generation estrogen-progestogen contraceptives (reimbursable)		
Levonorgestrel/ethinylestradiol and their generics	Monophasic: 30 µg	MINIDRIL LUDEAL GE
	Biphasic: 30 and 40 µg	ADEPAL
	Triphasic: 30, 40, and 30 µg	TRINORDIOL DAILY GE
Norgestrel/ethinylestradiol	Monophasic: 50 µg	STEDIRIL
3rd generation estrogen-progestogen contraceptives (reimbursable)		
Desogestrel/ethinylestradiol	30 µg	VARNOLINE CONTINU
3rd generation estrogen-progestogen contraceptives (non-reimbursable)		
Desogestrel/ethinylestradiol and their generics	20 µg	CYCLEANE 20 µg, MERCILON, Désogestrel/éthinylestradiol BIOGARAN 150 µg/ 20 µg
	30 µg	CYCLEANE 30 µg, VARNOLINE Désogestrel/éthinylestradiol BIOGARAN 150 µg/ 30 µg
Gestodene/ethinylestradiol and their generics	15 µg	MELODIA, MINESSE
	20 µg	MELIANE, CARLIN 75 µg/20 µg, EFEZIAL 75 µg/20 µg, FELIXITA 75 µg/20 µg, HARMONET, Gestodène/éthinylestradiol 75 µg/20 µg TEVA, ACTAVIS, ARROW, BIOGARAN, EG, RANBAXY, RATIOPHARM, SANDOZ, WINTHROP, ZYDUS
	30 µg	MINULET, MONEVA, CARLIN, EFEZIAL 75 µg/30 µg, FELIXITA 75 µg/30 µg, Gestodène/éthinylestradiol 75 µg/30 µg TEVA, ACTAVIS, ARROW, BIOGARAN, EG, RANBAXY, RATIOPHARM, SANDOZ, WINTHROP, ZYDUS
	Triphasic: 30, 40, and 30 µg	PHAEVA, TRI MINULET, PERLEANE
Norgestimate/ethinylestradiol	35 µg	CILEST, EFFIPREV
	Triphasic (for the progestogen): 35 µg	TRICILEST, TRIAFEMI
Other estrogen-progestogen contraceptives (non-reimbursable)		
Chlormadinone acetate /ethinylestradiol	30 µg	BELARA
Drospirenone/ethinylestradiol	30 µg	JASMINE
	20 µg	JASMINELLE, JASMINELLE CONTINU, YAZ

2.2.2 Non-strictly comparable products

- Other estrogen-progestogen contraceptives:
    - EVRA, transdermal patch (norelgestromin/ethinylestradiol) (non-reimbursable)
    - NUVARING, vaginal delivery system (etonogestrel/ethinylestradiol) (non-reimbursable)
- Progestogen-only contraceptives

2.3. Medicines with a similar therapeutic aim

Intrauterine devices, spermicides.

3. ANALYSIS OF AVAILABLE DATA

The company submitted 21 publications – 5 efficacy/safety studies and 16 studies of clinical and/or biological safety.

- Two efficacy studies and 7 safety studies were taken into account. Some of these studies used a proprietary product with the same composition as LEELOO but including 7 additional placebo tablets.
- The studies concerning intermediate criteria (determinations of laboratory parameters) or concerning a subgroup of a study already published elsewhere and a study of safety (weight and blood pressure) with few participants with a control group, i.e. 3 efficacy studies and 10 safety studies, were not taken into account.

A publication[1] including the populations of 2 efficacy studies that were not considered (publications of results for subgroups) was added to the analysis.

3.1. Efficacy

Information on the efficacy studies is shown in *Table 1*.

Table 1: Efficacy studies

Study	Method	Endpoints	Result
Endrikat *et al*[2]	- Open, randomised* study, in 3 parallel groups: 1) 20 µg EE/100 µg LNG (n= 380 - 4341 cycles) (mean age: 25.3 years) 2) 20 µg EE/500 µg NET (n = 255 - 2698 cycles) (mean age: 25.4 years) 3) 30 µg EE/150 µg LNG (n = 125 - 1505 cycles) (mean age: 26.1 years) - Women between 18 and 35 years of age - Duration of treatment: 13 cycles	- Pearl index	1) 0.9 2) 1.9 3) 0
Archer *et al*[1]†	- Non-comparative study (n =1708 - 26,554 cycles) - Treatment: 20 µg EE/100 µg LNG + 7 placebo tablets - Mean age: 27.2 years (17 to 49) - Regular cycles of 25 to 31 days or post abortum or post partum - Duration of treatment: up to 3 years - End of study when ≥ 20,000 cycles analysable - Patients removed from study if ≥ 3 consecutive pills forgotten	- Pearl index	0.88‡
Hite *et al*[3]	- Non-comparative observational study (n =12,843 - 70,796 cycles) - Treatment: 20 µg EE/100 µg LNG - Women wanting contraception for at least 6 months - Mean age: 24.1 years - Duration of treatment: 6 cycles	- Pearl index	0.44§

EE: ethinylestradiol; LNG: levonorgestrel; NET: norethisterone; *: randomisation 3/2/1; †: publication not provided, including the populations of two publications provided and thus not detailed[4,5] ; ‡ : 18 pregnancies; §: 24 pregnancies

The Pearl index given in the SPC for this proprietary product is 0.69.

1 Archer DF, Maheux R *et al.* Efficacy and safety of a low-dose monophasic combination oral contraceptive containing 100 microg levonorgestrel and 20 microg ethinyl estradiol (Alesse). North American Levonorgestrel Study Group (NALSG). Am J Obstet Gynecol 1999; 181: 39-44.

2 Endrikat J, Hite R *et al.* Multicenter, comparative study of cycle control, efficacy and tolerability of two low-dose oral contraceptives containing 20 µg ethinylestradiol/100 µg levonorgestrel and 20 µg ethinylestradiol/500 µg norethisterone. Contraception 2001;64:3-10

3 Hite R C, Bannemerschult R *et al.* Large observational trial of a new low-dose oral contraceptive containing 20 µg ethinylestradiol and 100 µg levonorgestrel (Miranova) in Germany. Eur J Contracept Reprod Health Care 1999;4:7-13

4 Carr B R, Delconte A. Using a low-dose contraceptive in women 35 years of age and over: 20 µg estradiol/100 µg levonorgestrel. Contraception 2002;65:397-402

5 Archer D, Maheux R *et al.* A new low-dose monophasic combination oral contraceptive (Alesse) with levonorgestrel 100 µg and ethinyl estradiol 20 µg. Contraception 1997;55:139-44

3.2. Adverse effects

Information on safety is shown in *Tables 2 and 3*.

Table 2: Cycle control

Study	Method	Endpoints	Result
Endrikat *et al*	- Open, randomised study, in 3 parallel groups: 1. 20 µg EE/100 µg LNG (n = 380) (mean age: 25.3 years) 2. 20 µg EE/500 µg NET (n = 255) (mean age: 25.4 years) 3. 30 µg EE/150 µg LNG (n = 125) (mean age: 26.1 years) - Duration of treatment: 13 cycles	- % of women with at least one episode of intermenstrual bleeding during cycles 2 to 7 - % of cycles without intermenstrual bleeding - % of women experiencing amenorrhea during the study	1. 43.9% 2. 72.7% 3. 15.7% 1. 87% 2. 67.6% 3. 95.9% 1. 7.1% 2. 20.6% 3. 0.9%
Archer *et al*	- Non-comparative study (n =1708 - 26,554 cycles) - Treatment: 20 µg EE/100 µg LNG + 7 placebo tablets - Duration of treatment: up to 3 years - Patients removed from study if ≥ 3 consecutive pills forgotten	- % of cycles with intermenstrual bleeding and/or spotting - % of cycles with amenorrhea	23.1% 1.9%
Hite *et al*	- Non-comparative observational study (n =12,843). - Duration of treatment: 6 cycles	- % of women who had - intermenstrual bleeding - amenorrhea - rate of drop out from study because of: - intermenstrual bleeding - metrorrhagia	1st cycle: 30.4% 6th cycle: 6% 1.1% 3.4% 1.8%
DelConte *et al* [6]	- Open, randomised study, in 2 parallel groups: 1. 20 µg EE/100 µg LNG + 7 plac. tabs (n = 84 – 274 cycles) (mean age: 27±7 years*) 2. 20 µg EE/1000 µg LNG + 7 plac. tabs (n = 89 – 289 cycles) (mean age: 28±7 years*) - Duration of treatment: up to 4 cycles - Patients removed from study if ≥ 3 consecutive pills forgotten	-% of normal cycles - % of cycles with intermenstrual bleeding - % of cycles with amenorrhea	1. 56.9% 2. 36% 1. 42% 2. 54% 1. 1.1% 2. 10%
Chavez *et al* [7]	Open, randomised study, in 2 parallel groups: 1. 20 µg EE/100 µg LNG + 7 plac. tabs (n = 139 – 384 cycles) (mean age: 28±7 years*) 2. 35 µg EE/500 µg , 750 µg, 1000 µg NET+ 7 plac. tabs (n = 150 – 400 cycles) (mean age: 28±7 years*) - Duration of treatment: up to 4 cycles - Patients removed from study if ≥ 3 consecutive pills forgotten	-% of normal cycles - % of cycles with intermenstrual bleeding - % of cycles with amenorrhea Pregnancies	1. 60.2% 2. 51.3% 1. 36.2% 2. 45.5% 1. 3.6% 2. 3.2% 1. n=1 2. n=2

EE: ethinylestradiol; LNG: levonorgestrel; NET: norethisterone; *: standard deviation

6 Del Conte A, Loffer F *et al.* Cycle control with oral contraceptives containing 20 micrograms of ethinyl estradiol. A multicenter, randomized comparison of levonorgestrel/ ethinyl estradiol (100 micrograms/20 micrograms) and norethindrone/ethinylestradiol (1000 micrograms/20 micrograms). Contraception 2001; 64:3-10

7 Chavez A, DelConte A. A comparison of cycle control with monophasic levonorgestrel/ethinylestradiol 100 µg/20 µg versus triphasic norethindrone/ethinylestradiol 500-750-1000 µg/35 µg: a multicenter, randomized, open-label study. Eur J Contracept Reprod Health Care 1999; 4:75-83

Table 2: Cycle control (continued)

Reisman *et al* [8]	Open, randomised study, in 2 parallel groups: 1. 20 µg EE/100 µg LNG + 7 plac. tabs (n = 155 – 453 cycles) (mean age: 27 ± 6 years *) 2. 35 µg EE/500 µg, 750 µg, 1000 µg NET+ 7 plac. tabs (n = 167 – 506 cycles) (mean age: 26 ± 6 years *) - Duration of treatment: 1 to 4 cycles - Patients removed from study if ≥ 3 consecutive pills forgotten	-% of normal cycles - % of cycles with intermenstrual bleeding - % of cycles with amenorrhea Pregnancies	1. 60.0% 2. 58.5% 1. 36.2% 2. 38.5% 1. 3.8% 2. 3.0% 1. n=1 2. n=2
Winkler *et al* [9]	Open, randomised study, in 2 parallel groups: 1. 20 µg EE/100 µg LNG (n = 498) (mean age: 28 years; 18-45) 2. 20 µg EE/150 µg DSG (n = 500) (mean age: 28 years; 18-45) - Cycles of 24 to 35 days - Duration of treatment: 6 cycles	Mean number of days with bleeding/spotting/cycle during cycles 2 to 6 - % of cycles with amenorrhea - menstrual irregularities (% of women treated) Discontinuation of treatment because of cycle problems (bleeding or amenorrhea)	1. 0.63 2. 0.48 1. 6% 2. 4% 1. 3.8% 2. 1.8% 1. n=13 2. n=3
Sabatini R *et al*[10]	Open, randomised study, in 3 parallel groups: 1. 20 µg EE/100 µg LNG (n = 94) (mean age: 31 ± 6 years *) 2. 15 µg EE/60 µg gestodene (n = 92) (mean age: 29 ± 6 years *) 3. 15 µg EE/120 µg etonogestrel vaginal ring (n = 94) (mean age: 30 ± 6 years *) - Duration of treatment: 12 cycles	- menstrual irregularities in cycles 3, 6, and 12 (% of women treated)	1. 22.5% ; 17% ; 12.7% 2. 35.8% ; 23.9% ; 13% 3. 9.5% ; 6.3% ; 4.2%

EE: ethinylestradiol; LNG: levonorgestrel; NET: norethisterone; DSG: desogestrel; * standard deviation

8 Reisman H, Martin D *et al*. A multicenter randomized comparison of cycle control and laboratory findings with oral contraceptives agents containing 100 µg levonorgestrel with 20 µg ethinylestradiol or triphasic norethindrone with ethinylestradiol. Am J Obstet Gynecol 1999;181:45-52

9 Winkler UH, Ferguson H. Cycle control, quality of life and acne with two low-dose oral contraceptives containing 20 µg ethinylestradiol. Contraception 2004;69:469-476

10 Sabatini R, Cagiano R *et al.* Comparison profiles of cycle control, side effects and sexual satisfaction of three hormonal contraceptives. Contraception 2006;74:220-223

Table 3: Other safety data

Study	Method	Adverse events	Result
Endrikat *et al*	- Open, randomised study, in 3 parallel groups: 1. 20 µg EE/100 µg LNG (n = 380) 2. 20 µg EE/500 µg NET (n = 255) 3. 30 µg EE/150 µg LNG (n = 125) - Duration of treatment: 13 cycles	Commonest adverse events (% of women treated) Rate of drop out from study because of adverse event Drop out from study because of serious adverse effect (n)	Headache 1. 18.4% ; 2. 20.4% 3. 16% Mastalgia 1. 8.2% 2. 13.7% 3. 8.8% Nausea 1. 7.6 2. 8.2 3. 6.4 1. 7% 2. 18% 3. 4% n = 1 – (surgically treated ovarian cyst- group 2)
Archer *et al*	- Non-comparative study (n =1708 - 26,554 cycles) - Treatment: 20 µg EE/100 µg LNG + 7 placebo tablets - Duration of treatment: up to 3 years - Patients removed from study if ≥ 3 consecutive pills forgotten	- Discontinuation of treatment because of adverse events (% of women treated) Serious adverse event	- 17%, of which: 2%: headache, metrorrhagia >1% hypertension, migraine, nausea, hypercholesterolemia, weight gain, depression, emotional lability, decreased libido, acne, amenorrhea, menorrhagia, metrorrhagia - Myocardial infarct
Hite *et al*	- Non-comparative observational study (n =12,843). - Duration of treatment: 6 cycles	% of women who had at least 1 adverse effect Commonest adverse events (% of women treated): - intermenstrual bleeding, metrorrhagia (see *Table 2*) - headache Rate of drop out from study because of ovarian cyst Serious adverse effects	12.3% 1.3% 0.15% 1 pelvic venous thrombosis 1 left occipital valve infarct
DelConte *et al*	- Open, randomised study, in 2 parallel groups: 1. 20 µg EE/100 µg LNG + 7 placebo tabs (n = 84 – 274 cycles) 2. 20 µg EE/1000 µg NET + 7 plac. tabs (n = 89 – 289 cycles) - Duration of treatment: up to 4 cycles - Patients removed from study if ≥ 3 consecutive pills forgotten	% of women who had at least 1 adverse event - Commonest adverse events in the 2 groups) - Drop out from study because of adverse event	1. 79.8% 2. 76.4% Headache, dysmenorrhea, infection 1. n = 6 (metrorrhagia, menorrhagia, nausea, nervousness, weight gain) 2. n = 3 (nausea, headache, amenorrhea)
Chavez *et al*	Open, randomised study, in 2 parallel groups: 1. 20 µg EE/100 µg LNG + 7 plac. tabs (n = 139 – 384 cycles) 2. 35 µg EE/500 µg, 750 µg, 1000 µg NET+ 7 plac. tabs (n = 150 – 400 cycles) - Duration of treatment: up to 4 cycles - Patients removed from study if ≥ 3 consecutive pills forgotten	% of women who had at least 1 adverse event - Commonest adverse events % of women who had at least 1 adverse effect Drop out from study because of adverse event Serious adverse effects	1. 79.1% 2. 76.7% Headache (1: 28.8%; 2: 30%) Dysmenorrhea (1: 28.8%; 2: 30%) Nausea (1: 14.4%; 2: 18.7%) Mastalgia (1: 7.2%; 2: 15.3%) Vomiting (1: 2.2%; 2: 7.3%) 1. 53.2% 2. 61.3% 1. 11.5% 2. 12% 1. n = 1 (cholecystitis) 2. n = 2 (1 CVA and 1 ovarian cyst)

EE: ethinylestradiol; LNG: levonorgestrel; NET: norethisterone; CVA: cerebrovascular accident; DSG: desogestrel

Table 3: Other safety data (continued)

Reisman *et al*	Open, randomised study, in 2 parallel groups: 1. 20 µg EE/100 µg LNG + 7 plac. tabs (n = 155 – 453 cycles) 2. 35 µg EE/500 µg, 750 µg, 1000 µg NET+ 7 plac. tabs (n = 167 – 506 cycles) - Duration of treatment: 1 to 4 cycles - Patients removed from study if ≥ 3 consecutive pills forgotten	% of women who had at least 1 adverse event Commonest adverse effects Drop out from study because of adverse event	1. 69.7% 2. 70.7% Dysmenorrhea (1 and 2: 17%) Nausea (1: 17%; 2: 16%) Headache (1: 19%; 2: 17%) 1. 12.3% 2. 5.4% Of which: nausea/vomiting (1: n = 5; 2: n = 4); headache (1: n = 4; 2: n = 1); intermenstrual bleeding (1: n = 3; 2: n = 1)
Winkler *et al*	Open, randomised study, in 2 parallel groups: 1. 20 µg EE/100 µg LNG (n = 498) 2. 20 µg EE/150 µg DSG (n = 500) - Duration of treatment: 6 cycles	Drop out from study because of adverse event (except cycle problems) Commonest adverse effect (% of women treated)	1. n = 7 2. n = 16 Headache (1: 2.4%; 2: 4%)
Sabatini R *et al*	Open randomised study, in 3 parallel* groups: 1. 20 µg EE/100 µg LNG (n = 94) (mean age: 31 years ± 6†) 2. 15 µg EE/60 µg gestodene (n = 92) (mean age: 29 years ± 6†) 3. 15 µg EE/120 µg etonogestrel - vaginal ring (n = 94) (mean age: 30 years ± 6†) - Duration of treatment: 12 cycles	Adverse effects in cycles 3, 6, and 12 - systematic collection (% of women treated) Decrease in sexual desire in cycle 12 – (% of women treated) Increase in sexual desire in cycle 12 Decrease in sexual satisfaction in cycle 12 Increase in sexual satisfaction in cycle 12 Discontinuation of treatment	Nausea 1. 19.1%; 9.5%; 7.4% 2. 14.1%; 7.6%; 5.4% 3. 6.3%; 4.2%; 2.1% Headache 1. 15.9%; 11.7%; 9.5% 2. 14.1%; 10.8%; 9.7% 3. 11.7%; 9.5%; 6.3% Mastalgia 1. 11.7%; 8.5%; 6.3% 2. 9.7%; 7.6%; 6.5% 3. 7.4%; 5.3%; 4.2% Irritability 1. 15.9%; 9.5%; 8.5% 2. 10.8%; 7.6%; 4.2% 3. 4.2%; 2.1%; 2.1% Depression 1. 8.5%; 7.4%; 6.3% 2. 8.6%; 6.5%; 7.6% 3. 4.2%; 2.1%; 1% Vaginal dryness 1. 12.7%; 9.5%; 6.3% 2. 30.4%; 16.3%; 8.6% 3. 2.1%; 0; 0 1: 31.9%; 2: 42.4%; 3: 8.5% 1: 26.5%; 2: 30.4%; 3: 75.5% 1: 26.5%; 2:41.3%; 3: 12.7% 1: 46.8%; 2: 22.8%; 3: 77.6% 1. 22.3% (n = 21) of which cycle problems: n = 7; loss of desire: n = 6 2. 30.4% (n = 28) of which cycle problems n = 13; vaginal dryness n = 7; loss of desire: n = 6 3. 11.7% (n = 11) of which cycle problems: n = 5 ;

EE: ethinylestradiol; LNG: levonorgestrel; NET: norethisterone; CVA: cerebrovascular accident; DSG: desogestrel; *: The number of patients is the same in cycles 3, 6, and 12. The publication does not mention the way in which any dropouts from the study were taken into account; †: standard deviation

Table 3: Other safety data (continued)

Coney *et al*[11]	Double-blind studies versus placebo‡ 1. 20 µg EE/100 µg LNG + 7 plac. tabs (n = 349) (mean age: 26.5 years ± 7.3†) 2. placebo (n = 355) (mean age: 26.9 ± 7.4†) - Duration of treatment: 6 cycles	Change in weight at end of study§ % of patients who had at least 1 adverse event Adverse events of similar frequency in the 2 groups¶ Commonest adverse events in the treated group¶ Discontinuation of treatment because of adverse event	1. 0.72 ± 2.64† 2. 0.56 ± 2.64† 1. 82.0% 2. 76.9% Headache, migraine, nausea, vomiting, mastalgia, weight gain Metrorrhagia, menstrual irregularities, allergic reaction (‖), menorrhagia, urticaria 1. n = 19 2. n = 20

EE: ethinylestradiol; LNG: levonorgestrel; NET: norethisterone; CVA: cerebrovascular accident; DSG: desogestrel; *: The number of patients is the same in cycles 3, 6, and 12. The publication does not mention the way in which any dropouts from the study were taken into account; †: standard deviation; ‡: Analysis of safety carried out on the combined results of the two randomised studies versus placebo; § last available measurement; ‖: none was considered to be attributable to the treatment; ¶: rates not specified

3.3. Conclusion

The Pearl index was 0.88 and 0.9 in 2 clinical studies and 0.44 in an observational study. The value for it shown in the SPC is 0.69 (95% CI: 0.30-1.36).

The percentage of cycles with intermenstrual bleeding in LEELOO group ranged from 13 to 42% in the studies, this bleeding being more common in the first few months of use.
The percentage of cycles with amenorrhea ranged from 1.9% to 7.1%. Aside from cycle problems, the commonest adverse events occurring in the LEELOO group were: headache (1.3% to 28.8% of patients), dysmenorrhea (17% to 28.8%), mastalgia (7.2% to 11.7%), nausea (7.6% to 19.1%), and vomiting (2.2%).
The clinical safety of LEELOO in the studies versus an active comparator does not appear to differ from that of the other oral contraceptives; however, in two clinical studies[2,9] the cycle problems were more common with LEELOO than with a comparator product.

The frequency of headache, migraine, nausea, vomiting, mastalgia, and weight gain was similar in the LEELOO and placebo groups whereas cycle problems and allergic reactions (considered not to be attributable to the treatment) were more common in the LEELOO group.
Discontinuation of treatment because of adverse events occurred in 7 to 22.3% of patients, depending on the study. In the placebo-controlled study, the percentages discontinuing the treatment were similar in the LEELOO and placebo groups. The commonest causes of treatment discontinuation were cycle problems and headache.

11 Coney P, Washenik K *et al.* Weight change and adverse event incidence with a low-dose oral contraceptive: two randomized, placebo-controlled trials. Contraception 2001;63:297-302

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The proprietary product falls under the category of preventive treatment.

The efficacy/adverse effect ratio is high.

Public health benefit
The public-health burden arising from unwanted pregnancies can be considered moderate, considering that, even though a high percentage of women use effective contraception, one in every three pregnancies in France is apparently unwanted[12].
Ensuring access to appropriate contraception and reducing the rate of elective abortions are public-health objectives defined by the Groupe Technique National de Définition des Objectifs (GTNDO) [National technical group for the setting of public-health objectives].
There is thus a public-health need, but meeting this need does not necessarily simply boil down to reimbursing the cost of an additional pill.
In the light of the available efficacy data and considering that there are alternatives and that the potential impact of the estrogen dose (lower in LEELOO than in other available 2nd generation pills) on thromboembolic events has not been investigated, it is not expected that LEELOO will benefit public health.

This proprietary product is a first-line medicinal product.

There are therapeutic alternatives.

The actual benefit of this proprietary product is substantial.

4.2. Improvement in actual benefit (IAB)

The proprietary product LEELOO does not provide an improvement in actual benefit (IAB V) in comparison with other second-generation oral contraceptives.

4.3. Therapeutic use

4.3.1 Therapeutic use

According to the clinical-practice recommendations of the Afssaps [French Healthcare Product Safety Agency], ANAES [National Health Accreditation and Assessment Agency], and INPES [National Prevention and Health Education Institute] (December 2004)[13] , any contraceptive method must be simple, effective, well tolerated, and reversible. It is currently thought that the contraceptive efficacy of the various types of oral estrogen-progestogen contraceptives administered in the long term is equivalent.
Before estrogen-progestogen contraception is prescribed, it is important to systematically investigate arterial or venous thromboembolic risk factors and take account of the contraindications and precautions for use. The choice of estrogen-progestogen depends on age, the occurrence of an abortion or recent childbirth, and the individual and familial history.

Oral estrogen-progestogen contraception is one of the methods of 1st choice for women who do not have any specific risk factor (cardiovascular, carcinological, hepatic, etc.). It is a very effective method when used in the optimal manner. New dosage forms (vaginal ring and patch that release estrogen-progestogens) have demonstrated their efficacy and may represent alternatives[13].

12 Bajos N, Leridon H, Goulard H, Oustry P, Job-Spira N; COCON Group. Contraception: from accessibility to efficiency. Hum Reprod. 2003;18:994-9.
13 Recommandations pour la pratique clinique Afssaps-ANAES-INPES : Stratégies de choix des méthodes contraceptives chez la femme [Strategies for choosing contraceptive methods in women]. December 2004

In terms of contraceptive efficacy and cycle control, there are no data to warrant giving preference to the prescription of a particular type of estrogen-progestogen pill (according to its generation or mono-, bi-, or triphasic character), which may lead to adjustments of prescription depending on individual tolerance of the pill tested[13].
All estrogen-progestogen contraceptives are associated with an increased risk of thromboembolic events[13] (level of evidence 3[14]).
However, there seems to be an even higher risk of venous thromboembolism with third-generation oral estrogen-progestogen contraceptives in comparison with second-generation oral estrogen-progestogen contraceptives (containing levonorgestrel). That is why the Transparency Committee has categorised the third-generation contraceptives as second-line therapies[15].
Two recent studies[16,17] likewise concluded that the thromboembolic risk associated with 2nd generation oral estrogen-progestogen contraceptives is lower than that associated with 3rd generation oral estrogen-progestogen contraceptives and suggest that this risk decreases with estrogen dose.
The arterial risk increases with age: from the age of 35, the risk/benefit ratio of this contraception should be re-evaluated regularly.
After 45 years of age estrogen-progestogens are not recommended on account of the increase in vascular and metabolic risk, so mechanical methods of contraception are recommended.
The literature data report a potential increase in the risk of some cancers, including breast cancer and cervix cancer (level of evidence 2)[18]. These cancers remain relatively uncommon in the youngest age groups, but increase with age[13]. A contrario, the literature shows possible beneficial effects of oral estrogen-progestogen contraception on the incidence of cancer of the endometrium (level of evidence 2), ovaries (level of evidence 2), and colon and rectum (level of evidence 2)[19].
As regards the carcinological risk of the medical devices that release estrogen-progestogens (vaginal ring and patch)[13] and oral estrogen-progestogens containing less than 30 µg ethinylestradiol, there is insufficient experience available.
A British cohort study carried out between 1968 and 2004[20] looked at the risk of cancer associated with the use of oral contraceptives. Estrogen-progestogen contraceptives accounted for 97% of the contraceptives used and progestogen-only contraceptives 3%; 75% of the contraceptives contained 50 µg ethinylestradiol, 12% contained more, and 10% contained less. Most of the women used more than one type of estrogen-progestogen oral contraceptive, a reduction in the estrogen dose being the usual pattern. This study suggests that oral contraception is not associated with an increased overall risk and that it reduces the

14 Grade of recommendations:
level 1: established scientific evidence (randomised comparative studies of high power, meta-analysis of randomised comparative studies, analysis of decision based on well conducted studies)
level 2: scientific assumption (randomised comparative studies of low power, well conducted non-randomised comparative studies, cohort studies)
level 3: low level of evidence (case-control studies)
level 4: low level of evidence (comparative studies involving substantial bias, retrospective studies, case series)
15 Transparency Committee – Opinion of 10 October 2007 – evaluation of 3rd generation oral contraceptives
16 van Hycklama Vlieg A, Helmerhorst FM *et al*. The venous thrombotic risk of oral contraceptives, effect of estrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921
17 Lidegaard O, Lokkegaard E et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009;339: b2890.
18 As a rough guide, the incidence of breast cancer ranges from 0.2/100,000 women per year between 15 and 19 years of age to 138/100,000 women per year between 40 and 44 years of age; the increase in the risk associated with the ongoing use of an estrogen-progestogen pill is around 25%. The incidence of cancer of the neck of the uterus ranges from 0.1/100,000 women per year between 15 and 19 years of age to 20/100,000 women per year between 40 and 44 years of age; the increase in cervical cancer risk associated with the use of an estrogen-progestogen pill is around 50% after 5 to 9 years of use. In the case of liver cancer, which is considered very rare (< 1/100,000 women per year between 40 and 44 years of age), the risk after 5 years of use is higher than in non-users by a factor of approximately 2.
19 As a rough guide, endometrial cancer is rare (< 5/100,000 women per year between 40 and 44 years of age) and the decrease in the risk associated with the ongoing use of an estrogen-progestogen pill is around 66% 5 years after discontinuation. The incidence of ovarian cancer ranges from 1/100,000 women per year between 15 and 19 years of age to 9/100,000 women per year between 40 and 44 years of age and the decrease in risk associated with the use of an estrogen-progestogen pill is around 30 % 5 to 20 years after discontinuation. The incidence of colorectal cancer ranges from 0.2/100,000 women per year between 15 and 19 years of age to 12/100,000 women per year between 40 and 44 years of age and the decrease in the risk is around 15 to 20%.
20 Hannaford PC. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioners' oral contraception study. BMJ 2007, 335: 651

risk of endometrial and ovarian cancer; on the other hand, in long-term users (8 years or more), the risks are apparently increased for cancers of the cervix and the central nervous system.
The main contraindications of estrogen-progestogen contraceptives are of a cardiovascular, carcinological, and hepatic nature.
Although progestogen contraception is reserved, by practitioners, for 2nd line use in women who have certain contraindications (notably cardiovascular ones), it, like estrogen-progestogens, ranks among the methods that are effective in ordinary use and very effective in optimal use[13].
The intrauterine device (IUD) is another 1st line contraceptive method[13].

4.3.2 Therapeutic use of the proprietary product
For oral estrogen-progestogen contraception, LEELOO is a first-line medicine.

4.4. Target population
There are about 11.4 million women between 18 and 44 years of age in France[21]. According to Inpes [National institute for health education and protection] (baromètre santé 2005)[22], 76.6% of sexually active women between 25 and 44 years of age use contraception. Estrogen-progestogen contraceptives are the main method used: 57.2%.

On the basis of the above, the target population for LEELOO would be about 5 million women.

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 use by hospitals and various public services in the indication and dosage of the Marketing Authorisation.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%

21 INSEE [National institute of statistics and economic studies] projection - 1 January 2008
22 http://www.inpes.sante.fr/index.asp?page=Barometres/baro2005_1R/ouvrage/presentation.asp