Cardiac and visual disorders confirmed

The known adverse effects of *ivabradine* include visual disorders, such as phosphenes (flashing lights) and blurred vision, as well as potentially severe bradycardia and other cardiac arrhythmias, conduction disorders, atrioventricular block and supraventricular arrhythmias (6).

The Associate study: bradycardia and visual disorders

In the Associate study, bradycardia occurred in 4.2% of patients treated with *ivabradine*, versus 0.5% of patients in the placebo group. Bradycardia was the most frequent reason for treatment withdrawal in the *ivabradine* group (2,3).

Phosphenes and other visual disorders affected 2% of patients in *ivabradine* group versus 0.9% of patients in the placebo group (2,3).

Beautiful study: bradycardia and visual disorders, etc.

In the Beautiful study, the incidence of cardiac adverse effects was about 6% in both groups. However, 23% of patients in the *ivabradine* group discontinued treatment (versus 16% in the placebo group), mostly because of bradycardia (6% in the *ivabradine* group, versus 1% in the placebo group) (4).

Visual disorders affected 0.4% of patients in the *ivabradine* group versus 0.2% of patients in the placebo group. Treatment was withdrawn in 0.5% of patients in the *ivabradine* group because of visual adverse effects such as phosphenes, blurred vision, etc., versus 0.2% of patients in the placebo group. These visual adverse effects disappeared after treatment cessation (4).

The *Lancet* article on the Beautiful study implies that the proportion of patients who stopped treatment due to visual adverse effects was 0.1% higher than the proportion of patients who complained of these adverse effects. This inconsistency illustrates the difficulty of analysing data on adverse effects contained in clinical trial reports (4).

It should also be noted that, in the Beautiful trial, the frequency of psychological adverse effects was 0.3% with *ivabradine* versus 0.1% with placebo (4).

Finally, *ivabradine* is metabolised by cytochrome isoenzyme CYP 3A4, hence a high risk of drug interactions (1,6).

In practice

Far from challenging the conclusions we reached in 2006, the results of these two more recent trials reinforce our conclusions: when patients with stable angina cannot receive a betablocker, *ivabradine* has a less favourable risk-benefit balance than *verapamil* (in the absence of heart failure) or *amlodipine*. *Verapamil* has well-documented efficacy in reducing mortality in patients with coronary heart disease (7). In addition, *verapamil* has long been used, especially in this indication, and its adverse effects are well documented.

Ivabradine should simply be avoided, given the lack of any proven therapeutic advantage and persisting uncertainties on its short-term and long-term adverse effects, especially cardiac and visual disorders.

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1- Prescrire Editorial Staff "Ivabradine" *Prescrire Int* 2007; **16** (88): 53-56.
2- European Medicines Agency - CHMP "European Public Assessment Report – Procoralan. Scientific discussion N° H-C-597-II-10". posted on the EMA website 22 January 2010: 35 pages.
3- Tardif JC et al. "Efficacy of the If current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial" *Eur Heart J* 2009; **30**: 540-548.
4- Fox K et al. "Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomized, double-blind, placebo-controlled trial" *Lancet* 2008; **372**: 807-816.
5- Prescrire Rédaction "La "valeur p" résume-t-elle la pertinence d'une comparaison?" *Rev Prescrire* 2008; **28** (298): 621-622.
6- Prescrire Rédaction "2-3-6. Patients sous ivabradine" *Rev Prescrire* 2009; **29** (314 suppl. interactions médicamenteuses).
7- Prescrire Rédaction "vérapamil LP et angor stable - Isoptine LP° 240 mg. Un recours dans certaines situations" *Rev Prescrire* 2000; **20** (208): 491-492.

Published in ***Rev Prescrire*** **June 2010; 30 (320): 476-2-1/476-2-2**

Ulipristal and postcoital contraception

"To the Editor

Your article on EllaOne° (ulipristal) (French edition 314, p. 886-889; Prescrire International 106 p.53) contained a number of errors or surprising omissions on the part of a supposedly objective and serious journal. The sentence "Ulipristal marketing appears mostly a commercial ploy, better not be taken in by it" reflects the bias in this article.

I wish to remind your readers of certain facts that will show why, in our opinion, the above sentence is defamatory. When HRA Pharma was created in 1996, emergency contraception did not exist, because, for various reasons, the large pharmaceutical groups did not want to become involved in this field. We took the risk of developing a dedicated emergency contraceptive based on a progestin alone (without oestrogen), based on studies conducted by WHO. This led to the development of NorLevo° (levonorgestrel), a drug whose acceptable safety profile has made it available without a medical prescription, even for minors. Our willingness to take this risk made it possible for the public authorities to implement these measures. Nevertheless, when NorLevo° was launched, we were already aware of its limitations and of the need to develop an even more effective product: this is why, in 2000, we acquired the rights to ulipristal acetate, whose pharmacological properties suggested it would be more effective than levonorgestrel. It took us eight years, and investment of more than 20% of our annual turnover, to demonstrate the efficacy and safety of this product, based on large controlled studies (several thousand subjects) as part of a particularly thorough programme, unprecedented for an emergency contraceptive (including levonorgestrel). EllaOne° received European marketing authorisation for the entire 0-120 h window after poorly protected or unprotected intercourse. Your readers may wish to consult the EMA public assessment report (www.emeaeuropa.eu/humandocs/PDFs/EPAR/ellaone/H-1027-fr1-pdf) for an objective view of its advantages and limitations, and to rectify the factual errors in your article. It is evident that the cost of this development programme would be reflected in the sales price of the finished product. It should be noted, however, that HRA Pharma provides this drug, at the same price as NorLevo, to French family planning centres, so that even the poorest women may benefit.

Since its inception, our company has had a strong sense of social responsibility, well ▶▶

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▶ *before this concept became fashionable: HRA Pharma funds and participates in various contraception training programmes, and supplies products (NorLevo°, IUDs, etc.), to countries in Africa and Latin America (www.actionshrapharma.com). Furthermore, the company has kept Gymiso° (misoprostol 200 mg) on the market solely so that the law on home-based termination can be implemented. In general, HRA Pharma only markets products that fill previously unmet medical needs, and invests in true innovation.*

The reader will therefore understand that the notion of "commercial ploy" is alien to the spirit of our company and will no doubt agree that it is at the very least unfortunate that these slanderous allegations should find their way into a "factual" article".

André Ulmann
President of the HRA
Pharma monitoring committee

André Ulmann criticises "a number of errors or surprising omissions" in a *Prescrire* article, without mentioning a single specific error or omission. The European Medicines Agency public assessment report mentioned in Mr. Ulmann's letter corresponds to reference 1 in the *Prescrire Int* article published in issue 106 pp 54-55.

Postcoital contraception existed before HRA Pharma. We published a review article on postcoital contraception in February 1995 (1).

This 1995 article focuses on the use of the IUD for postcoital contraception, which was described as "an effective method, provided it is inserted within 5 days following unprotected intercourse"; one of the references provided in support of this statement was a text that appeared in *Population Reports* in 1983. This use was not officially recognised in France, but there was no basis for opposing it.

This 1995 article also states that hormone-based postcoital contraception had been tested since the 1960s, initially for rape victims.

Hormone-based postcoital contraception was first marketed in the 1980s. Schering PC4°, a combination of *ethinylestradiol* and *levonorgestrel*, used in accordance with the Yuzpe protocol, was marketed for postcoital contraception in the UK in 1984 (2). The same product was marketed in Switzerland, under the brand name Tetragynon°, in the late 1980s. It was also manufactured by Schering, a company that had been heavily involved in developing and marketing contraceptives for decades (2,3).

Yet the number of countries in which at least one product was authorised for oral postcoital contraception was still limited in the mid-1990s (2). An international movement to promote this type of contraception emerged, and women residing in France benefited from the introduction of Tetragynon° (authorised in 1998), followed by NorLevo° (authorised in 1999) (2,4-7). In summary, it is therefore incorrect to claim that *"in 1996, emergency contraception did not exist"*. HRA Pharma was not the first company to market an oral postcoital contraceptive, even in France.

Do not confuse information, training and promotion. Companies in general, and specifically drug companies, do have social responsibilities. However, as they are also subject to major commercial constraints, they should not, in our opinion, fund or otherwise interfere with the training of healthcare professionals. Yet many companies do so, including HRA Pharma.

In a competitive environment, risk-taking, rights acquisitions, investments, costly clinical trials, etc. are legitimate concerns for HRA Pharma, as they are for all drug companies.

But it is inaccurate to claim that EllaOne° fills an *"unmet medical need"*, as taking *levonorgestrel* 72 to 120 hours after intercourse is an effective and relatively safe form of postcoital contraception. This use is not one of the indications approved in the marketing authorisation. However, healthcare professionals can prescribe the drug for other uses when clinical studies show a favourable risk-benefit balance in these other settings.

True, instead of doing nothing at all or obtaining a licence extension for a generic product, HRA Pharma preferred to invest in the development of a new product based on a new active ingredient: this was a perfectly normal commercial decision.

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1- Prescrire Rédaction "Contraception post-coïtale" *Rev Prescrire* 1995; **15** (148): 126-129.
2- Glasier A "Emergency postcoital contraception" *N Engl J Med* 1997; **337** (15): 1058-1064.
3- "Martindale The Extra Pharmacopoeia" The Pharmaceutical Press, London 1989: 1392-1393.
4- "Tétragynon°". In French datasheet compendium: "Dictionnaire Vidal" Vidal, Paris 2002: 1784.
5- Prescrire Rédaction "éthinylestradiol+lévonorgestrel-Tétragynon°. Pour la contraception d'urgence" *Rev Prescrire* 1999; **19** (194): 253-255.
6- Besins-Iscovesco "NorLevo° - Un progrès d'aujourd'hui" May 1999: 2 pages.
7- Prescrire Editorial Staff "Levonorgestrel" *Prescrire Int* 2000; **9** (45): 202-204.

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