

Emergency Contraceptives

Executive Summary¹⁻³

- The Uniform Formulary offers two forms of emergency contraceptive tablets: levonorgestrel (0.75 mg single dose and a 1.5 mg two-dose regimen) and ulipristal acetate (Ella) for prevention of unintended pregnancies.
- Levonorgestrel is effective when taken within 72 hours of unprotected sexual intercourse, with efficacy declining over time.
- Ulipristal acetate has sustained effectiveness (with no loss over time) for up to 120 hours after unprotected sexual intercourse.
- Levonorgestrel (Plan B, Plan B One Step, and generic equivalents) are all available over-the-counter without point of sale restrictions or a prescription; ulipristal acetate (Ella) is only available via prescription.
- Military Treatment Facility (MTF) pharmacies are required to carry Plan B One Step but may carry Ella.

Background^{1-17,19-20}

Contraceptive agents were previously reviewed for Uniform Formulary (UF) placement in August 2011, with the last emergency contraceptive update in May 2013. For prevention of unintended pregnancies, the three methods of emergency contraception include the use of copper intrauterine device, emergency contraceptive pills (ECPs), and use of combined hormone contraceptive pills. This subclass review focuses on the two oral hormonal ECPs: levonorgestrel and ulipristal acetate, both of which are currently classified as UF.

Levonorgestrel is a progestin-only ECP available in two strengths: 0.75 mg (two tablets, each taken 12 hours apart) and 1.5 mg (one single-dose tablet), which must be taken within 72 hours of unprotected sexual intercourse. Levonorgestrel 0.75 mg is available over-the-counter (OTC) for ages 17 and older and via prescription for all other ages. Levonorgestrel 1.5 mg is available OTC with no point of sale restrictions and, as of 30 April 2016, all levonorgestrel 1.5 mg tablet formulations will be available without age restrictions to all females of reproductive capacity.

Ulipristal acetate is a progesterone agonist/antagonist; it is available as a single 30 mg tablet, which may be taken for up to 120 hours after unprotected sexual intercourse. Currently, there are no ulipristal generic products available to the branded product (Ella).

Table 1. Drugs in Emergency Contraceptives Subclass

Generic Name						
levonorgestrel 0.75 mg	Plan B	Duramed/ Barr	July 1999	2 doses; each taken 12 hours apart (within 72 hours of UPSI)	OTC: ages \geq 17 RX: other ages	Yes
levonorgestrel 1.5 mg	Plan B One Step	Duramed/ Barr	July 2009	1 dose (taken within 72 hours of UPSI)	OTC: all ages (as of 4/30/2016)	Yes
ulipristal acetate 30 mg	Ella	Afaxys	Aug 2010	1 tablet (within 120 hours of UPSI)	Prescription Only	None

UPSI: unprotected sexual intercourse

Summary of the Evidence¹⁻²⁰

Efficacy

- Both levonorgestrel and ulipristal emergency contraceptive methods prevent unintended pregnancy by delaying or inhibiting ovulation before the luteinizing hormone (LH) surge reaches peak. Neither formulation is effective in inhibiting ovulation at or after LH peak.
 - Levonorgestrel is effective at preventing pregnancy for up to 72 hours after unprotected sexual intercourse; however, its efficacy declines over time.
 - Ulipristal acetate is as effective as levonorgestrel at preventing pregnancy within 0-72 hours of unprotected sexual intercourse, but is more effective than levonorgestrel at 72-120 hours after unprotected sexual intercourse; its efficacy is sustained from 0-120 hours after intake.
- In terms of relative effectiveness, ulipristal acetate appears to have a more favorable efficacy over levonorgestrel for emergency contraception. A meta-analysis and pooled data from two randomized, multicenter trials found that women who

used ulipristal acetate had a lower risk of becoming pregnant compared to those who used levonorgestrel for emergency contraception.

- From 0-24 hours of UPSI: odds of pregnancy are 65% lower in women using ulipristal acetate versus levonorgestrel
- From 0-72 hours of UPSI: odds of pregnancy are 42% lower in women using ulipristal acetate versus levonorgestrel
- From 72-120 hours of UPSI: ulipristal acetate is more effective than levonorgestrel at preventing unintended pregnancies
- Pooled data show ulipristal acetate prevented 67% of expected pregnancies versus 52% with levonorgestrel.
- There are no trials (to date) specifically designed to study the relationship between efficacy of emergency contraception and body weight.
 - The above meta-analysis favored the use of ulipristal acetate over levonorgestrel in patients with body mass index (BMI) up to 35 kg/m², while concluding that levonorgestrel is considered to be less effective in women with a BMI > 25 kg/m².
 - World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use, 2015 recommends that any emergency contraceptive can be used in obese women without restrictions and with no safety concerns. The guideline does note that emergency contraceptives may be less effective among women with BMI ≥ 30 kg/m² than in women with BMI < 25 kg/m².
- Emergency contraceptive failure rates are 0.6% to 3.1% for levonorgestrel and 0.9% to 2.1% for ulipristal acetate.

Safety

- Although levonorgestrel and ulipristal acetate use is contraindicated during an existing or suspected pregnancy, these drugs are not teratogenic or abortifacient. Use of these two emergency contraceptives does not interrupt existing pregnancy, affect the course of pregnancy, or increase the risk of ectopic pregnancy.
- Safety profiles are similar for both levonorgestrel and ulipristal acetate. The most commonly reported adverse reactions are headache, nausea, and abdominal pain, followed by dysmenorrhea, menses delay, fatigue, dizziness, and breast tenderness.
- Co-administration of drugs affecting the hepatic cytochrome P450 enzyme system (CYP3A4 inducers) and antiretroviral drugs may reduce efficacy of levonorgestrel and ulipristal acetate. Co-administration of progestin-containing hormonal contraceptives should be avoided for up to five days after intake of ulipristal acetate as they may impair the ability of ulipristal acetate to delay ovulation.

Other Factors: Affordable Care Act (ACA) Implementation¹⁸

- Under the “ACA, FAQs Implementation Part XXVI,” health plans are required to cover both levonorgestrel and ulipristal acetate methods of emergency contraception as a component of preventive health care services for women. Specifically, health plans must cover, without cost sharing, at least one form of birth control under each contraceptive method and may utilize reasonable medical management techniques to encourage a specific item within the chosen contraception method.
- At this time, TRICARE is **not required** to be in parity with the ACA regarding availability of the emergency contraceptives at zero cost share.
 - Neither levonorgestrel nor ulipristal acetate is available at the TRICARE Mail Order Pharmacy due to narrow timing index of the dose.
 - Levonorgestrel falls under the TRICARE OTC Program with waiver of prescription and copayment requirement at the Retail Network point of service; cost-effective products are available at the MTF at zero cost share and without prescription requirement.
 - Ulipristal acetate is a prescription-only, branded product with no generics on the market. It is available at zero cost share at the MTF and may be adjudicated as a Tier 1 drug for low co-pay at the retail point of service.
 - Statute changes will be required to make contraceptives available at zero cost share in the Retail Network.
- Congress is in the process of drafting regulatory authority for “Expansion of TRICARE-covered Preventive Health Care Services” with provision to waive copayments for preventive services (NDAA 17).

References

1. Ella [package insert]. HRA Pharma. Revised March 2015.
2. Plan B One Step & Plan B [package insert]. Barr Pharmaceuticals. Revised July 2009.
3. Bullock H and Salcedo J. Emergency Contraception. *Obstetrics and Gynecology Clinics*. 2015; 42(4):699-712.
4. CDC MMWR. U.S. Medical Eligibility Criteria for Contraceptive Use, 2015. WHO Medical Eligibility Criteria for Contraceptive Use, 5th edition. <http://www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm>. Accessed Apr 7, 2016.
5. CDC MMWR. U.S. Selected Practice Recommendations for Contraceptive Use, 2013. MMWR. 2013;62(No. RR-5):1-60.
6. Cleland K, Raymond EG, Westley E, et al. Emergency contraception review: evidence-based recommendations for clinicians. *Clin Obstet Gynecol*. 2014; 57(4):741–50.
7. Contraceptive method failure rate table. <http://www.arhp.org/Publications-and-Resources/Quick-Reference-Guide-for-Clinicians/choosing/failure-rates-table>. Accessed Feb 25, 2016.
8. Emergency Contraception. Practice Bulletin No. 152. *Obstet Gynecol*. 2015;126(3):e1. Accessed Feb 25, 2016.
9. Glasier A, Cameron ST, Blithe D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception*. 2011;84(4):363-7.
10. Glasier A. Emergency contraception: clinical outcomes. *Contraception*. 2013;87(3):309.
11. Glasier A, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. *Lancet* 2010;375:555-62.
12. Glasier A, et al. The rationale and use of ulipristal acetate as first line emergency contraception: biological and clinical evidence. *Gynecol Endocrinol* 2014;30(10):688-90.
13. Halpern V, Raymond EG, Lopez LM. Repeated use of pre- and postcoital hormonal contraception for prevention of pregnancy. (Cochrane Database Syst Rev. 2014;9:CD007595). Accessed Apr 1, 2016.
14. Kahlenborn C, Peck R, Severs WB. Mechanism of action of levonorgestrel emergency contraception. *Linacre Q*. February, 2015;82(1):18–33.
15. McNicholas C, Zhao Q, Secura G, Allsworth JE, et al. Contraceptive failures in overweight and obese combined hormonal contraceptive users. *Obstet Gynecol*. 2013 Mar;121(3):585-92.
16. Mody SK, Han M. Obesity and contraception. *Clin Obstet Gynecol*. 2014;57(3):501–07.
17. Robinson JA and Burke AE. Obesity and hormonal contraceptive efficacy. *Womens Health (Lond)*. 2013;9(5):453-66.
18. Rosato E, Farris M, Bastianelli C. Mechanism of action of ulipristal acetate for emergency contraception: a systematic review. *Front Pharmacol*. 2015;6:315.
19. Shohel M, Rahman MM, et al. A systematic review of effectiveness and safety of different regimens of levonorgestrel oral tablets for emergency contraception. *BMC Womens Health*. 2014;14:54.
20. U.S. Department of Labor. FAQs about Affordable Care Act Implementation (Part XXVI). Feb 11, 2015. <http://www.dol.gov/ebsa/faqs/faq-aca26.html>. Accessed Mar 11, 2015.
21. Yuzpe Regimen/oral contraceptives that may be used for emergency contraception in the US. <http://ec.princeton.edu/questions/dose.html>. Accessed Mar 12, 2016.
22. Ziemann M, Barbieri RL, Eckler K. Emergency contraception. Up to Date. Jan 2016. Accessed Feb 25, 2016. http://www.uptodate.com.stimson.idm.oclc.org/contents/emergency-contraception?source=search_result&search=emergency+contraception&selectedTitle=1%7E140. Accessed Feb 25, 2016.

Abbreviations and Acronyms

ACA	– Affordable Care Act
BMI	– body mass index
ECP	– emergency contraceptive pill
FDA	– U.S. Food and Drug Administration
LH	– luteinizing hormone
MTF	– military treatment facility
OTC	– over-the-counter
UF	– Uniform Formulary
UPSI	– unprotected sexual intercourse
WHO	– World Health Organization