

Therapeutics Initiative

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Emergency contraceptive pills in Canada

Plain Language Summary

What are emergency contraceptive pills (ECPs)?

ECPs are drugs used to prevent pregnancy after unprotected sex or a suspected failure of regular birth control (condom or barrier failure or forgetting to take regularly an oral contraceptive). In Canada, two types are available: levonorgestrel (sold under various brands) and ulipristal acetate (ella®). Both work by delaying the release of eggs (ova) from the ovaries.

Is one choice more effective?

ECPs should be taken as soon as possible after unprotected sex. Within 72 hours (3 days), research studies show that levonorgestrel and ulipristal work equally well.

What about effectiveness after 3 days?

From 72 to 120 hours (3 to 5 days) after unprotected sex, we're not sure which pill works better. Research in small groups of people suggests that ulipristal might stay effective for up to 5 days, while levonorgestrel might stay effective for up to 4 days. Research studies may never be done to learn for sure which pill is more effective during this extended interval.

What about for people with higher body weight?

There have been concerns that these pills may be less effective in people who weigh more than 80 kg or have a body mass index over 30. Some studies suggested a possible reduction in effectiveness, but recent reviews and results of a randomized controlled trial did not confirm that. We don't know yet whether higher body weight or body mass index reduces their effects at the standard doses.

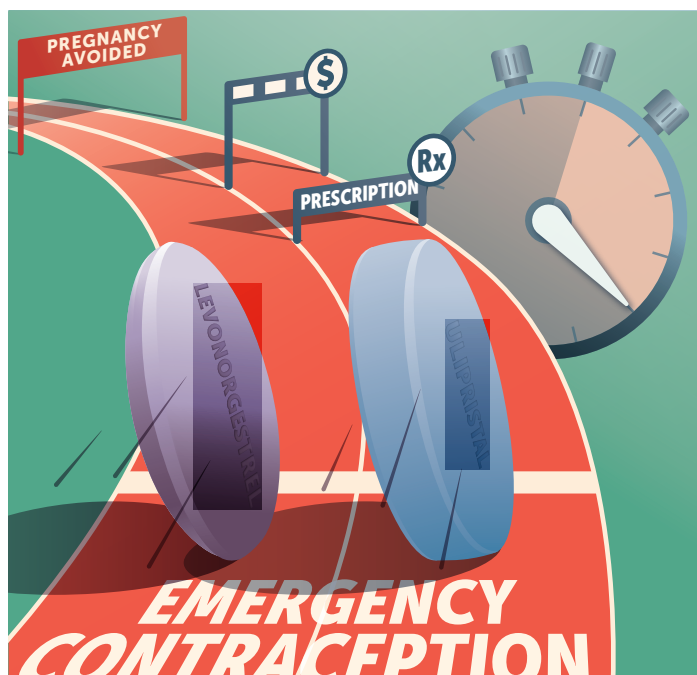
Is it easy to get these pills in British Columbia?

In British Columbia, generic levonorgestrel is easily available and free of charge, while ulipristal needs a prescription and costs about \$40.

Conclusion

Both pills prevent pregnancy within 72 hours of unprotected sex. Beyond 72 hours and up to 120 hours, it is still uncertain whether ulipristal is more effective. We also don't know if higher body weight or higher body mass index reduces the effectiveness of these drugs. This information can help people to make informed decisions about using emergency contraception, based on their individual circumstances.

Keywords: Body Mass Index, Emergency Contraception, Levonorgestrel, Ovulation Inhibition, Postcoital Contraceptives, Systematic Review, Ulipristal.



Abstract

Background: Two emergency contraceptive pills (ECPs) are licensed in Canada to prevent pregnancy after unprotected intercourse or suspected contraceptive failure. Both inhibit or delay ovulation. Levonorgestrel (PLAN B® and generics) has been used since the early 1970's for "morning after" contraception, and was approved in Canada in 1999 for use within 72 hours (3 days) of sexual intercourse. Ulipristal acetate (ella®) was approved in Canada in 2015 for use within 120 hours (5 days). It is uncertain whether one drug is more efficacious beyond 72 hours after sexual intercourse, or for people whose body weight exceeds 80 kg or BMI (body mass index) exceeds 30 kg/m². In British Columbia, generic levonorgestrel is easy to obtain and free of charge. Ulipristal requires a prescription and costs about \$40.

Methods: We conducted a systematic review to compare the efficacy and safety of levonorgestrel with ulipristal.

Results: Two randomized controlled trials (RCTs) compared levonorgestrel with ulipristal for emergency contraception. For use within 72 hours (3 days) of unprotected intercourse, we found no significant difference in pregnancy rates and short-term safety between levonorgestrel and ulipristal. From 72 to 120 hours (3 to 5 days) of unprotected intercourse, comparative efficacy is not well established - primarily related to small sample sizes. Limited and inconclusive data from one non-randomized study suggest consistent efficacy of ulipristal up to 120 hours, whereas an analysis of 4 RCTs of levonorgestrel suggested that its efficacy decreased only beyond 96 hours after intercourse. Based on similarly low quality data, there has been concern that efficacy of both levonorgestrel and ulipristal may decrease at body weights >80 kg or BMI >30 kg/m². This is challenged by the findings of 2 reviews, and by a recent RCT.

Conclusions: Within 72 hours (3 days) of unprotected intercourse, the relative efficacy of levonorgestrel and ulipristal to prevent unwanted pregnancy is not established conclusively. From 72 to 120 hours (3 to 5 days), relative efficacy is also not well established. It remains uncertain whether body weight >80 kg or BMI >30 kg/m² reduce efficacy of ECPs at standard doses, at any time point.



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Emergency contraceptives: Which pill will you recommend?

Vignette: A 30-year-old woman had unprotected intercourse on Thursday evening. She wants to avoid an unintended pregnancy, but her busy schedule distracted her from seeking emergency contraception. She prefers not to pursue the option of a copper IUD. It is now Monday (post-coitus Day 4), and she hurries to a pharmacy for advice. She weighs 90 kg, and has read online that levonorgestrel may be less effective than ulipristal after Day 3, or in women whose weight exceeds 80 kg. **What will you recommend to prevent pregnancy?**

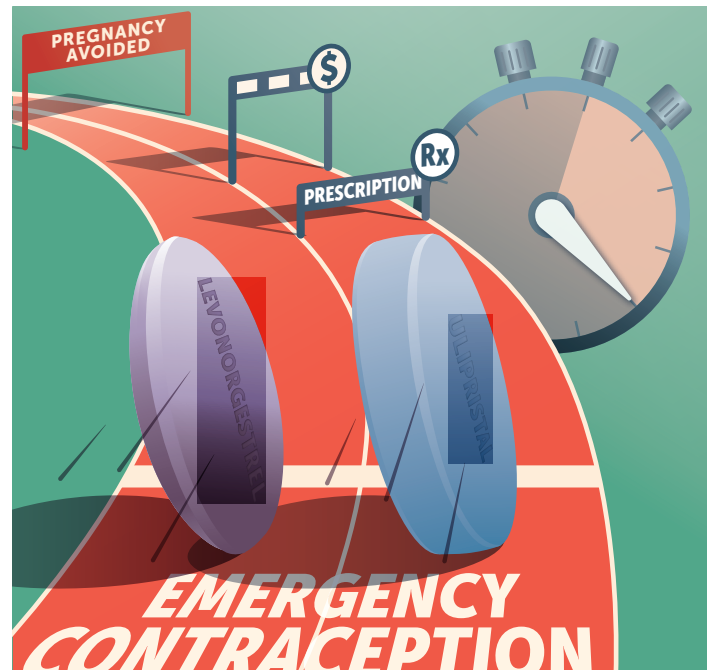
Summary and Conclusions

- Emergency contraceptive pills (ECPs) should be taken as soon as possible after unprotected sexual intercourse. Obtaining an ECP in advance for emergency use can facilitate this.
- Within 72 hours, comparative efficacy of levonorgestrel and ulipristal is not established conclusively. There is no difference in short-term safety and tolerability.
- Between 72 and 120 hours after sex, comparative efficacy is also not well established.
- Offer an ECP, regardless of a woman's weight or body mass index (BMI).
- Levonorgestrel ECP is available without prescription and free to BC residents. Ulipristal costs about \$40 and requires a prescription from a licensed clinician.

What are emergency contraceptive pills?

Emergency contraception (EC) can prevent pregnancy after unprotected sexual intercourse or a recognized failure of contraception. It is readily available in British Columbia.¹ A copper intrauterine device (IUD) is approved for this purpose in Canada, and effective for up to 7 days post-coitus, if not longer.² It also provides long-term contraception. A levonorgestrel IUD is not approved for EC in Canada and not proven effective for EC.³

Emergency contraceptive pills (ECPs), taken within 5 days after sexual intercourse, are recommended for women to avoid an unwanted pregnancy. However, their efficacy decreases over time, and ECPs are ineffective when taken after the luteinizing hormone (LH) surge that triggers ovulation. It is uncertain whether one drug is more efficacious beyond 72 hours after sexual intercourse, or for body weight >80 kg or BMI (body mass index) >30 kg/m². In Canada, two products are approved.



An influential Canadian 2015 guideline (updated in 2021) concluded that evidence from randomized clinical trials (RCTs) favoured ulipristal.⁴ Because of uncertainty whether this conclusion is justified by evidence, we conducted a systematic review and critical appraisal of available RCTs.

Levonorgestrel 1.5 mg

Levonorgestrel is the l-enantiomer of norgestrel (a racemic progestogen).⁵ It has been used worldwide for over 50 years for continuous and emergency ("morning after") contraception. Health Canada approved it in 1999 for emergency contraception within 72 hours (3 days) of sexual intercourse. Since 2005 it has not required a prescription. Levonorgestrel inhibits or delays ovulation when taken prior to the beginning of the LH surge.

While levonorgestrel is approved for use within 72 hours after sex, it may work for up to 120 hours (5 days). But since efficacy declines with time after intercourse, the 1.5 mg tablet should be ingested as soon as possible – preferably within 24 hours.⁵ It is available behind the counter in pharmacies and in some community health clinics. In BC, generics (BACKUP PLAN ONESTEP[®], CONTINGENCY ONE[™]) are fully covered. PLAN B[®], the more expensive brand name product, is a "partial benefit".⁶

Ulipristal acetate 30 mg (Pr ella[®])

Health Canada approved ulipristal in 2015 to prevent pregnancy, when taken within 120 hours (5 days) of unprotected intercourse or suspected contraceptive failure.⁷ It is a selective progesterone receptor modulator that inhibits or delays ovulation when taken before the peak of the LH surge. **Unlike levonorgestrel, it requires a prescription from a healthcare provider.** In BC this includes pharmacists, midwives, and some naturopaths, in addition to physicians and nurse practitioners. Ulipristal is taken as a single oral dose of 30mg.¹⁷ With dispensing fee, the current cost in BC is about \$40.



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Adverse effects

Levonorgestrel and ulipristal share a similar safety profile. Adverse effects noted in randomized controlled trials (RCTs) include headache, menstrual cramps, nausea, fatigue, abdominal pain, vomiting, and altered menstrual cycle. Serious adverse effects (SAEs) are rare.^{5,7,8,9}

Comparative efficacy and safety: TI systematic review

Because of uncertainties about the effects of timing and weight or body mass on the relative efficacy of levonorgestrel and ulipristal, we undertook our own systematic review (SR).¹⁰ Like the authors of a prior 2019 Cochrane SR,¹¹ we identified only 2 head-to-head RCTs. Together, they randomized 3,893 participants deemed eligible at enrolment to levonorgestrel 1.5mg or ulipristal 30mg - **regardless of weight or BMI**. Both compared efficacy (total N evaluable for efficacy = 3,448) and safety (total N = 3,770). Both trials used “non-inferiority” experimental designs intended only to demonstrate that ulipristal was not less efficacious than levonorgestrel. To evaluate efficacy, investigators excluded women subsequently determined by hormonal assays to have been pregnant at randomization, or who took additional emergency contraception after enrolment, or whose pregnancy status after treatment was unknown.

The first non-inferiority RCT, published in 2006, was a double-blind study sponsored by the US National Institutes of Health.⁸ From 1999-2001, investigators enrolled 1,672 participants, **within 72 hours after unprotected intercourse**, from family planning clinics and academic research centres in the United States (mean age 24.3 years; weight and BMI not reported). Efficacy was evaluated for 1,549 of the 1,672 women randomized (93%). Pregnancy occurred in 13/774 women who took levonorgestrel (1.7%; 95% CI 0.8-2.6%) vs 7/775 who took ulipristal (0.9%; 95% CI 0.2-1.6%). The relative risk of pregnancy with ulipristal (vs levonorgestrel) was 0.54 (95% CI 0.22-1.34). The authors concluded that ulipristal was non-inferior.

Pregnancy after treatment within 72 hours (efficacy-evaluable population)

Outcome	RCT published 2006 ⁸ Sponsor: US NIH		RCT published 2010 ⁹ Sponsor: HRA Pharma		Meta-analysis ¹⁰ treatment within 72 hours	
	Levonorgestrel 1.5mg* (enrolled N = 840)	Ulipristal 50mg** (enrolled N = 832)	Levonorgestrel 1.5mg (enrolled N = 1,117)	Ulipristal 30mg (enrolled N = 1,104)	Levonorgestrel 1.5mg (enrolled N = 1,891)	Ulipristal 30mg (enrolled N = 1,879)
Pregnancy in women for whom efficacy was evaluable	13 / 774 (1.7%)	7 / 775 (0.9%)	22 / 852 (2.6%)	15 / 844 (1.8%)	35 / 1,626 (2.2%)	22 / 1,619 (1.4%)

* Dosed as 0.75mg and 0.75mg, 12 hours apart

** 50mg non-micronized ulipristal is considered pharmacokinetically equivalent to the 30mg micronized dose approved in Canada

After 72 hours, is one drug better?

Levonorgestrel vs ulipristal: The second non-inferiority RCT described above also assessed pregnancy in women treated between 72 and 120 hours (3 to 5 days) after unprotected intercourse.⁹ Of the 1,899 women randomized for whom efficacy was evaluable, only 203 (<11%) were treated from 72 to 120 hours. A **post-hoc comparison** of pregnancy after treatment during this later interval favoured ulipristal numerically: levonorgestrel 3/106 women vs ulipristal 0/97. The authors claimed a putative statistically

The second non-inferiority RCT was published in 2010.⁹ Designed, funded, managed, and analyzed by HRA Pharma (the French manufacturer of ulipristal), it was single-blinded – with investigators aware of treatments. From 2007 to 2009, women were enrolled **within 120 hours (5 days) of unprotected intercourse** from family planning clinics in the United States, the United Kingdom, and Ireland (mean age 24.7 years, mean BMI 25.2 kg/m²). Amongst the 2,221 women randomized to treatment, efficacy was evaluated in 1,899 (86%) - of whom 1,696 were treated within 72 hours (3 days). **The pre-specified primary outcome - pregnancy in women treated within 72 hours** - occurred in 22/852 women who took levonorgestrel (2.6%; 95% CI 1.7-3.9%) vs 15/844 who took ulipristal (1.8%; 95% CI 1.0-3.0%). The relative risk for ulipristal (vs levonorgestrel) was 0.69 (95% CI 0.36-1.32), and the authors also concluded that ulipristal was non-inferior to levonorgestrel. For a pre-specified **secondary outcome** of pregnancy in women **treated within 120 hours (5 days)** after unprotected intercourse, the corresponding rates were: levonorgestrel 25/958 (2.6%) and ulipristal 15/941 (1.6%). The relative risk with ulipristal (vs levonorgestrel) was 0.57 (95% CI 0.29-1.09).

Is one drug better within 72 hours of intercourse?

Because the pre-specified primary outcome for both head-to-head RCTs was pregnancy after emergency contraception within 72 hours (3 day) of unprotected intercourse, our TI meta-analysis compared that outcome.

For women who took emergency contraception within the 72 hour window, the combined incidence of pregnancy numerically favours ulipristal (1.4%) vs levonorgestrel (2.2%): relative risk 0.63 [95% CI 0.37-1.08]. With a low baseline risk of pregnancy and relatively small sample sizes, the confidence interval of the odds ratio crosses 1.00. We conclude that ulipristal is non-inferior to levonorgestrel.¹⁰ Because of the number of participants in both trials whose pregnancy status was not known from follow-up, we have limited confidence in this estimate. There were no deaths with either treatment, and no difference in total serious adverse events.

significant difference (“p=0.037”) favouring the sponsor’s product. However, pregnancy after treatment between 72 and 120 hours was not a pre-specified outcome. A **post-hoc** subgroup analysis can suggest a hypothesis to be tested appropriately by a subsequent RCT, but is not a scientifically appropriate basis to support ulipristal’s superiority for use after 72 hours.

Levonorgestrel: An analysis of data from 4 United Nations/World Health funded RCTs compared levonorgestrel with alternative treatments not approved in Canada for emergency contraception.¹² Efficacy of levonorgestrel

was evaluable in 6,794 women, including 5,489 in the 2 RCTs that included treatment up to 120 hours after intercourse. Compared with treatment in the first 24 hours, delaying levonorgestrel until Day 5 increased the risk of pregnancy almost 6-fold (OR 5.8; 95% CI 2.87-11.8). However, **this estimate is based on only 230 women who took levonorgestrel during the final interval of 97 to 120 hours.** For treatment on Day 1 vs Days 2-4, the likelihood of pregnancy did not differ.

Ulipristal: A non-randomized, uncontrolled study of ulipristal 30mg, also sponsored by the French manufacturer HRA Pharma, enrolled women seeking emergency contraception between 48 and 120 hours after unprotected intercourse at 45 United States family planning clinics.¹³ The authors reported sustained efficacy of ulipristal for up to 120 hours (5 days), **but this study did not compare ulipristal with levonorgestrel.**

ECPs are effective regardless of body weight

In 2014, the European Medicines Agency (EMA) concluded that data for levonorgestrel were “too limited and not robust enough to conclude with certainty that contraceptive effect is reduced with increased bodyweight.” For ulipristal, the EMA also concluded that despite a “possible trend for a reduced contraceptive effect, the data are too limited and insufficiently precise to draw definite conclusions.”¹⁴ EMA’s Committee for Medicinal Products for Human Use provided the simple advice that **regardless of weight, women seeking to avoid pregnancy should take ECPs as soon as possible after unprotected intercourse.** Subsequent studies and reviews agree with the EMA’s conclusion.^{15,16}

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A newly published RCT (2024) sponsored by the US National Institutes of Health attempted to explore whether, in women weighing ≥ 80 kg with mean BMI of 37 kg/m², a double dose of levonorgestrel (3mg) might be more effective than the standard dose of 1.5mg.¹⁷ Women seeking emergency contraception within 72 hours of intercourse were randomized to levonorgestrel 1.5mg or 3mg, or to ulipristal 30mg. The study was halted early prior to enrolling the planned sample size of 1,200. Amongst 486 efficacy-evaluable women, the overall pregnancy rate was 1% - lower than expected. However, from hormone assays drawn at randomization, the investigators found that 37% of the women seeking emergency contraception were post-ovulatory (when oral EC is no longer effective), and 23% had evidence of recent hormonal contraceptive use.¹⁸

In this study there was **no significant difference between treatments:** 1 pregnancy in 173 women given levonorgestrel 1.5mg, 1 in 158 who took 3mg, versus 3 pregnancies amongst 157 who received ulipristal 30mg. Slow enrolment, the low risk of pregnancy in nearly half of the women enrolled, and early termination of this RCT (for fertility) precluded definitive conclusions. The authors concluded that it remains unknown whether for weight >80 kg there could be a real difference in effectiveness between levonorgestrel at 1.5mg vs 3mg, or vs ulipristal 30mg.

Vignette resolution: *Regardless of her weight or BMI, your patient could choose either levonorgestrel or ulipristal. You advise her to take an ECP today, and to obtain an extra tablet to reserve for immediate use in case of future need. Generic levonorgestrel is free of charge in BC, and does not require a prescription. Ulipristal requires a prescription and an out-of-pocket expense of about \$40.*

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