Literature search

Our literature search was based on searching the following databases at the Prescrire library: Embase/Excerpta Medica Drugs and Pharmacology (1991-2nd quarter 2010), Medline (1950-2010 June, week 4), The Cochrane Library (CDSR, DARE, HTA; 2010 issue 2) and Reactions (1992-6 July 2010); and systematic consultation of clinical pharmacology textbooks (Martindale The Complete Drug Reference, and Meyler's).

This article was prepared using the standard Prescrire methodology, which includes dual verification of the choice of documents, triple verification of their analysis, external review, and multiple quality controls.

1- "Hormonal contraceptives". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 5 July 2010: 75 pages.
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3- Prescrire Rédaction "Contraceptifs estroprogestatifs oraux: faire un tri parmi la pléthore de spécialités" *Rev Prescrire* 2009; **29** (309): 496-497.
4- Prescrire Rédaction "éthinylestradiol + drospirénone comme contraceptif: un dosage de plus" *Rev Prescrire* 2007; **27** (279): 19.
5- Prescrire Editorial Staff "Ethinylestradiol 30 µg + drospirenone" *Prescrire Int* 2002; **11** (61): 145.
6- "Drospirenone". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 5 July 2010: 7 pages.
7- Prescrire Rédaction "8-1. Patientes sous contraceptif hormonal" *Rev Prescrire* 2010; **30** (326 suppl. interactions médicamenteuses).
8- Lidegaard Ø et al. "Hormonal contraception and risk of venous thromboembolism: national follow-up study" *BMJ* 2009; **339**: b 2890doi:10.1136/bmj.b2890.
9- van Hylckama Vlieg A et al. "The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study" *BMJ* 2009; **339**: b 2921doi:10.1136/bmj.b2921.
10- Prescrire Rédaction "Facteurs de confusion: sources de biais majeurs" *Rev Prescrire* 2009; **29** (310): 618-619.
11- Shapiro S and Dinger J "Risk of venous thromboembolism among users of oral contraceptives: a review of two recently published studies" *J Fam Plann Reprod Health Care* 2010; **36** (1): 33-38.
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13- Seeger JD et al. "Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives" *Obstet Gynecol* 2007; **110**: (3) 587-593.
14- European Medicines Agency "Pharmacovigilance Working Party (PhVWP) March 2010 plenary meeting" 25 March 2010. www.ema.eu accessed 12 July 2010: 15 pages.
15- Bégaud B "Dictionnaire de pharmaco-épidémiologie" ARME-Pharmacovigilance éditions, 1998: 56.
16- Prescrire Rédaction "Idées-Forces Prescrire: embolie pulmonaire thrombotique, en bref" *Rev Prescrire* updated June 2009. Full text available at www.prescrire.org: 3 pages.
17- Prescrire Rédaction "Evra° et risque de thrombose accru: RCP étoffé" *Rev Prescrire* 2009; **29** (311): 663.

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Benfluorex: how many deaths?

In November 2009, *benfluorex* (ex Mediator°) was withdrawn from the French market. It had been available for 33 years, despite a lack of proven clinical benefit. *Benfluorex*, an appetite suppressant, is related to *dexfenfluramine* (ex Isomeride°), a drug carrying a known risk of pulmonary arterial hypertension and valve disease (1,2).

In November 2010 the French Health Products Safety Agency (Afssaps) reported the results of a second study based on the French national health insurance database and focusing on 303 000 patients exposed to *benfluorex* in 2006. Follow-up was 4 years (2006 to 2009) for hospitalisations for valve disease and 4.5 years for deaths (3). A total of 597 patients were hospitalised at least once for valve failure or multiple valve disease. Half of these patients had valve replacement surgery and 64 of them died, 33 following heart surgery. 46 deaths were attributed to valve disease. The risk of hospitalisation for valve disease fell markedly two years after *benfluorex* withdrawal.

For a total exposure of 7 million person-years between 1979 and 2009, the authors estimated that 500 deaths were attributable to *benfluorex*. The risk of hospitalisation was about 0.5 per 1000 patients exposed to *benfluorex* (4). Follow-up was limited to 5 years only. The real figures may be higher, owing to confusion in the hospital coding system and failure to take into account some cases of pulmonary arterial hypertension.

Patients who have taken *benfluorex* should be on the lookout for symptoms of pulmonary arterial hypertension and valve damage.

1- Prescrire Editorial Staff "Benfluorex: yet more valve disorders" *Prescrire Int* 2010; **19** (105): 17.
2- Prescrire Editorial Staff "Benfluorex. EU marketing authorisation finally withdrawn" *Prescrire Int* 2010; **19** (109): 206.
3- Afssaps "Mediator° (chlorhydrate de benfluorex) - Études sur les données de remboursement de l'Assurance maladie (SNIIRAM)" 16 November 2010 + Weill A et al. "Benfluorex, valvulopathies cardiaques et décès" 28 September 2010. afssaps.sante.fr accessed 23 November 2010: 1 + 19 pages.
4- Afssaps "Mediator° et ses génériques - recommandations concernant le dépistage d'atteintes valvulaires et le suivi des patients exposés au benfluorex - Lettre aux professionnels de santé" 2 December 2010. afssaps.sante.fr accessed 3 December 2010: 2 pages.

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Dextropropoxyphene and cardiac disorders: new data

In late 2010 the FDA released new data on *propoxyphene*, the US name of *dextropropoxyphene,* which is sold in combination with *paracetamol* (1). In a randomised, double-blind, placebo-controlled study lasting 11 days, healthy volunteers received *propoxyphene* at increasing doses, up to a maximum of 900 mg (1).

The QT interval increased by 29.8 ms seven hours after the last dose of 600 mg and by 38.2 ms two hours after the last dose of 900 mg. QT prolongation by more than 20 ms is generally considered to be associated with a substantial risk of arrhythmia. The study was halted when these effects were observed.

QT prolongation in healthy volunteers receiving about twice the maximal daily dose recommended in the French summary of product characteristics (SPC) for *dextropropoxyphene* combinations is in keeping with previous clinical cases, including reports of deaths in the UK (2,3). The pharmacokinetic behaviour of *dextropropoxyphene* creates a risk of accumulation in patients with renal failure and in elderly subjects (3).

This study provides a further reason for avoiding *dextropropoxyphene* before it is effectively removed from the French market (4).

1- U.S. FDA "FDA drug safety communication: FDA recommends against the continued use of propoxyphene" 19 November 2010. www.fda.gov accessed 24 November 2010: 3 pages.
2- Afssaps "Médicaments contenant du dextropropoxyphène: nouvelles données américaines concernant le risque cardiaque chez des volontaires sains - Communiqué" 22 November 2010. afssaps.sante.fr accessed 23 November 2010: 3 pages.
3- Prescrire Editorial Staff "Paracetamol + dextropropoxyphene: planned withdrawal from the British market" *Prescrire Int* 2005; **14** (78): 145.
4- Prescrire Rédaction "Dextropropoxyphène: réussir à s'en passer, et à mieux soigner" *Rev Prescrire* 2009; **29** (311): 683-686.