FSRH The Faculty of Sexual & Reproductive Healthcare

Clinical Guidance: Drug Interactions with Hormonal Contraception

May 2022 | FSRH

Drug Interactions with Hormonal Contraception (May 2022)

1. Purpose and scope

This update of the FSRH CEU Drug Interactions with hormonal contraception guidance gives general information about the types of drug interaction that relate to hormonal contraception. Such interactions could affect (increase or reduce) exposure to contraceptive hormones (and thus contraceptive effectiveness and safety of hormonal contraception). Contraceptive hormones may themselves affect (increase or reduce) exposure to other drugs that an individual is taking (and thus effectiveness and safety of those drugs). It is essential, therefore, that contraceptive providers take a drug history and check for drug interactions prior to provision of hormonal contraception.

The guidance document no longer includes lists of examples of drugs that interact with hormonal contraception: this function is much more effectively and robustly fulfilled by the accessible, comprehensive, and regularly updated drug interactions resources provided by the **British National Formulary** and the **University of Liverpool HIV Drug Interaction Checker**.

At the time of publishing, FSRH CEU is finalising a guidance document on interactions between contraception and HIV drugs.

Suggested good practice points
☑ **Always ask about use of prescription, non-prescription and recreational drug use, and use of herbal preparations and dietary supplements when providing contraception.**
☑ **Check the BNF drug interactions checker or via the BNF app to ensure that you are using up-to-date drug interactions information. (If you have a Medicines Complete login, you can search for interactions between multiple drugs at Stockley's Drug Interactions).**
☑ **For interactions between hormonal contraception and drugs used for management of HIV/viral hepatitis, please see the University of Liverpool HIV Drug Interaction Checker/University of Liverpool HEP Drug Interaction Checker.**

2. What evidence do we have to inform drug interactions with hormonal contraception?

For many drugs, there is not direct study evidence to inform how they affect exposure to contraceptive hormones, effectiveness of contraception, or how contraceptive hormones affect the activity of the drug. Often, we rely on extrapolation from studies of interaction between other drugs to predict expected drug interactions with hormonal contraception. Sometimes the only available evidence is a small number of individual case reports that suggest an interaction.

Even if it is known that a drug reduces exposure to contraceptive hormones, there is rarely study evidence to inform how significantly that reduction affects contraceptive effectiveness. And as serum levels of contraceptive hormones vary widely between individuals using the same contraceptive method, drug interactions could affect contraceptive effectiveness differently for different individuals.

Generally, therefore, FSRH CEU guidance tends to err on the side of caution if there is potential for an interaction that could reduce effectiveness of contraception. This is particularly true during use of teratogenic or potentially teratogenic drugs (some of which are, themselves, enzyme inducers) when effectiveness of contraception is crucial to avoid fetal exposure to the teratogen. **As an example, see FAQ for information relating to topiramate.**

3. Types of drug interactions

3.1 Pharmacokinetic drug interactions

Pharmacokinetic drug interactions occur when one drug alters the absorption, distribution, metabolism, or excretion of another, changing its bioavailability. Key pharmacokinetic interactions that relate to hormonal contraception are described below.

3.1.1 Pharmacokinetic interactions that could reduce contraceptive effectiveness

The most important pharmacokinetic interaction affecting hormonal contraception is with **drugs that *induce* hepatic cytochrome P450 enzymes** and increase clearance of contraceptive hormones. This could result in reduced contraceptive effectiveness of all combined hormonal contraceptive methods, all progestogen-only pills, the etonogestrel implant and oral emergency contraception. Contraceptive effectiveness of the progestogen-only injection (which achieves high serum progestogen levels), locally acting levonorgestrel-releasing intrauterine systems (and the copper IUD) is not apparently affected by enzyme-inducing drugs.

Other important pharmacokinetic drug interactions that could affect exposure to contraceptive hormones result from reduced absorption due to use of drugs that induce vomiting or severe diarrhoea, drugs that alter gut transit, chelating drugs, and drugs that alter gastric pH.

There has previously been concern about the effect of broad-spectrum antibiotics on contraceptive effectiveness of combined hormonal contraception because of **interference with enterohepatic circulation of estrogens**. Ethinylestradiol and progestogens are conjugated in the liver and intestinal mucosa and the conjugates are excreted in faeces. Some of the ethinylestradiol conjugates (but not progestogen conjugates) undergo cleavage by colonic bacteria and the active ethinylestradiol is reabsorbed. This enterohepatic circulation of ethinylestradiol varies between individuals but is not considered to contribute significantly to contraceptive effectiveness of combined hormonal contraception. So, although use of non-enzyme-inducing antibiotics could affect colonic flora and reduce enterohepatic circulation of ethinylestradiol (or estradiol), established guidance (supported by the available evidence) is that contraceptive effectiveness of combined hormonal contraception is not affected. **No additional contraceptive precaution is required during use of an antibiotic unless the antibiotic is an enzyme inducer or the antibiotic (and/or the illness being treated) causes vomiting or diarrhoea. See FSRH CEU statement.**

3.1.2 Pharmacokinetic interactions that could increase exposure to contraceptive hormones

Concomitant use **of drugs that *inhibit* cytochrome P450** with hormonal contraception could result in increased exposure to contraceptive hormones and potentially increased side effects. In the case of ethinylestradiol, elevated serum levels could theoretically result in increased risk of thrombosis.

3.1.3 Pharmacokinetic interactions of contraceptive hormones that could affect exposure to other drugs being taken

Use of contraceptive hormones can affect exposure to other drugs that an individual is taking, with potential loss of effectiveness of those drugs if exposure is reduced, or toxicity if exposure is increased. For example, combined hormonal contraception induces glucuronidation of lamotrigine and reduces lamotrigine exposure. This could reduce seizure control during use of combined hormonal contraception and risk lamotrigine toxicity during any hormone-free interval.

3.2 Pharmacodynamic drug interactions

Pharmacodynamic drug interactions occur between when the pharmacological effect of one drug influences the pharmacological effect of another by synergy or antagonism. For example, progestogen-only contraception could reduce the effectiveness of ulipristal acetate emergency contraception because of opposing action at progesterone receptors.

Drospirenone is an aldosterone antagonist with potassium-sparing properties. Use of the drospirenone progestogen-only pill (DRSP POP) is not recommended during use of potassium-sparing diuretics or potassium supplements that also increase serum potassium. Pharmacodynamic interaction between the DRSP POP and drugs such as ACE inhibitors and angiotensin II receptor antagonists could also potentially increase risk of hyperkalaemia.

4. Contraception during use of enzyme-inducing drugs

Hepatic clearance of contraceptive hormones is increased during use of an enzyme-inducing drug and for some time after stopping the enzyme inducer (see section 3.1.1).

Key information
Enzyme-inducing drugs could reduce contraceptive effectiveness of all combined hormonal contraception, all progestogen-only pills, the etonogestrel implant and oral emergency contraception.
Suggested good practice points
☑ **Individuals using an enzyme-inducing drug should be offered a reliable contraceptive method that is unaffected by the enzyme inducer. Intrauterine contraception and depot medroxyprogesterone acetate (either intramuscular or subcutaneous) are appropriate options - for medically eligible individuals - in this situation.**
☑ **Individuals using an enzyme-inducing drug who require emergency contraception should be advised that effectiveness of oral emergency contraception could be reduced. They should be offered a copper IUD if indicated. If a copper IUD is unacceptable, unsuitable or unavailable, a double dose (3mg) of levonorgestrel oral emergency contraception or a single dose (30mg) of ulipristal acetate oral emergency contraception can be offered if indicated, with advice that effectiveness is unknown.**
☑ **Short-term users (<2 months) of an enzyme inducer may wish to consider continuing their existing method of contraception and using condoms reliably in addition during use of the enzyme inducer and for 28 days after it has been stopped (this is not recommended during use of a teratogen).**

Quick reference guide: enzyme-inducing drugs and contraception			
Method	**Key information and guidance**		**Additional information**

CHC (combined pill, patch or vaginal ring)	✖	**Contraceptive effectiveness could be reduced.**
		
		Use not advised during use of the enzyme inducer and for 28 days after stopping it.
		
		Recommend an alternative effective method.
			• Users of enzyme-inducing drugs should **always** be advised to use an alternative effective contraceptive method that is not affected by enzyme induction.
			• Users of enzyme-inducing drugs **(except the potent enzyme inducers rifampicin/rifabutin)** for whom alternative effective contraception is not acceptable may, in exceptional circumstances, consider use of two ethinylestradiol (EE) monophasic combined oral contraceptive pills together containing a total of 50µg of EE (30µg + 20µg). These should be used in a continuous regimen (or tricycled with a shortened hormone-free interval of 4 days).
			  ○ The user should be aware that contraceptive effectiveness is not guaranteed and that there could be increased risk of thrombosis if exposure to EE is increased.
			  ○ Use of two combined contraceptive patches or two combined contraceptive rings together is not recommended.

✔ No interaction: method suitable ? Potential interaction: caution required ✖ Known interaction: avoid and advise alternative method			

Continued on next page

Quick reference guide: enzyme-inducing drugs and contraception (continued)			
Method	**Key information and guidance**		**Additional information**
POP (traditional POP, DSG POP and DRSP POP)		**Contraceptive effectiveness could be reduced.** **Use not advised during use of the enzyme inducer and for 28 days after stopping it.** **Recommend an alternative effective method.**	• Use of two progestogen-only pills together is not recommended in this situation.
ENG-IMP		**Contraceptive effectiveness could be reduced.** **Use not advised during use of the enzyme inducer and for 28 days after stopping it.** **Recommend an alternative effective method.**	• Use of two implants together is not recommended.
DMPA		**No expected effect on contraceptive effectiveness.** **No need for extra precautions.**	• Serum progestogen levels are expected to remain adequate.
LNG-IUS		**No expected effect on contraceptive effectiveness.** **No need for extra precautions.**	• Local progestogen effect on endometrium unaffected by enzyme induction.
Cu-IUD		**No effect on contraceptive effectiveness.** **No need for extra precautions.**	• Unaffected by enzyme induction. • The Cu-IUD is the most effective method of emergency contraception.
LNG-EC		**Effectiveness for emergency contraception *could* be reduced.** **Offer a Cu-IUD if appropriate. If Cu-IUD not appropriate or not acceptable, consider offering double dose LNG-EC.**	• Double dose LNG-EC (2 x 1.5 mg LNG tablets taken together) can be offered within 96 hours of unprotected sexual intercourse if Cu-IUD is declined or unsuitable. • The effectiveness of 3 mg oral LNG for emergency contraception in this situation is unknown.
UPA-EC		**Effectiveness for emergency contraception *could* be reduced.** **Offer a Cu-IUD if appropriate.**	• Use of double dose UPA-EC is not recommended. • The effectiveness of UPA-EC compared to that of double-dose (3mg) LNG in this situation is unknown.
 No interaction: method suitable  Potential interaction: caution required  Known interaction: avoid and advise alternative method			
Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; DRSP POP, drospirenone progestogen-only pill; DSG POP, desogestrel progestogen-only pill; EC, emergency contraception; IMP, progestogen-only implant; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill; LNG, levonorgestrel; UPA, ulipristal acetate.			

5. Contraception during use of drugs that cause vomiting or severe diarrhoea

Severe drug-induced diarrhoea or vomiting is predicted to reduce the bioavailability of oral contraceptive steroids.

Quick reference: Contraception and drugs that cause vomiting or severe diarrhoea		
Method	**Key information and guidance**	
CHC **POP**	?	• Follow missed pill rules if vomiting occurs within a few hours of pill taking (see manufacturer instructions) or if severe diarrhoea persists for >24 hours • If an individual has persistent vomiting or diarrhoea, consider non-oral contraception • Consistent use of condoms is recommended
IMP **DMPA** **LNG-IUS** **Cu-IUD**	✓	• No interaction • No need for additional precautions
LNG-EC **UPA-EC**	?	• Note that the Cu-IUD is the most effective method of EC and is unaffected by vomiting and diarrhoea. • If vomiting occurs within 3 hours of pill taking or severe diarrhoea persists for >24 hours, a repeat dose should be given
✓ No interaction: method suitable ? Potential interaction: caution required ✗ Known interaction: avoid and advise alternative method		
Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; EC, emergency contraception; IMP, progestogen-only implant; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill; LNG, levonorgestrel; UPA, ulipristal acetate.		

6. Interaction between ulipristal acetate and other hormonal contraception

Ulipristal acetate is a progesterone receptor modulator that could compete with contraceptive progestogens at the progestogen receptor (see Section 3.2). Quick starting hormonal contraception after ulipristal acetate 30mg taken for emergency contraception (UPA-EC) can reduce the ability of the UPA-EC to delay ovulation. Theoretically, UPA could reduce effectiveness of hormonal contraception, but this has not been demonstrated to date in clinical studies.

Quick reference: Use of ulipristal acetate with (or around the time of use of) other hormonal contraception		
Method	**Key information and guidance**	
CHC **POP** **IMP** **DMPA**	?	• Hormonal contraception should not be quick started until 5 days after UPA-EC administration • Consistent use of condoms is recommended during the 5 days waiting and until the method started becomes effective • UPA-EC could be less effective if a progestogen has been used in the previous 7 days
LNG-IUS	?	• LNG-IUS should not be inserted until pregnancy can be excluded • UPA-EC could be less effective if a progestogen has been used in the previous 7 days
Cu-IUD	✓	• No interaction • No need for additional precautions
LNG-EC	?	• LNG-EC should not be used until 5 days after UPA-EC administration • LNG-EC can be used more than once in the same cycle if there is further unprotected intercourse
UPA-EC	✓	• UPA-EC can be used more than once in the same cycle if there is further unprotected intercourse
✓ No interaction: method suitable ? Potential interaction: caution required ✗ Known interaction: avoid and advise alternative method		
Contraceptive methods: CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, progestogen-only injectable: depot medroxyprogesterone acetate; EC, emergency contraception; IMP, progestogen-only implant; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill; LNG, levonorgestrel; UPA, ulipristal acetate.		

7. What information about drug interactions should be provided to the user?

Having checked that there are no relevant drug interactions, the contraceptive provider should:

- Inform individuals using (or considering use of) combined hormonal contraception, progestogen-only pills and the etonogestrel implant about the potential for interactions with prescription, non-prescription and recreational drugs, and herbal preparations/dietary supplements. They should be advised to seek the advice of a healthcare professional before starting any new drugs, herbal preparations, or supplements.

- Advise users of intrauterine contraception (both the copper IUD and levonorgestrel-releasing intrauterine systems) and injectable contraception that the contraceptive effectiveness of these methods is not known to be affected by any drug interactions.

8. An important reminder about contraception during use of teratogenic (or potentially teratogenic) drugs

It is essential that individuals using known teratogenic drugs or drugs with potential teratogenic effects use highly effective contraception both during use of the teratogen and for the recommended timeframe after discontinuation. **A pregnancy prevention plan should be in place to ensure there is no risk of conception.**

Note that some teratogenic drugs are also enzyme-inducers.

During use of a teratogen that is NOT an enzyme inducer (and no other enzyme-inducing drug being taken) use of the etonogestrel implant, the copper IUD or a levonorgestrel-releasing IUS is recommended. If combined hormonal contraception, a progestogen-only pill or depot medroxyprogesterone acetate is used, condoms should be used reliably in addition.

During use of a teratogen that is an enzyme inducer or a potential enzyme inducer (or if an enzyme-inducing drug is also being taken) use of the copper IUD, a levonorgestrel-releasing IUS, or depot medroxyprogesterone acetate PLUS condoms is recommended. Use of combined hormonal contraception, progestogen-only pills and the etonogestrel implant is not recommended.
See **FSRH CEU guidance** and **MHRA guidance**.

Detailed information regarding teratogenic drugs is available from the **UK Teratology Information Service (UKTIS) website**.

9. Frequently asked questions

Q: Does topiramate affect contraceptive effectiveness of oral contraception and the etonogestrel implant?

A: The evidence suggests that topiramate has enzyme-inducing activity at higher, but not at lower doses.[1,2] **As topiramate is a teratogen**, and because there is wide inter-individual variability in metabolism of contraceptive hormones, FSRH CEU suggests that it is preferable to err on the side of caution and consider topiramate a potential enzyme inducer, regardless of dose.

<u>Recommended contraceptive options with topiramate (see Section 8 above for clarification)</u>: Cu-IUD, LNG-IUS, DMPA plus condoms.

References

1. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* (1997) 38, 317–23.
2. Doose DR, Wang S-S, Padmanabhan M, Schwabe S, Jacobs D, Bialer M. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. *Epilepsia* (2003) 44, 540–9

Q: What advice should be given to users of hormonal contraception who are having surgery about the effect of sugammadex on contraceptive effectiveness?

A: Sugammadex (used to reverse neuromuscular blockade induced during surgery) is likely to bind some serum contraceptive progestogen (and, with less affinity, estrogen). The effect is short-lived: sugammadex has a half-life of <2 hours and most is excreted well within 24 hours after administration. The Summary of Product Characteristics for sugammadex[1] suggests that exposure to progestogen might be reduced by about one third and that administration of a bolus dose of sugammadex might be equivalent to one missed dose of oral contraception (combined or progestogen-only pills).

Risk of pregnancy associated with administration of sugammadex to users of hormonal contraception would be expected to be low, particularly with the LNG-IUS (which acts locally on endometrium) or DMPA (which achieves high serum progestogen levels).

<u>Suggested good practice:</u> Erring on the side of caution, and aligning with the SPC recommendation, FSRH CEU suggests that following a bolus of sugammadex users of oral contraception should follow missed pill rules for one missed pill (assuming otherwise correct pill use) and users of non-oral hormonal contraception should use condoms for 7 days after sugammadex.

Reference

1. emc. Merck Sharp & Dohme (UK) Limited. Bridion 100mg/ml solution for injection. Last updated on emc 11 March 2022. Available online here (accessed 01/04/2022)

Q: Does hormonal contraception affect dose requirement of thyroxine?

A: Oral HRT can increase requirement for thyroxine in some individuals with hypothyroidism by increasing thyroid binding globulin. A similar effect might be expected with combined oral contraception. There is not study evidence to indicate a clinically important effect of combined contraception on thyroxine exposure, but it is possible that thyroxine dose would require adjustment (increase) when combined oral contraception is started. Transdermal HRT, which avoids first-pass hepatic metabolism appears to have less effect on thyroid binding globulin; it is not known whether this is true also for non-oral combined hormonal contraception.[1]

<u>Suggested good practice:</u> In individuals taking thyroxine, consider checking TFT about 6 weeks after initiation of combined hormonal contraception.

Reference

1. Preston CL (ed), *Stockley's Drug Interactions*. Thyroid hormones + Oestrogens. Last modification:09-Mar-2015. London: Pharmaceutical Press. Available online here (accessed 01/04/2022).

Q: What contraception is suitable for someone using lamotrigine?

A: There are two important considerations relating to interaction between lamotrigine and hormonal contraception:

1. Effect of contraceptive hormones on lamotrigine

Estrogen in combined hormonal contraception appears to induce glucuronidation of lamotrigine, significantly reducing serum lamotrigine levels. This could result in reduced seizure control (or reduced effectiveness of lamotrigine for other indications) when combined hormonal contraception is started and during pill taking. Conversely, there could be a risk of lamotrigine toxicity during any hormone-free interval taken. It is possible that the effect of combined hormonal contraception on glucuronidation of lamotrigine may be reduced if an individual is also taking valproate (which inhibits glucuronidation).

Desogestrel might increase exposure to lamotrigine in some individuals. Evidence relating to effect of other progestogen-only contraceptives on serum lamotrigine levels is extremely limited.

See overall suggested good practice points for lamotrigine/hormonal contraception below.

2. Effect of lamotrigine on contraception

Lamotrigine appears to reduce (modestly) exposure to contraceptive progestogens: a small study of concomitant use of combined hormonal contraception (ethinylestradiol/levonorgestrel) and lamotrigine demonstrated reduced exposure to levonorgestrel and reduced ovarian suppression and breakthrough bleeding (although no ovulation was observed). The resulting effect on contraceptive effectiveness of combined hormonal contraception is not known (and interaction between lamotrigine and progestogen-only contraceptives has not been studied). It is possible that lamotrigine could reduce effectiveness of hormonal contraception.[1]

Suggested good practice points: If use of combined hormonal contraception is unavoidable, lamotrigine dose may need to be increased (potentially as much as two-fold) and serum lamotrigine levels monitored to avoid reduction in effectiveness of lamotrigine. It is suggested that a continuous combined hormonal contraceptive regimen (with no hormone-free interval) is used to avoid cyclical changes in lamotrigine levels.

Individuals using lamotrigine who commence a progestogen-only contraceptive should be vigilant for signs of lamotrigine toxicity (dizziness, ataxia, diplopia). Consider monitoring serum lamotrigine levels when the progestogen is stopped.

It is suggested that when hormonal contraception is started or stopped by an individual using lamotrigine, this should be done in consultation with the individual's GP or neurologist/psychiatrist so that any dose adjustments required can be made.

It is possible that contraceptive effectiveness of combined hormonal contraception, all progestogen-only pills and the etonogestrel implant could be reduced during use of lamotrigine. There are no study data to inform this. It is suggested that, erring on the side of caution, additional reliable use of condoms should be advised with these contraceptive methods. Contraceptive effectiveness of depot medroxyprogesterone acetate and levonorgestrel-releasing intrauterine systems (as well as copper intrauterine devices) is not expected to be affected by lamotrigine.

Reference

1. Preston CL (ed), *Stockley's Drug Interactions*. Combined hormonal contraceptives + Lamotrigine. Last modification: 24-Apr-2017. London: Pharmaceutical Press. Available online here (accessed 01/04/2022).

Q: Is griseofulvin an enzyme inducer?

A: Griseofulvin does not appear to be an enzyme inducer, but there are some individual case reports describing change in bleeding pattern and/or pregnancy in users of oral hormonal contraception during concomitant use of griseofulvin. The mechanism by which griseofulvin might affect contraceptive effectiveness is unknown.[1]

Suggested good practice: Risk of contraceptive failure is uncertain, but because griseofulvin is a potential teratogen, caution is recommended. Users of combined hormonal contraception, progestogen-only pills and the etonogestrel implant should be advised to use condoms reliably in addition. It is considered that contraceptive effectiveness of depot medroxyprogesterone acetate and levonorgestrel-releasing intrauterine systems (as well as copper intrauterine devices) is unlikely to be affected by griseofulvin.

Reference

1. Preston CL (ed), *Stockley's Drug Interactions*. Hormonal contraception + Griseofulvin. Last modification:03-Apr-2018. London: Pharmaceutical Press. Available online here (accessed 01/04/2022).

Q: Is ulipristal acetate affected by drugs that affect gastric pH?

A: In one small study a single very low (10mg) dose of ulipristal acetate was administered either alone or during use of esomeprazole. Exposure to ulipristal acetate was reduced.[1] It is not known how this would affect effectiveness of ulipristal acetate 30mg for emergency contraception, and effectiveness of ulipristal acetate for emergency contraception in individuals using other drugs that increase gastric pH has not been studied.

It is possible that drugs that increase gastric pH could reduce effectiveness of ulipristal acetate 30mg for emergency contraception. Other hormonal contraceptives are not affected.

Suggested good practice: If emergency contraception is required during use of a drug that increases gastric pH, FSRH CEU suggests that a copper IUD should be offered if indicated. If a copper IUD is not appropriate or is not acceptable, levonorgestrel oral emergency contraception can be offered within 96 hours of unprotected intercourse. Ulipristal acetate oral emergency contraception can be offered, but it is possible that effectiveness could be reduced.

Reference

1. Pohl O, Osterloh I, Lecomte V, Gotteland JP. Changes in gastric pH and in pharmacokinetics of ulipristal acetate - a drug-drug interaction study using the proton pump inhibitor esomeprazole. *Int J Clin Pharmacol Ther* (2013) 51, 26–33

Acknowledgements

This guidance was developed by the FSRH CEU with expert support from Claire Preston, Editor of Stockley's Drug Interactions (Pharmaceutical Press)

The Clinical Effectiveness Unit (CEU) was formed to support the Clinical Effectiveness Committee of the Faculty of Sexual & Reproductive Healthcare (FSRH), the largest UK professional membership organisation working at the heart of sexual and reproductive healthcare (SRH). The CEU promotes evidence-based clinical practice, and it is fully funded by the FSRH through membership fees. It is based in Edinburgh, and it provides a member's enquiry service, evidence-based guidance, new SRH product reviews and clinical audit/research. Find out more here.

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Registered Charity No: 1019969 FSRH, 10-18 Union Street, London, SE1 1SZ