Is ▼Drovelis a major breakthrough in contraception?

Listen to Podcast
dtb.bmj.com

What you need to know

- Drovelis is a combined oral contraceptive (COC) that consists of 24 active pink tablets containing estetrol and drospirenone and 4 inactive white lactose tablets.
- Estetrol is a synthetic version of an oestrogen molecule produced by the fetal liver.
- Data on contraceptive efficacy from one study met the European Medicine Agency's regulatory standard for preventing pregnancy.
- Common adverse effects include metrorrhagia, headache, acne, vaginal haemorrhage and dysmenorrhoea.
- There are limited data on long-term efficacy or adverse effects.
- Drovelis is significantly more expensive than many other COCs.

Introduction

More than 3 million prescriptions for combined hormonal contraceptives (CHCs) are dispensed annually in England alone, at a cost of £22 million.[1] The majority of such prescriptions are for combined oral contraceptives (COCs). ▼Drovelis is a newly licensed COC and the first product in the UK to contain the oestrogen estetrol, a synthetic version of an oestrogen molecule produced by the fetal liver, and the progestogen drospirenone.[2] A company press release states that it has 'been working on Estetrol, a native hormone produced by the human body during pregnancy, for more than ten years to develop a new generation contraceptive pill with a clear benefit/risk aiming to improve women's quality of life'.[3] The company also claims that the product 'promises to be a major breakthrough in a space where there hasn't been any innovation in decades'.[3] Here we review the effectiveness and place of this new product.

Contraceptive efficacy

Contraceptive efficacy can be assessed by measuring the number of unplanned pregnancies that occur over a specified time period while contraception is used.[4] One method of determining the efficacy of contraceptives uses the Pearl Index, which is defined as the number of unintended pregnancies per 100 women-years of using a contraceptive and ranges from 0 (no pregnancies) to 1200 (all participants became pregnant in the first month).[4 5] The results can be expressed as the unadjusted Pearl Index ('user and method failure'), which represents the failure rate with 'typical' use and includes all pregnancies and all cycles of contraceptive use, except those in which additional methods have been used.[4 6] Alternatively, the results can be expressed as the adjusted Pearl Index ('true pill failure'), which excludes pregnancies that can be reliably attributed to non-adherence to the contraceptive.

Regulatory approval of contraceptives

The European Medicine Agency's (EMA) regulatory guideline on the requirements for clinical trials that assess efficacy of steroid contraceptives accepts non-comparative studies for new steroids provided that a sufficient number of cycles have been studied 'to obtain the desired precision of the estimate of contraceptive efficacy'.[7] It suggests that the studies should be large enough 'to give the overall Pearl Index (number of pregnancies per 100 woman years) with a two-sided 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1 (pregnancies per 100 woman years).'[7]

Comparative effectiveness

The effectiveness of any contraceptive method depends on using it correctly and consistently. By using efficacy data, it is possible to compare different contraceptive methods (table 1).

About Drovelis

Drovelis is a new COC that contains estetrol (E4) and drospirenone (DRSP).[2] E4 is a synthetic version of the natural molecule produced by the fetal liver.[2 8] It has not previously been used in

Table 1 Contraceptive effectiveness[18 23]

	Percentage of women with an unintended pregnancy in the first year of use	
	Typical use (%)	Perfect use* (%)
No contraception	85	85
Female condom	21	5
Male condom	18	2
Combined oral contraceptives	9	0.3
Combined vaginal ring	9	0.3
Combined transdermal patch	9	0.3
Progestogen-only pills	9	0.3
Progestogen-only injectables	6	0.2
Copper intrauterine device	0.8	0.6
Levonorgestrel intrauterine system	0.2	0.2
Progestogen-only implant	0.05	0.05

*When used consistently and correctly.

Estetrol 14.2 mg and drosperinone 3 mg

- Brand name: ▼Drovelis.
- Formulation: 24 active pink tablets containing estetrol 14.2mg plus drospirenone 3mg and 4 inactive white tablets containing lactose.
- Indication: oral contraception.
- Contraindications: these include presence or risk of venous or arterial thromboembolism, severe hepatic disease (including liver tumours), severe renal disease, sex steroid-influenced malignancies, undiagnosed vaginal bleeding, migraine with aura, and hypersensitivity to the contents of the tablets.
- Adverse effects: most commonly reported adverse reactions are metrorrhagia, headache, acne, vaginal haemorrhage and dysmenorrhoea.
- Administration: 1 tablet/day for 28 consecutive days starting with 24 active pink tablets, followed by 4 inactive white tablets.
- Classification: prescription-only medicine subject to additional monitoring (▼).
- Market authorisation holder: Gedeon Richter Plc.

licensed contraceptives or other products in the UK.[8 9] E4 has antigonadotropic activity and produces a dose-dependent decrease in serum follicle-stimulating hormone and luteinising hormone levels.[9] Overall exposure to E4 is similar irrespective of food intake.[2] DRSP has been used as a component of COCs for many years.[9] It has progestagenic, antigonadotropic, antiandrogenic and mild antimineralocorticoid properties, and overall exposure to DRSP is similar regardless of food intake.[2]

Each 28-day cycle of Drovelis consists of 24 active pink tablets that contain E4 14.2 mg plus DRSP 3mg and 4 inactive white lactose tablets.[2] One tablet is taken every day at about the same time in the order shown on the blister pack. Each pack starts with 24 active pink tablets, followed by 4 inactive white tablets. Each subsequent pack is started the day after the last tablet of the previous pack.[2]

Efficacy data

Marketing authorisation for Drovelis was based on outcomes from two phase III randomised control trials.[9] The studies were open-label, single-arm trials that assessed the safety and efficacy of the product in participants in Europe/Russia and the USA/Canada.[10 11]

Both trials recruited heterosexually active healthy premenopausal women (aged 18–50 years in Europe/Russia and aged 16–50 years in the USA/Canada) with a body mass index (BMI) of ≤35 kg/m^2, a history of regular menstrual cycles when not using hormonal contraception and a negative serum pregnancy test before starting the study.[10 11] Participants agreed to use E4/DRSP as their primary method of contraception for 13 cycles (12 months). The primary outcome was contraceptive efficacy (Pearl Index) in women aged 18–35 years (Europe/Russia) and 16–35 years (USA/Canada) who had at least one cycle with one act of intercourse per cycle with no other contraceptive use. Secondary outcomes were contraceptive efficacy, bleeding pattern and general safety in women aged ≤50 years.[10 11]

Europe/Russia data

The study was conducted in 69 sites across nine countries and screened 1744 women aged 18–50 years (1515 aged 18–35 years) and enrolled 1577 women (1373 aged 18–35 years) with 1553 women (1353 aged 18–35 years) who started using E4/DRSP and 1218 women (1052 aged 18–35 years) who completed 13 cycles.[10] Overall, 99% of participants were 'white', 0.6% were 'Asian' and 0.5% were 'black/African–American'.

There were 13 692 cycles in 1313 participants aged 18–35 years.[10] Five pregnancies occurred of which three were considered method failures. In women aged 18–35 years, the Pearl Index was 0.47 pregnancies/100 woman-years (95% CI 0.15 to 1.11) and the method failure Pearl Index was 0.29 pregnancies/100 woman-years (95% CI 0.06 to 0.83).

Scheduled bleeding was reported by >90% of participants per cycle and generally occurred between day 26 of the cycle and day 3 of the next cycle with a median duration of 4 to 5 days.[10] The percentage of women who had episodes of unscheduled bleeding and/or spotting ranged from 13% to 19%. Among women who experienced bleeding/spotting there was a median of 3 days of unscheduled bleeding and/or spotting.

Reasons for discontinuation after the start of study treatment included adverse events not related to bleeding, withdrawal of consent and adverse events related to bleeding.[10]

The most common treatment-related adverse effects were metrorrhagia (5.0%), vaginal haemorrhage (4.3%), acne (3.8%) and headache (2.8%).[10] The mean change in body weight compared with baseline was 0.68 kg and the mean change in BMI from baseline was 0.3 kg/m^2. One serious adverse effect (lower extremity venous thromboembolism [VTE]) was considered to be treatment related.

USA/Canada data

The study was conducted at 77 centres in the USA and Canada.[11] The investigators screened 2918 women aged 16–50 years (2623 aged 16–35 years) and enrolled 2148 women (1939 aged 16–35 years) with 1864 women (1674 aged 16–35 years) who started using E4/DRSP and 1016 women (899 aged 16–35 years) who completed 13 cycles. Overall, 70% of participants were 'white', 20% were 'black/African–American' and 5% were 'Asian'.

There were 12 763 cycles in 1524 participants aged 16–35 years.[11] Twenty-six pregnancies occurred, all of which were in US women, 11 related to poor pill compliance, 1 followed use of St. John's wort, and 14 were considered to be method failures. In women aged 18–35 years, the Pearl Index was 2.65 pregnancies/100 woman-years (95% CI 1.73 to 3.88), and the method failure Pearl Index was 1.43 pregnancies/100 woman-years (95% CI 0.78 to 2.39).

Days of scheduled bleeding and/or spotting days were stable throughout the study with a median duration of 4–5 days.[11] The percentage of women who had episodes of unscheduled bleeding and/or spotting ranged from 15% to 30%. There was a mean duration of 4 days of unscheduled bleeding and/or spotting among those who reported unscheduled bleeding/spotting.

The most common reason for discontinuation among enrolled participants was loss to follow-up.[11]

Common treatment-related adverse effects included metrorrhagia (4.4%), headache (3.5%), acne (2.8%) and dysmenorrhoea (2.8%).[11] The mean change in BMI from baseline was 0.4 kg/m^2. There were two treatment-related serious adverse effects (hospitalisation for depression and one ectopic pregnancy). Two participants had clinically significant elevated potassium levels.

Trial funding

Both studies were funded by Estetra SRL, a subsidiary of Mithra Pharmaceuticals, and medical writing support was provided by an external agency.[10 11]

Trial registration

Clinical trial registration (https://clinicaltrials.gov/) numbers: NCT02817841 and NCT02817828.[10 11]

Pooled data

Data from the USA/Canada study and the Europe/Russia study were pooled to evaluate the contraceptive efficacy of E4/DRSP for up to 13 cycles.[12] The pooled Pearl Index in the primary efficacy group was 1.52 (95% CI 1.04 to 2.16) pregnancies per 100 women-years based on 31 pregnancies in 2837 women with 26 455 cycles of use. The method failure Pearl Index was 0.84 (95% CI 0.49 to 1.34) pregnancies per 100 women-years.

European Medicines Agency (EMA) assessment

In the USA/Canada study, the Pearl Index for the primary outcome was higher than that in the Europe/Russia study, and the difference between the upper limit of the 95% confidence interval and the point estimate exceeded the value specified in the EMA's regulatory guidance on measuring efficacy of steroid contraceptives.[9] A higher Pearl Index has been reported in other studies of contraceptives conducted in the USA compared with studies conducted in Europe. Although adherence was slightly lower in the USA/Canada study compared with the Europe/Russia study (98.7% vs 99.4%), it was not clear whether this would have caused the difference in Pearl Index between the studies.[9] In its licensing assessment, the EMA focused on the data from the Europe/Russia study rather than data from the USA/Canada study.

US Food and Drug Administration (FDA) assessment

The FDA regulatory guidance on assessment of contraceptive efficacy takes into consideration the point estimate for the Pearl Index and the upper boundary of its 95% confidence interval.[13] For CHCs, the upper boundary of the 95% CI is typically <5. If there are differences in efficacy data between studies conducted in different geographical areas, the FDA uses data from study sites in USA and Canada. As a result, the FDA licensing decision was based on data from the USA/Canada study and the FDA concluded that there was 'substantial evidence of effectiveness primarily by the overall Pearl Indes data from the US/Canada study' which was supported by the data from the Europe/Russia study.[14]

Unwanted effects

The summary of product characteristics (SPC) reports that common adverse reactions (from ≥1/100 to <1/10) include acne; mood disorders and disturbances; libido disorder; abdominal pain, nausea; breast pain; metrorrhagia, vaginal haemorrhage, dysmenorrhoea, menorrhagia; headache; and weight fluctuation.[2] Uncommon adverse reactions (from ≥1/1000 to <1/100) include vaginal and urinary tract infections; depression; migraine; vomiting, diarrhoea; alopecia; breast swelling; vaginal discharge, dyspareunia; and fatigue. Rare adverse reactions (from ≥1/10000 to <1/1000) include mastitis; hyperkalaemia; hypertension, hypotension, venous thrombosis and thrombophlebitis; constipation, dyspepsia; ectopic pregnancy; and dysfunctional uterine bleeding.[2]

In its assessment report, the EMA noted that the treatment-emergent adverse effects profile 'appears similar to what is known for other CHCs and what would be expected from the mode of action an oestrogen and a progestogen'.[9]

VTE risk

In its guideline on combined hormonal contraception, the UK Faculty of Sexual and Reproductive Healthcare (FSRH) highlighted the effect of progestogen type on VTE risk.[15] Although the risk of VTE is very low, the EMA published a comparison of the estimated incidence of VTE risk with CHC according to the progestogen component (see table 2).[16] The EMA's estimate of absolute risk of VTE with CHCs is between 5 and 12 per 10 000 women per year of use compared with 2 per 10 000 non-CHC users per year (table 2).

Table 2 Estimated incidence of risk of VTE with CHC[16]

Progestogen in CHC	Estimated incidence (per 10 000 women per year of use)
Non-pregnant non-user	2
Levonorgestrel, norethisterone, norgestimate	5–7
Etonogestrel, norelgestromin	6–12
Desogestrel, drospirenone, gestodene	9–12

CHC, combined hormonal contraceptive; VTE, venous thromboembolism.

The EMA data indicated that CHCs containing levonorgestrel, norethisterone or norgestimate had the lowest risk of VTE.[16]

In its assessment report for Drovelis, the EMA highlighted two VTE events that were both considered to be related to treatment.[9] The EMA concluded that based on the available data, 'no claims regarding the relative risk for VTE with Drovelis in comparison with other CHCs can be made'. An international surveillance study will assess the risk of VTE and 'characterize and compare the risks of Drovelis with levonorgestrel-containing combined oral contraceptives in a study population that is representative of the actual users of these preparations'.[17]

The US FDA's review of E4/DRSP concluded that 'limited safety data in overweight and obese individuals raise uncertainties regarding whether there is a differential efficacy and safety of DRSP/E4 in these individuals'.[14] In the US, a postmarketing study will assess the risk of VTE with DRSP/E4 and be used to determine if additional studies are necessary in people with higher BMI.

Contraindications

The SPC states that as there are no epidemiological data for E4-containing CHCs, the contraindications for ethinylestradiol-containing CHCs are considered to apply.[2] These include

- Presence or risk of venous or arterial thromboembolism.
- Severe renal insufficiency or acute renal failure.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substances or to any of the excipients.

If any of the conditions appear for the first time during use of E4/DRSP, it should be stopped immediately.[2] Other contraindications to the use of CHCs include[18]

- Smoking ≥15 cigarettes/day.
- Blood pressure consistently ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic).
- Vascular disease.
- Migraine with aura.
- Atrial fibrillation.

Interactions

The SPC states that interactions can occur with medicinal products that induce microsomal enzymes, resulting in increased clearance of sex hormones, which may lead to breakthrough bleeding and/or contraceptive failure.[2]

Interactions have been reported with several groups of medicines.[2] These include medicines that increase the clearance of CHCs (eg, carbamazepine, rifampicin and St John's wort); medicines with variable effects on the clearance of CHCs (eg, combination HIV

Table 3 Summary of advice for a single missed active pink tablet[2 19]

Days	Advice
1–7	Take the forgotten tablet as soon as possible (even if this means taking two tablets at the same time). Continue taking the tablets at the usual time and use extra precautions (eg, a condom) for the next 7 days while taking the tablets correctly. If the woman has had sex in the week before forgetting the tablet, there is a risk of a pregnancy.
8–17	Take the forgotten tablet as soon as possible (even if this means taking two tablets at the same time). Continue taking the tablets at the usual time. Protection against pregnancy is not reduced and extra precautions are not needed.
18–24	Option 1: take the forgotten tablet as soon as possible (even if this means taking two tablets at the same time). Continue taking the tablets at the usual time. Discard the inactive white tablets and start the next strip of tablets. Option 2: stop the active pink tablets and go directly to the four inactive white tablets and then start a new strip.

treatment); and medicinal products that decrease the clearance of CHCs (eg, strong CYP3A4 inhibitors).

Missed pill advice

The SPC and patient information leaflet provide details of what to do if an active pink tablet is missed (table 3).[2 19] The SPC advises that the management of missed tablets is guided by two principles:

- The recommended hormone-free tablet interval is 4 days, and tablet-taking must never be discontinued for longer than 4 days.
- Uninterrupted active pink tablet-taking for 7 days is required to attain adequate suppression of the hypothalamic–pituitary–ovarian axis.[2]

If a woman is less than 24 hours late in taking an active pink tablet, contraceptive protection is not reduced. The tablet should be taken as soon as possible and further tablets taken at the usual time.[2] Contraceptive protection may be reduced if a woman is more than 24 hours late in taking an active tablet.

Advice from a healthcare professional should be sought if more than one active pink tablet is missed in a cycle.

Postponing a withdrawal bleed

To delay a period, the SPC advises omitting the inactive white tablets from the current blister pack and going to a new blister pack and finishing it (including the four inactive white tablets).[2 19]

FSRH review

A summary produced by FSRH concluded that contraceptive effectiveness of E4/DRSP is comparable to that of other COCs.[8] The FSRH noted that limited evidence on E4/DRSP suggests a similar safety and adverse effect profile to existing COCs.

What other bulletins say

Prescrire International does not recommend the combination of E4 and DRSP.[20] It considers that DRSP has an unfavourable harm-benefit balance and that little is known about the harms associated with E4. It concludes that 'there are other contraceptives, with much better-established harms and benefits, to offer women'.

The Medical Letter notes that the combination of E4 and DRSP 'appears to be as effective in preventing pregnancy as other recently approved oral contraceptives, but there is no acceptable evidence that it is safer.[21] Until data from large comparative trials become available, generic combination oral contraceptives available at a fraction of the cost are preferred.'

Cost

A 3-month supply of Drovelis costs £25.80 compared with £2.82 for a 3-month supply of a COC containing ethinylestradiol and levonorgestrel and between £8.30 and £14.70 for a 3-month supply of a COC containing ethinylestradiol and DRSP.[22]

Conclusion

▼Drovelis is a newly licensed combined oral contraceptive (COC) containing the oestrogen estetrol (E4), a synthetic version of a molecule produced by the fetal liver, and the progestogen drosperinone (DRSP). Although DSRP is the component of several COCs, E4 has not been used in any licensed medicine in the UK.

Two open-label non-comparative studies have assessed the safety and efficacy of the combination of E4 and DRSP. The Pearl Index for the primary outcome was in line with the European Medicines Agency's regulatory guideline on measuring efficacy of steroid contraceptives in one of the studies. Common adverse effects include metrorrhagia, headache, acne, vaginal haemorrhage and dysmenorrhoea.

No advantages have been demonstrated for Drovelis over standard COCs in terms of efficacy or adverse effects and no long-term safety data are available for E4. Combined hormonal contraceptives (CHCs) that contain DRSP are associated with a slightly higher risk of venous thromboembolism compared with CHCs containing levonorgestrel, norethisterone or norgestimate. Drovelis is also more expensive than many other COCs. As there is no compelling evidence that it is more effective or safer than other COCs, or that it is a major breakthrough in contraceptive management, we cannot recommend the use of Drovelis over established COCs.

Competing interests None declared. Refer to the online supplementary files to view the ICMJE form(s).

Provenance and peer review Commissioned; externally peer reviewed.

References

1 OpenPrescribing.net, Bennett Institute for Applied Data Science, University of Oxford. Combined hormonal contraceptives and systems [online]. 2022. Available: https://openprescribing.net/analyse/#org=CCG&numIds=7.3.1&denom=nothing&selectedTab=summary [Accessed 24 Jan 2023].
2 Drovelis 3 mg/14.2 mg film-coated tablets. *Summary of product characteristics, GB.* Gedeon Richter Plc, 2022.
3 Gedeon Richter Plc. Positive CHMP opinion for a novel oral contraceptive [online]. 2021. Available: https://www.gedeonrichter.com/en/news/210326 [Accessed 24 Jan 2023].
4 Trussell J, Hatcher RA, Cates W, *et al.* A guide to interpreting contraceptive efficacy studies. *Obstet Gynecol* 1990;76:558–67.
5 Trussell J. Methodological pitfalls in the analysis of contraceptive failure. *Stat Med* 1991;10:201–20.
6 What role for Qlaira in contraception? *Drug Ther Bull* 2010;48:102–5.
7 European Medicines Agency. Clinical investigation of steroid contraceptives in women - scientific guideline [online]. 2006. Available: https://www.ema.europa.eu/en/clinical-investigation-steroid-contraceptives-women-scientific-guideline#current-effective-version-section [Accessed 24 Jan 2023].
8 Faculty of Sexual & Reproductive Healthcare. FSRH CEU new product review: drovelis estetrol/drospirenone combined oral contraceptive [online]. 2019. Available: https://www.fsrh.org/

standards-and-guidance/documents/fsrh-ceu-new-product-review-drovelis-estetroldrospirenone/ [Accessed 24 Jan 2023].
9 European Medicines Agency. Drovelis [online]. 2021. Available: https://www.ema.europa.eu/en/documents/assessment-report/drovelis-epar-public-assessment-report_en.pdf [Accessed 24 Jan 2023].
10 Gemzell-Danielsson K, Apter D, Zatik J, *et al.* Estetrol-drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. *BJOG* 2022;129:63–71.
11 Creinin MD, Westhoff CL, Bouchard C, *et al.* Estetrol-drospirenone combination oral contraceptive: north american phase 3 efficacy and safety results. *Contraception* 2021;104:222–8.
12 Jensen JT, Kaunitz AM, Achilles SL, *et al.* Pooled efficacy results of estetrol/drospirenone combined oral contraception phase 3 trials. *Contraception* 2022;116:37–43.
13 US Food and Drug Administration. Establishing effectiveness and safety for hormonal drug products intended to prevent pregnancy guidance for industry [online]. 2019. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishing-effectiveness-and-safety-hormonal-drug-products-intended-prevent-pregnancy-guidance [Accessed 24 Jan 2023].
14 US Food and Drug Administration. Multi-disciplinary review and evaluation NDA 214154 nextstellis (drospirenone and estetrol tablets) [online]. 2021. Available: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214154Orig1s000MultidisciplineR.pdf [Accessed 24 Jan 2023].
15 Faculty of Sexual & Reproductive Healthcare. FSRH guideline combined oral contraception [online]. 2020. Available: https://www.fsrh.org/standards-and-guidance/documents/combined-hormonal-contraception/ [Accessed 24 Jan 2023].
16 European Medicines Agency. Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks [online]. 2014. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Combined_hormonal_contraceptives/European_Commission_final_decision/WC500160277.pdf [Accessed 24 Jan 2023].
17 European Medicines Agency. Part VI: summary of the risk management plan [online]. 2021. Available: https://www.ema.europa.eu/en/documents/rmp-summary/drovelis-epar-risk-management-plan-summary_en.pdf [Accessed 24 Jan 2023].
18 Faculty of Sexual & Reproductive Healthcare. UK medical eligibility criteria for contraceptive use [online]. 2019. Available: https://www.fsrh.org/documents/ukmec-2016/ [Accessed 24 Jan 2023].
19 Gedeon Richter Plc. Package leaflet: information for the user Drovelis 3 mg/14.2 mg film-coated tablets [online]. 2022. Available: https://www.medicines.org.uk/emc/files/pil.14169.pdf [Accessed 24 Jan 2023].
20 Estetrol + drospirenone (Drovelis) for oral contraception. *Prescrire Int* 2022;241:229–30.
21 Estetrol/drospirenone (Nextstellis) – a new combination oral contraceptive. *The Medical Letter* 2021;63:101–3.
22 NHS Business Services Authority. NHS electronic drug tariff [online]. 2022. Available: https://www.drugtariff.nhsbsa.nhs.uk/ [Accessed 24 Jan 2023].
23 National Institute for Health and Care Excellence. Clinical knowledge summaries - how effective are the available contraceptive methods [online]. 2022. Available: https://cks.nice.org.uk/topics/contraception-assessment/background-information/comparative-effectiveness-of-contraceptive-methods/ [Accessed 24 Jan 2023].

DOI: 10.1136/dtb.2022.000074