Prescrire's literature search up to 31 January 2017

In response to our request for information, MSD provided us with administrative documents and packaging items.

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2- Prescrire Editorial Staff "Raltegravir. HIV-infected children at least 2 years of age: only after prior treatment failure" *Prescrire Int* 2014; **23** (152): 206.
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4- EMA - CHMP "Public assessment report for Isentress. EMEA/H/C/000860/X/0044/G" 26 June 2014: 57 pages.
5- HAS - Commission de la transparence "Avis-Isentress 100 mg, granulés pour suspension buvable" 18 November 2015: 19 pages.
6- European Commission "SPC + PIL-Isentress" 14 November 2016: 160 pages.

Levonorgestrel for emergency contraception after an enzyme inducer: double the dose

The efficacy of *levonorgestrel* is reduced by approximately one-half with concomitant use of a hepatic enzyme inducer. When *levonorgestrel* is used for emergency contraception, a double dose (two tablets of *levonorgestrel* 1.5 mg, i.e. 3 mg) is recommended when an enzyme inducer has been taken in the previous 4 weeks.

The progestogen *levonorgestrel* is a drug of choice for emergency contraception. In this situation, a dose of 1.5 mg is taken, at best within 72 hours following unprotected sexual intercourse or when there are concerns about the reliability of the contraceptive method used.

Insertion of an intrauterine device (IUD) within 5 days is another effective option and is not subject to pharmacokinetic interactions.

As the progesterone receptor agonist-antagonist *ulipristal* has not been in use for as long as *levonorgestrel*, the harms and benefits of this option are less well established (1,2).

Levonorgestrel and ulipristal: affected by enzyme inducers. Like other hormonal contraceptives, *levonorgestrel* and *ulipristal* are metabolised by the cytochrome P450 enzyme system. Enzyme-inducing drugs enhance the metabolism of hormonal contraceptives and reduce their effects, resulting in decreased contraceptive efficacy.

Full enzyme induction can take 2 to 3 weeks to develop and a similar period of time to subside after discontinuation of the enzyme inducer. The main enzyme-inducing drugs include antiepileptics, antiretrovirals, antitubercular drugs and St John's wort (3-6).

Double dose of levonorgestrel for patients exposed to an enzyme inducer during the previous 4 weeks. In mid-2016, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended doubling the dose of *levonorgestrel* used for emergency hormonal contraception (i.e. a dose of 3 mg instead of 1.5 mg) for women who have taken an enzyme-inducing drug during the previous 4 weeks and are "*unwilling or unable to use*" a copper IUD (4,7).

This recommendation is mainly based on the results of a pharmacokinetic study conducted in 21 women who received 600 mg per day of the enzyme-inducing antiretroviral *efavirenz* and 1.5 mg of *levonorgestrel*. Plasma levels of *levonorgestrel* were measured for 12 hours after its administration, and showed "*consistent and marked reduction by about half*", as well as a 45% decrease in the maximum *levonorgestrel* plasma concentration (4,7).

The CHMP recommended adding this dose adjustment to the European summaries of product characteristics (SPCs), patient leaflets and boxes of *levonorgestrel*-containing drugs with a dose strength of 1.5 mg (7,8).

Since the aim of using the 3 mg dose of *levonorgestrel* is to counteract the effect of the enzyme inducer, the adverse effects will probably be similar to those that occur when the 1.5 mg dose is taken without an enzyme inducer (4,7).

As of 6 February 2017, the SPC for the *ulipristal* product approved for emergency contraception states that "*concomitant use (…) with CYP3A4 inducers (…) may result in a decreased efficacy of ellaOne. For women who have used enzyme-inducing drugs in the past 4 weeks, ellaOne is not recommended*" (9).

In practice When a patient needs emergency contraception, it is useful to ask her about the drugs and plant-based medicines she has taken during the previous month. If it emerges that she has taken an enzyme inducer, and IUD insertion is not possible or desired, taking 3 mg of *levonorgestrel*, i.e. two 1.5 mg tablets, seems a reasonable option for reducing the risk of unintended pregnancy.

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Selected references from Prescrire's literature search

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