



Therapeutic Class ReviewSM

Women's Health

levonorgestrel 90 mcg/ethinyl estradiol 20mcg (Lybrel[®])

December 2007

New Product for Review:

Levonorgestrel 90mcg/ethinyl estradiol 20mcg
(Lybrel[®])[Wyeth]

Dossier Provided by Manufacturer:

Dossier Evaluation: 2, missing PE model

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Available Therapeutic Alternatives:

Numerous – see products tables on pages 5 through 7.

Executive Summary

- Why the interest in suppressing menstruation?
 - As a matter of convenience, some women prefer not to have regular menstrual periods.
 - There are numerous unproven claims of other health benefits associated with long-term suppression, which has led to off-label use in a variety of conditions for the past 30 years.
- LNG 90 mcg/EE 20 mcg (Lybrel) key points:
 - The active components of LNG 90 mcg/EE 20 mcg (Lybrel) are present in several marketed cyclic combination oral contraceptives (COCs); consequently, approval was granted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.¹
 - LNG 90 mcg/EE 20mcg (Lybrel) is supplied in 28-day pill packs, and all pills are active. One pill is taken orally daily on a continuous basis, with no hormone-free interval.
 - LNG 90 mcg/EE 20 mcg (Lybrel) is the only COC that is FDA-approved for continuous use.
 - Women who choose LNG 90 mcg/EE 20 mcg (Lybrel) are exposed to a slightly lower cumulative dose of estrogen than those using extended-cycle COCs or traditional cyclic COCs containing 30mcg EE.
 - Reported adverse events are as expected for the class.
 - Pregnancy may not be recognized as quickly as with traditional COCs because amenorrhea may be attributed to use of LNG 90 mcg/EE 20 mcg (Lybrel).
- Guidelines
 - We found no national or international guidelines specifically addressing use of continuously-dosed oral contraceptives.

- Expert opinion
 - Wyeth recently sponsored a Gallup poll, which reported that 97% of OB/GYNs thought it was safe to use oral contraceptives continuously, without a placebo phase, in the appropriate patient population.²
 - In 2003, an ACOG-sponsored Gallup poll reported that 99% of female OB/GYNs believe continuously-dosed oral contraceptives are safe and more than half have tried suppressing their own periods.³
 - ACOG⁴ and ARHP⁵ clearly support the use of extended-cycle and continuous COCs.
 - A Cochrane review⁶ concluded that continuous pill-taking (for longer than 28 consecutive days) appears a reasonable approach for oral contraception.

Evidence⁷

- LNG 90 mcg/EE 20 mcg (Lybrel) appears to have similar efficacy (prevention of pregnancy) compared to the numerous COCs on the preferred/formulary list. Pearl index = 1.60 (95% CI=0.96, 2.49).
- LNG 90 mcg/EE 20 mcg (Lybrel) has no proven health benefit beyond prevention of pregnancy.
- The incidence of bleeding/spotting episodes decreased with continuous use of LNG 90 mcg/EE 20 mcg (Lybrel) over time.
 - Only 541/921 (58.7 %) of subjects evaluated during cycle 13 achieved amenorrhea (“put their period on hold”).
 - On an ITT basis, only 541/2,134 (25.4 %) of subjects achieved amenorrhea during cycle 13.
- Considerations in Subpopulations⁸:
 - Pediatrics: LNG 90 mcg/EE 20 mcg (Lybrel) is only indicated in females after menarche.
 - Geriatrics: LNG 90 mcg/EE 20 mcg (Lybrel) has not been studied in women over 50.
 - Gender: LNG 90 mcg/EE 20 mcg (Lybrel) is only indicated in females after menarche.
 - Race, ethnicity: No formal studies on the effect of race were conducted.
 - Hepatic, renal disease: No formal studies have evaluated the effect on patients with renal or hepatic disease; however, hormones may be poorly metabolized in this setting.

Conclusion

LNG 90 mcg/EE 20 mcg (Lybrel) is non-preferred/non-formulary because:

- There is no reliable evidence that LNG 90 mcg/EE 20 mcg (Lybrel) is superior to available preferred/formulary alternatives in prevention of pregnancy.
- There is no reliable evidence that LNG 90 mcg/EE 20 mcg (Lybrel) provides any additional health benefits beyond prevention of pregnancy.
- LNG 90 mcg/EE 20 mcg (Lybrel) does not appear to fulfill its promise to put a woman’s period “on hold” in a large percentage of cases. About 1 in 4 women who begin Lybrel will be “period free” after 1 year of continuous therapy.⁷

Products

TABLE 1- NEWER BRAND PRODUCTS:

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	Usual Dose/Route	Potential Off-label Uses ^c
LNG/EE (Lybrel [®])	5/2007	5/2010	1 tablet orally daily, continuous dosing	COCs have been used off-label in the following conditions or to decrease incidence of: menstrual cycle irregularity iron-deficiency anemia mood disorders acne dysmenorrhea functional ovarian cysts ectopic pregnancies fibroadenomas and fibrocystic disease of the breast acute pelvic inflammatory disease endometrial and ovarian cancer Note: YAZ, Ortho-Tricyclen, and Estrostep are three COCs that have FDA approved indications for acne. Yaz has FDA approval for PMDD.
LNG/EE (Seasonique [®])	5/2006	5/2009	1 active tablet orally daily on days 1-84, followed by 1 tablet containing EE only on days 85-91.	
Drospirenone/EE (Yasmin [®])	5/2001	10/2013	1 active tablet orally daily on days 1-21, followed by 1 inert tablet on days 22-28.	
Drospirenone/EE (YAZ [®])	3/2006	10/2013	1 active tablet orally daily on days 1-24, followed by 1 inert tablet on days 25-28.	
Etonogestrel/EE (NuvaRing [®])	10/2001	4/2018	Insert ring vaginally, remove on day 21.	
Norelgestromin/EE (Ortho-Evra [®])	11/2001	6/2015	Apply patch topically, leave in place for one week. Replace with new patch once a week for 2 more weeks. Remove patch on day 22 of cycle.	

^a Date applies to approval date for the original brand name medication where there are now generics available. .

^b Based on patents listed in Orange Book as of August 2007.

^c As listed in © 1974 - 2007 Thomson MICROMEDEX database.

TABLE 2- MONOPHASIC ORAL CONTRACEPTIVES PRODUCTS (GROUPED BY GENERIC EQUIVALENCY)

Formulary	Medication Products (EE = ethinyl estradiol)	Mfg	AWP Cost per cycle*
Yes	ALESSE® = levonorgestrel 0.1mg/ EE 20 mcg	Wyeth	\$40.84
Yes	LEVLITE® = levonorgestrel 0.1mg/EE 20 mcg	Berlex	\$38.85
Yes	Levonorgestrel/EE 20mcg (AVIANE) AB-rated generic Alesse®	Barr	\$35.16
Yes	Levonorgestrel/EE 20 mcg(LUTERA) AB-rated generic Alesse	Watson	\$35.16
Yes	Levonorgestrel/EE 20 mcg (LESSINA) AB-rated generic Levlite	Barr	\$34.96
Yes	Levonorgestrel/EE 20 mcg (SRONYX) AB-rated generic Levlite	Watson	\$35.16
Yes	ORTHO-CEPT® = desogestrel 15mcg / EE 30 mcg	Ortho	\$55.33
Yes	DESOGEN® = desogestrel 15 mcg / EE 30mcg	Organon	\$46.13
Yes	Desogestrel 15 mcg /EE 30 mcg (APRI) AB-rated generic	Barr	\$30.52
Yes	Desogestrel 15 mcg /EE 30 mcg (Reclipsen) AB-rated generic	Watson	\$39.35
Yes	Desogestrel/EE (Solia) AB-rated generic	Prasco Labs	\$30.52
No	YASMIN® = drospirenone 3mg / EE 30mcg	Berlex	\$59.06
No	YAZ® = drospirenone 3mg / EE 20 mcg	Berlex	
Yes	ORTHO-CYCLEN® = norgestimate 0.25mg / EE 35mcg	Ortho	\$54.23
Yes	Norgestimate 0.25mg /EE 35 mcg (MONONESSA) (Note: Watson brand via supply agreement w/Ortho) – same as Ortho-Cyclen	Watson	\$34.10
Yes	Norgestimate 0.25mg / /EE 35 mcg (SPRINTEC) AB-rated generic	Barr	\$32.23
Yes	Norgestimate 0.25mg /EE 35 mcg (PREVIFEM) AB-rated generic	Teva	\$32.23
No	OVCON® = 0.4 norethindrone / 35mcg EE	WC Prof Products	\$49.83
Yes	MODICON® = 0.5 norethindrone /35 mcg EE	Ortho	\$60.35
Yes	ORTHO-NOVUM® = 1mg norethindrone with 35mcg EE or mestranol 50mcg)	Ortho	\$55.33
Yes	NORINYL® 1+35; 1+50 (AB-rated Brand of Ortho-Novum) = 1 mg norethindrone + EE 35mcg = 1 mg norethindrone + mestranol 50 mcg	Watson	\$50.35
Yes	Norethindrone/EE (NECON) AB-rated generic to Modicon® 0.5 mg norethindrone/35mcg EE AB-rated generic Ortho-Novum® 1mg norethindrone/35mcg EE	Watson	\$32.14 \$29.47
Yes	Norethindrone/EE (NORTREL) generic 0.5mg norethindrone/35mcg EE - AB-rated to Modicon® 1mg/35mcg EE - AB-rated to Ortho-Novum® 1/35	Barr	\$32.17 \$29.50
Yes	Norethindrone/EE (BREVICON) generic AB-rated to Modicon® (0.5mg norethindrone/35mcg EE)	Watson	\$52.51
Yes	ORTHO-NOVUM (1+50) = 1mg norethindrone/ 50mcg mestranol)	ORTHO	\$55.33
Yes	NORINYL 1+50; (AB-rated Brand to Ortho-Novum)	Watson	\$50.35
Yes	Norethindrone/Mestranol (NECON) AB-rated generic	Watson	\$29.47

*AWP (average wholesale price) based on First Data Bank as of September 2007 for 1 month of therapy.

TABLE 3- BIPHASIC ORAL CONTRACEPTIVES PRODUCTS (GROUPED BY GENERIC EQUIVALENCY)

Preferred	Drug (EE = ethinyl estradiol)	Mfg	AWP per cycle*
No	MIRCETTE® = desogestrel 0.15mg / 20mcg EE (x 21 days) + 10mcg EE (5 days)	Organon	\$64.09
Yes	Desogestrol/EE (KARIVA) AB-rated generic	Barr	\$57.67
Yes	Norethindrone/EE (NECON) AB-rated generic of Ortho-Novum 10/11	Watson	\$32.14

*AWP (average wholesale price) based on First Data Bank as of September 2007 for 1 month of therapy.

TABLE 4- TRIPHASIC ORAL CONTRACEPTIVES PRODUCTS (GROUPED BY GENERIC EQUIVALENCY)

Preferred	Drug (EE = ethinyl estradiol)	Mfg	AWP per cycle*
Yes	TRI-NORINYL® = norethindrone (0.5mg, 1mg, 0.5mg) + EE 35mcg	Watson	\$50.35
Yes	Norethindrone/EE (Aranelle) generic AB-rated to Tri-Norinyl	Barr	\$39.35
Yes	Norethindrone/EE (Leena) generic AB-rated to Tri-Norinyl	Watson	\$39.35
Yes	ORTHO-NOVUM® 7-7-7 = norethindrone (0.5mg, 0.75mg, 1mg) + EE 35 mcg	Ortho	\$29.85
Yes	Norethindrone/EE (NORTREL) generic AB-rated to Ortho-Novum® 7-7-7	Barr	\$32.23
Yes	Norethindrone/EE (NECON) generic AB-rated to Ortho-Novum® 7-7-7	Watson	\$32.20
Yes	TRI-LEVLEN 28 = Levonorgestrel 0.05mg / 30mcg EE + Levonorgestrel 0.075 mg / 40 mcg EE + Levonorgestrel 0.125mg / 30m cg EE	Berlex	\$36.34
Yes	TRIPHASIL® = Levonorgestrel 0.05mg / 30mcg EE + Levonorgestrel 0.075 mg / 40 mcg EE + Levonorgestrel 0.125mg / 30m cg EE	Wyeth	\$36.88
Yes	Levonorgestrel/EE (TRIVORA) generic AB-rated to Triphasil®, Tri-Levlen®	Watson	\$27.49
Yes	Levonorgestrel/EE (ENPRESSE) generic AB-rated to Triphasil®, Tri-Levlen®	Duramed/Barr	\$27.49
Yes	ORTHO TRI-CYCLLEN® = Norgestimate (0.18mg, 0.215mg, 0.25mg) + EE 35mcg	Ortho	\$48.08
Yes	Norgestimate/EE (TRI-SPRINTEC) AB-rated generic to Ortho Tri-Cyclen®	Barr	\$39.32
Yes	Norgestimate/EE (TRINESSA) AB-rated generic to Ortho Tri-Cyclen®	Watson	\$39.32
Yes	Norgestimate/EE (TRI-PREVIFEM) AB-rated generic to Ortho Tri-Cyclen®	Teva	\$39.32
Yes	ORTHO TRI-CYCLLEN® LO = Norgestimate (0.18mg, 0.215mg, 0.25mg) + EE 25 mcg	Ortho	\$55.51
Yes	ESTROSTEP® FE = norethindrone 1mg + EE 20-30-35 mcg + Fe 75mg	Warner-Chilcott	\$63.51
No	CYCLESSA® = desogestrel 0.10 – 0.125 – 0.150 mg + EE 25 mcg	Organon	\$45.29
Yes	Desogestrel/EE (VELIVET)	Barr	\$33.64

*AWP (average wholesale price) based on First Data Bank as of September 2007 for 1 month of therapy.

TABLE 5- OTHER CONTRACEPTIVE PRODUCTS: RINGS/PATCHES

Preferred	Drug	Mfg	AWP per cycle*
Yes	NuvaRing® = three month ring provides etonogestrel 1.2mg + 15mcg EE per day	Ortho	\$49.81
Yes	OrthoEvra® = weekly patch provides norelgestromin 0.15 mg and EE 20 mcg per day	Watson	\$56.53

*AWP (average wholesale price) based on First Data Bank as of September 2007 for 1 month of therapy.

TABLE 6- PROGESTIN ONLY ORAL CONTRACEPTIVE PRODUCTS (GROUPED BY GENERIC EQUIVALENCY)

Preferred	Drug	Mfg	AWP per cycle*
Yes	ORTHO MICRONOR® = norethindrone 0.35mg	Ortho	\$64.25
Yes	Norethindrone 0.35mg (ERRIN) generic AB-rated to Ortho-Micronor®	Barr	\$36.92
Yes	Norethindrone 0.35mg (JOLIVETTE) generic AB-rated to Ortho-Micronor®	Watson	\$36.92
Yes	NOR-Q-D® = norethindrone 0.35mg	Watson	\$55.91
Yes	Norethindrone 0.35mg (NORA-BE®) (Holds same NDA as NOR-QD) - recognized as generic	Watson	\$36.92
Yes	Norethindrone 0.35mg (CAMILA) generic AB-rated to Nor-QD®	Barr	\$36.92

*AWP (average wholesale price) based on First Data Bank as of September 2007 for 1 month of therapy.

TABLE 7- EMERGENCY CONTRACEPTIVE PRODUCTS

Preferred	Drug	Mfg	AWP per cycle*
Yes	PLAN B = levonorgestrel 0.75mg	Duramed/Barr	\$36.86

*AWP (average wholesale price) based on First Data Bank as of September 2007 for 1 month of therapy.

TABLE 8- EXTENDED-CYCLE OR CONTINUOUS-USE ORAL CONTRACEPTIVE PRODUCTS

Preferred	Drug (EE = ethinyl estradiol)	Mfg	AWP per cycle
No	LYBREL® = levonorgestrel (0.09mg) + EE 20 mcg	Wyeth	\$55.00*
Yes	levonorgestrel (0.15mg) + EE 30mcg (Jolesa) generic AB-rated to SEASONALE®	Barr	\$160.67 ^a
No	SEASONIQUE® = levonorgestrel (0.15mg) + EE 30mcg + EE 10mcg	Duramed	\$178.78 ^a

* Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of September 2007 for 1 month therapy.

^a Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of September 2007 for 91 days of therapy.

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