

## Does St John's Wort interact with Emergency Hormonal Contraception?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals  
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### Background

St John's Wort (SJW) is the common name for the plant *Hypericum perforatum* and is a popular herbal remedy for the management of mild to moderate depression [1, 2].

Emergency contraception is used to prevent pregnancy after an unprotected or inadequately protected act of sexual intercourse [3, 4].

Oral emergency hormonal contraception (EHC) available in the UK include a progestogen; levonorgestrel (e.g. Levonelle™) and the progesterone receptor modulator, ulipristal acetate (EllaOne™). The usual dose of levonorgestrel as EHC is a single dose of 1.5mg taken within 72 hours of unprotected sexual intercourse (use between 72 and 96 hours has also been used in an off-licensed manner). The usual dose of ulipristal acetate as EHC is a single dose of 30mg taken within 120 hours of unprotected sexual intercourse [4-6].

### Answer

No single mechanism of action has been established for emergency contraception, the mode of action varies according to the day of the menstrual cycle on which intercourse occurs and emergency contraception is administered. Both levonorgestrel and ulipristal acetate appear to inhibit or delay ovulation. In addition, ulipristal may alter the endometrium and inhibit implantation of a fertilised egg. Emergency contraception is only effective before implantation has occurred and pregnancy is established [3, 4].

SJW has several active constituents including hypericin, hyperforin and adhyperforin. *In vitro* studies have shown that hyperforin is a potent inducer of the cytochrome P450 enzymes, particularly CYP3A4, CYP1A2 and CYP2C9, as well as affecting the P-glycoprotein cellular transport system [1]. Clinically important interactions between SJW and CYP3A4 substrates have been reported in with SJW wort products containing hyperforin 1 mg or more [2, 7]. The isoenzyme CYP3A4 appears to be the major route for inactivation of most contraceptive steroids, including levonorgestrel and ulipristal [8, 9].

### Levonorgestrel

In September 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) published a Drug Safety Alert regarding the concomitant use on levonorgestrel-containing EHC and medicines that hepatic-enzyme inducers [10]. This alert is based on a review of Levonelle™ conducted by the European Medicines Agency (EMA) in May 2016 [11]. The MHRA alert states that concomitant administration of the antiretroviral efavirenz (a potent CYP3A4 inducer) reduces plasma levels of levonorgestrel by around 50%. Although drug interaction data with other CYP3A4 inducers have not been conducted, they are expected to produce similar reductions in plasma levels, leading to potential reduction in efficacy and subsequent pregnancy. They recommend that, if the patient is currently taking or has taken a CYP3A4 inducer within the past 4 weeks (including SJW), a copper intrauterine device (non-hormonal emergency contraception) should be used. If this is not possible, a double-dose of levonorgestrel (3mg as a single dose) should be taken to compensate for the reduced plasma levels. This advice is concurrent with the Faculty of Sexual and Reproductive Healthcare clinical guidelines for emergency contraception [4].

The Summary of Product Characteristics of levonorgestrel-containing EHC has been updated to reflect the information presented in the EMA review. The licensed dose of levonorgestrel-containing EHC includes using a 3mg dose in patients who are currently taking or has taken a CYP3A4 inducer within the past 4 weeks, including SJW. It is important to note that the combination of a double dose of levonorgestrel during concomitant use of an enzyme inducer has not been studied [5].

### Ulipristal

*In vitro* data indicate that ulipristal acetate is predominantly metabolised by CYP3A4, and to a small extent by CYP1A2 and CYP2A6 [6]. Therefore enzyme inducers, such as SJW which induce the CYP3A4 enzyme, may decrease plasma concentrations and the effectiveness of ulipristal acetate.

A pharmacokinetic study demonstrated that 1 dose of ulipristal 30 mg when co-administered with the strong inducer rifampin 600 mg once daily for 9 days decreased the maximum plasma concentration and total systemic exposure (as shown by Area Under the Curve) of ulipristal by 90% and 93% respectively. Other CYP3A4 inducers are expected to interact similarly [9].

The Summary of Product Characteristics for ellaOne™ states that concurrent use with CYP3A4 inducers can lead to reduced plasma levels and subsequent decreased efficacy. It recommends that women who have used enzyme-inducing drugs in the past 4 weeks (including SJW) should not use ellaOne™ and consider non-hormonal emergency contraception instead [6].

The Faculty of Sexual and Reproductive Healthcare clinical guidelines for emergency contraception also advise against the use of ulipristal acetate EHC in patients who are taking or who have taken CYP3A4 inducers in the past 4 weeks, including SJW [4].

### Summary

- Levonorgestrel is a progestogen commonly used in hormonal contraceptives to inhibit ovulation. Ulipristal acetate is a selective progesterone receptor modulator.
- St John's Wort (SJW) is the common name for the plant *Hypericum perforatum* and is a popular herbal remedy for the management of mild to moderate depression.
- SJW has several active constituents including hypericin, hyperforin and adhyperforin. Hyperforin is a potent inducer of the cytochrome P450 enzymes, particularly CYP3A4, which appears to be the major route for inactivation of most contraceptive steroids, including levonorgestrel and also ulipristal acetate.
- Patients currently taking SJW or who have taken it in the past 4 weeks who require emergency contraception should be recommended to use a copper intrauterine device.
- If this is not possible, a double-dose of levonorgestrel-containing EHC (3mg as a single dose) can be used, although the interaction between double-dose levonorgestrel and enzyme-inducers has not been studied.
- The use of ulipristal acetate EHC is not recommended in patients who are taking or who have taken SJW in the past 4 weeks.

### Limitations

This Q&A only discusses the impact of SJW on EHC efficacy and does not discuss other factors that can alter EHC efficacy (e.g. time between unprotected sexual intercourse and consumption of EHC, body weight, day of menstrual cycle and other drug interactions).

This Q&A does not discuss the potential for SJW to interact with other hormonal contraception. A separate Q&A that addresses this can be found [here](#).

### References

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## Quality Assurance

### Prepared by

Tim Meadows, East Anglia Medicines Information Service

### Date Prepared

22/04/2020

### Checked by

Sarah Cavanagh, East Anglia Medicines Information Service

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12/05/2020

### Search strategy

- References checked: BNF, EMC, NHS Evidence, Martindales: the Complete Drug Reference, AFHS Drug Information, Drugex, Stockley's Drug Interactions, Natural Medicines Database, Herbal Medicines, MHRA, EMA, NICE Clinical Knowledge Summaries, FSRH, Maudsleys
- Embase: *Hypericum Perforatum* AND (levonorgestrel OR ulipristal). Limited to 2016-2020
- Medline: *Hypericum* AND (levonorgestrel OR ulipristal[af]). Limited to 2016-2020