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Letter to the Editor

Ulipristal Acetate and liver-injuries: while Esmya is revoked, EllaOne is allowed in repeated self-administrations possibly exceeding UPA toxic-dosing with Esmya.

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To the Editor

Ulipristal Acetate (UPA), an antagonistic Selective Progesterone-Receptor Modulator (SPRM), is the active-principle of two drugs: Esmya and ellaOne. While Esmya for fibroid treatment has been revoked because of severe liver-injuries, the emergency-contraceptive EllaOne is allowed in repeated self-administrations possibly exceeding UPA toxic-dosing with Esmya.

ESMYA - Micronized-UPA, 5mg-tablets in blisters of 28. It was taken daily for three to six months to treat uterine fibroids, after EMA (European Medicines Agency) authorization in 2012. It needed medical prescription and treatment was supervised by experienced doctors. It reduced progesterone-induced fibroid growth.

Due to the appearance of serious liver injuries in 8 Esmya-treated patients, the EMA Pharmacovigilance-Risk-Assessment-Committee (PRAC) started an evaluation (EMA/791062/2017)[1] that concluded that UPA had a possible role in injuries. EMA recommended measures to minimize the risk (EMA/355940/2018)[2]: contraindication if liver problems; information to patients; liver-tests before, during and after treatment; repeated courses only to inoperable women.

On September 4th 2020, a further review by EMA-PRAC confirmed that UPA 5mg can cause liver injury, including the need for liver transplantation. Since *it was not possible to identify which patients were most at risk or measures that could reduce the risk*, the PRAC concluded that the risks outweighed its benefits and Esmya should not be marketed in the EU (EMA/455818/2020)[3].

The strict post-marketing surveillance made it possible to link Esmya-administration to side-effects. The time from Esmya first-intake to hepatic failure ranged from few days to six months[4].

ELLAONE - Micronized-UPA, 30mg single-dose tablets, authorized for emergency contraception.

Both the 2018 and 2020 EMA-PRAC Reports on Esmya-related risk[2,3] specify that with ellaOne *there is no concern about liver injury*.

When the Members of EMA-CHMP (Committee-Human-Medicinal-Products) recommended ellaOne for marketing-authorization in 2009, they acknowledged that UPA accumulates in tissues, with a high tissue-to-plasma ratio (EMEA/261787/2009,page 13)[5]. They acknowledged that repeated UPA-administrations (even scheduled monthly) lead to a progressive accumulation in the liver, eventually resulting *in liver-toxicity.* Consequently, EMA-CHMP authorized single-dose administration and warned against repeated self-administration.

However, in 2015 this scenario changed: the EMA-CHMP removed the warning against repeated self-administration and made ellaOne-supply "*not subject to medical prescription*" (EMA/73099/2015)[6]. Since then, the repeated self-administration of ellaOne in the same cycle is allowed and suggested as *safe*, without any medical supervision.

Up-to-date, no cases of hepatotoxicity have been reported after single-dose administration of ellaOne; however, the patient 2 in Meunier's series[4] evidenced severe liver injury after taking Esmya (UPA 5mg) for 3 days (15mg=half ellaOne) to 26 days. Women on Esmya-treatment were strictly surveilled, while those taking ellaOne are unidentified: eventual adverse events could hardly be attributable to an undocumented drug-self-administration.

Indeed, liver-toxicity seems due to UPA-accumulation, while circulating levels of either UPA or its metabolites[7] have no impact on safety. The life-threatening DILI (drug-induced-liver-injury), including autoimmune hepatitis, associated with UPA in post-marketing surveillance may be partially explained by

UPA physiochemical (high lipophilicity) and pharmacokinetic (hepatic metabolism, long half-life, inhibition of liver transporters, reactive metabolite formation) features[8].

The most challenging form of DILI is the so-called idiosyncratic one: it is unpredictable, usually unrelated to the dose and is characterized by a variable onset-time. DILI is an important public health issue: not only it strengthens the importance of the post-marketing phase, when urgent withdrawal sometimes occurs for rare unanticipated liver-toxicity, but also shows the imperfect predictivity of pre-clinical models and the lack of validated biomarkers beyond traditional, non-specific, liver-function tests[9].

The removal of the warning against repeated use was requested and obtained by HRA-Pharma, basing on HRA2914-554 Study (Report-pages 6-9)[6] that examined the effect of *repeated* administration of ellaOne on ovulation, menstrual cycle and safety. EllaOne was given weekly (Q7D, twelve women) or every 5 days (Q5D, eleven women) for 8 consecutive weeks since the first day of the menstrual cycle. No safety-issues emerged for *those* 23 women, suggesting that, *should ellaOne be used more than once in the same cycle*, *the safety profile is similar to that for a single administration*[6]. The repeated self-administration of EllaOne in the same cycle was authorized as *safe*[6].

Overlooking the fact that almost every woman had normal ovulations during the repeated self-administration of ellaOne, officially presented as anti-ovulatory[10], the total UPA-dosing for women was 270mg in Q7D and 360mg in Q5D. These amounts are presented as *safe*, but are equal to or greater than Esmya-dosing in the same 8 weeks, UPA 280mg: the UPA-dosing leading two patients to liver transplantation[4]; besides, the single UPA-bolus to liver was six time-higher than with Esmya.

The burden of DILI is likely underestimated: clinical trials are usually underpowered to identify rare idiosyncratic events and most data come from post-marketing retrospective studies. DILI occurs only in a small fraction of exposed-subjects[9]: with UPA the percentage was 1/10.000: 8 out of 80.0000 Esmya-patients, but ellaOne is taken by millions of women every year and repeated-self-administration cannot be quantified. EllaOne is not subject to medical prescription, so no data are available for post-marketing evaluation.

Liver-toxicity due to Esmya-administration were still unreported in 2015, when the EMA-CHPM removed the warning against the repeated self-administration of ellaOne, but nowadays it seems difficult to state that ellaOne-self-administration is always safe. The PRAC-EMA assessed definitively that UPA has a direct responsibility in inducing liver-injuries[2,3]. Besides, it is commonly known that ellaOne can be taken repeatedly by millions of women whenever unprotected-sex-intercourse recurs, in whichever period of the cycle (ellaOne Package-Leaflet). In the light of the above, it is easy to argue that repeated self-administration can lead to a total UPA-intake even exceeding the UPA-amounts responsible of the dramatic DILI officially[2,3] attributed to Esmya. As well, it is easy to argue that nothing can either discourage or only restrict ellaOne-repeated self-administration: not only women are not informed about its risks, but, furthermore, they are reassured that even closely-repeated self-administrations are as safe as a single-tablet self-administration[6].

The overall metabolic impact of Ulipristal and/or its side-effects are still unknown. EllaOne frequent self-administration for subsequent contraceptive-emergencies is authorized as a correct and safe behaviour, but is likely to present a danger, in the absence of medical supervision, due to the progressive UPA-accumulation in the liver.

CONCLUSIONS

The repeated-self-administration of ellaOne, micronized-UPA 30mg, likely can be associated with hepatotoxicity in unaware women. However, further investigations are required to understand the underlying pharmacological mechanisms, to define the UPA-toxic-thresholds and to assure women the best protection.

Information to women and to the Medical Community seems mandatory to preserve women's health.

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