

Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

Oral Contraceptives

Overview:

Oral contraceptives prevent conception by suppressing ovulation. Combination oral contraceptives suppress the hypothalamic-pituitary system, decreasing the secretion of gonadotropin-releasing hormone (GnRH). Progestins blunt luteinizing hormone (LH) release, and estrogens suppress follicle-stimulating hormone (FSH). Additionally, oral contraceptives induce changes in the cervical mucus increasing the difficulty of sperm entry into the uterus, and alter endometrial tissue reducing the likelihood of implantation. Oral contraceptives first received U.S. Food and Drug Administration (FDA) approval in the 1960's. There are many combined oral contraceptive formulations and progestin only formulations available in the U.S; the majority of which are available generically.

Combination oral contraceptives are classified as either low dose monophasic (<50mcg estrogen), high dose monophasic (≥50mcg estrogen), biphasic (<50mcg estrogen; two sequences of progestin or estrogen doses), triphasic (<50mcg estrogen; three sequences of progestin and/or estrogen doses), extended cycle (active drug for >21 days followed by pill-free interval), or continuous cycle (no pill-free interval). Ethinyl estradiol is the estrogen present in most combined oral contraceptives. Mestranol, which is metabolized to ethinyl estradiol (50mcg mestranol is equivalent to 35mcg ethinyl estradiol), is present in Ortho-Novum[®] 1/50 and Norinyl 1+50, which are older products. The progestin component of combination oral contraceptives varies according to potency; with desogestrel, levonorgestrel, and norgestrel being the most potent, and norethindrone being the least potent. Norgestrel is the most androgenic progestin followed by norethindrone and ethynodiol. Desogestrel and norgestimate have the least androgenic activity, and drospirenone, present in Yasmin[®] and Yaz[®], has progestogenic, anti-androgenic, and anti-mineralocorticoid activity. Estrogenic side effects include breast tenderness, sodium/fluid retention, nausea, vomiting, headache, and heavy menstrual bleeding, while a lack of estrogen can cause early or mid-cycle breakthrough bleeding, increased spotting, and hypomenorrhea. Progestogenic side effects include breast tenderness, increased insulin resistance, altered carbohydrate metabolism, headache, fatigue, and mood changes; too little progestin can cause late breakthrough bleeding. Androgenic side effects include acne, weight gain, increased LDL cholesterol, decreased HDL cholesterol, and hirsutism.

Low dose monophasic oral contraceptives, which are those containing <50mcg estrogen, minimize the risk of estrogenic side effects, but those with <30mcg estrogen are associated with more spotting, and less margin of error for missed pills. Available products include Levlite[®], Loestrin[®] 1/20, Loestrin[®] 1.5/30, Loestrin[®] Fe 1/20, Loestrin[®] Fe 1.5/30, Nordette[®], Lo Ovrall[®], Ortho-Cept[®], Yasmin[®], Demulen[®] 1/35, Ortho Cyclen[®], Ortho-Novum[®] 1/50, Ovcon[®]-35, Modicon[®], and Ortho-Novum[®] 1/35. All are available generically.

High dose monophasic oral contraceptives contain ≥50mcg estrogen, and have a higher incidence of estrogenic side effects and risk of thromboembolism. These products should only be used if medically indicated, such as in patients with potential for drug interactions. Combination oral contraceptives with < 30mcg of estrogen may carry a higher contraceptive failure risk if given concomitantly with medications that decrease ethinyl estradiol absorption (antibiotics) or increase ethinyl estradiol metabolism (phenytoin). Available products include Ovcon[®]-50, Demulen[®] 1/50, and their generic equivalents.

Biphasic and triphasic oral contraceptives were designed to more closely mimic hormone levels during the menstrual cycle. An increased progestin dose at the end of the cycle may help prevent premenstrual breakthrough bleeding; higher estrogen:progestin ratio at the beginning of the cycle can help prevent breakthrough bleeding early in the cycle after onset of menses, and an increase in both estrogen and progesterone mid-cycle may help avoid breakthrough bleeding that occurs mid-cycle. Available biphasic products include Mircette[®], Ortho-Novum[®] 10/11, and their generic equivalents. Available triphasic products include Estrostep[®] Fe, Ortho Tri-Cyclen[®], Ortho Tri-Cyclen[®] Lo, Cyclessa[®], Triphasil[®], Tri-Norinyl[®], and Ortho Novum[®] 7/7/7. All of these agents are available in generic formulations. Estrostep[®] Fe and Ortho Tri-Cyclen[®] have an additional indication for use in the treatment of moderate acne vulgaris in females ≥15 years of age.

The first four-phasic oral contraceptive, Natazia[®], recently received FDA approval. Natazia[®] contains estradiol valerate rather than the synthetic estrogen ethinyl estradiol, as well as the new progestin, dienogest, which has anti-androgenic effects similar to drospirenone. The dosing regimen of Natazia[®] increases the dose of dienogest and decreases the estradiol dose during the cycle to help prevent breakthrough bleeding.

Extended cycle oral contraceptives typically eliminate the pill-free interval for two or three cycles to achieve an extended cycle. Seasonale[®] provides 84 active tablets, followed by a 7-day pill-free interval, and is generically available. Seasonique[®] and LoSeasonique[®] contain 84 active tablets followed by 7 low dose estrogen tablets. Extended cycle oral contraceptives may result in an

increase in unscheduled bleeding, but minimize duration of withdrawal bleeding (shorter menses) and improve menstrual related symptoms such as headache, anemia, menorrhagia, and dysmenorrhea. Loestrin[®]-24 Fe and Yaz[®] contain 24 active tablets and 4 placebo tablets, and are also considered extended cycle oral contraceptives. Yaz[®] has two additional indications: for treatment of moderate acne vulgaris in females ≥ 14 years of age, and treatment of symptoms of premenstrual dysphoric disorder (PMDD). The first continuous cycle oral contraceptive, Lybrel[®], was approved by the FDA in May 2007 and is taken every day without a pill-free interval. Lybrel[®] may reduce menstrual related symptoms, but may increase breakthrough bleeding and spotting, especially during initial use.

Progestin only oral contraceptives contain a lower dose of progestin than combination oral contraceptives (norethindrone 0.35mg), can be started immediately post-partum, and are preferred in women who are breastfeeding, or those with a contraindication to estrogen. Available products include Ortho Micronor[®] and Nor-QD[®]; both of which are available in generic formulations. Another progestin only agent, Plan B[®], which contains levonorgestrel, has been approved for use as an emergency contraceptive agent. Plan B[®] is available both over-the-counter (OTC) and by prescription and requires a prescription for females ≤ 17 years of age. A generic formulation of Plan B[®], known as Next Choice[™], is available by prescription only.

Adverse reactions associated with oral contraceptives include thrombotic events such as deep vein thrombosis, cardiac events/coronary artery disease, hypertension, cancer of the breast/reproductive organs, headache, breast tenderness, changes in bleeding patterns, nausea, and vomiting. Risk of thromboembolism with combination oral contraceptives has been associated with the dosage of estrogen. Earlier formulations contained as much as 100mcg/day of estrogen and some of the major risks associated with combination oral contraceptives were identified in studies evaluating these older products. Newer formulations contain as low as 20mcg/day, potentially alleviating some of these risks, however there are no studies demonstrating that products containing less than 30mcg of estrogen offer a safety advantage in regard to thromboembolic risk. Patients should not receive combination oral contraceptives that contain 50mcg of estrogen unless medically indicated. Controversy exists regarding the risk of deep vein thrombosis and the use of desogestrel, due to multiple case control studies suggesting almost double the risk compared to levonorgestrel, norgestrel, norgestimate, and norethindrone.

Generic Name	Brand Names	Type	Manufacturer	Generic
Desogestrel/ Ethinyl Estradiol	Cyclessa [®]	Triphasic	Organon	Y
	Mircette [®]	Biphasic	Organon	Y
	Ortho-Cept [®]	Low Dose Monophasic	Ortho-McNeil	Y
Dienogest/ Estradiol Valerate	Natazia [®]	Four-phasic	Bayer	N
Drospirenone/ Ethinyl Estradiol	Yasmin [®]	Low Dose Monophasic	Bayer Healthcare	Y
	Yaz [®]	Extended Cycle	Bayer Healthcare	N
Ethinodiol Diacetate/Ethinyl Estradiol	Demulen [®] 1/35*	Low Dose Monophasic	Searle	Y
	Demulen [®] 1/50*	High Dose Monophasic	Searle	Y
Levonorgestrel	Plan B [®]	Emergency Contraceptive	Duramed	Y (Rx Only)
	Plan B [®] One- Step	Emergency Contraceptive	Duramed	N
Levonorgestrel/ Ethinyl Estradiol	Levlite [®]	Low Dose Monophasic	Bayer Healthcare	Y
	LoSeasonique [®]	Extended Cycle	Barr	N
	Lybrel [®]	Continuous Cycle	Wyeth	N
	Nordette [®]	Low Dose Monophasic	Barr	Y
	Seasonale [®]	Extended Cycle	Barr	Y
	Seasonique [®]	Extended Cycle	Barr	N
	Triphasil [®] *	Triphasic	Wyeth	Y
Norethindrone	Nor-QD [®]	Progestin Only	Watson	Y
	Ortho Micronor [®]	Progestin Only	Ortho-McNeil	Y
Norethindrone/ Ethinyl Estradiol	Modicon [®]	Low Dose Monophasic	Ortho-McNeil	Y
	Ortho-Novum [®] 1/35	Low Dose Monophasic	Ortho-McNeil	Y
	Ortho-Novum [®] 7/7/7	Triphasic	Ortho-McNeil	Y

Generic Name	Brand Names	Type	Manufacturer	Generic
	Ortho-Novum [®] 10/11*	Biphasic	Ortho-McNeil	Y
	Ovcon [®] -35*	Low Dose Monophasic	Warner Chilcott	Y
	Ovcon [®] -50	High Dose Monophasic	Warner Chilcott	N
	Tri-Norinyl [®]	Triphasic	Searle	Y
Norethindrone/ Ethinyl Estradiol/ Ferrous Fumarate	Femcon [®] Fe (chewable)	Low Dose Monophasic	Warner Chilcott	N
Norethindrone/ Mestranol	Ortho-Novum [®] 1/50*	Low Dose Monophasic	Ortho-McNeil	Y
Norethindrone Acetate/Ethinyl Estradiol	Loestrin [®] 1/20	Low Dose Monophasic	Barr	Y
	Loestrin [®] 1.5/30	Low Dose Monophasic	Barr	Y
Norethindrone Acetate/Ethinyl Estradiol/ Ferrous Fumarate	Estrostep [®] Fe	Triphasic	Warner Chilcott	Y
	Loestrin [®] Fe 1/20	Low Dose Monophasic	Barr	Y
	Loestrin [®] Fe 1.5/30	Low Dose Monophasic	Barr	Y
	Loestrin [®] 24 Fe	Extended Cycle	Warner Chilcott	N
Norgestrel/ Ethinyl Estradiol	Lo Ovral [®]	Low Dose Monophasic	Wyeth	Y
	Ovral [®] *	High Dose Monophasic	Wyeth	Y
Norgestimate/ Ethinyl Estradiol	Ortho-Cyclen [®]	Low Dose Monophasic	Ortho-McNeil	Y
	Ortho Tri- Cyclen [®] Lo	Triphasic	Ortho-McNeil	Y
	Ortho Tri- Cyclen [®]	Triphasic	Ortho-McNeil	Y

*Brand name product no longer available

Summary:

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use them as a method of contraception. Those agents that contain 50mcg of estrogen should not be used unless medically indicated. Three of the

currently available agents, Estrostep[®] Fe, Ortho Tri-Cyclen[®], and Yaz[®], have an additional indication for use in moderate acne vulgaris . Yaz has a third indication: for use in the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. Oral contraceptives are commercially available containing progestins alone or in combination with an estrogen. Combination products are classified as low dose monophasic, high dose monophasic, biphasic, triphasic, four-phasic, extended cycle, or continuous cycle. Plan B[®], a progestin only agent, is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Combination oral contraceptives are considered equally effective. Progestin-only contraceptives are considered safer for women with specific disease states and conditions. In preventing pregnancy, or in terms of cycle control, no product has definitively demonstrated superiority. However, biphasic, triphasic, and four-phasic products may improve breakthrough bleeding at specific times during the menstrual cycle. Selection of a preferred agent should be based on patient medical history, clinical need for specific phasic formulations, side effect profile, generic availability, and cost effectiveness.