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Benfluorex: increasing reports of valve disorders

● ***Benfluorex*** **is an amphetamine appetite suppressant derived from *fenfluramine*. In France, about 30 cases of pulmonary arterial hypertension and a similar number of valve disorders, often involving several valves, were reported between 1998 and 2009.**

● ***Benfluorex*** **has the same adverse effects as those that led to the withdrawal of amphetamine appetite suppressants such as *fenfluramine*. There is no proven benefit that justifies exposing patients to these risks.**

● **The French National Pharmacovigilance Committee simply proposed "*to await the results of planned and ongoing studies*". However, it would be in patients' best interests to withdraw this drug from the market.**

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Benfluorex, an amphetamine appetite suppressant derived from *fenfluramine*, has been marketed in France and other countries since 1976. Its cardiovascular adverse effects have long been known but, until recently, they have not received much media attention (1-5).

Pulmonary arterial hypertension. A review of reports of pulmonary arterial hypertension and valve disorders was conducted by the Besançon Pharmacovigilance Centre and examined by the French National Pharmacovigilance Committee in July 2009 (1).

In total, 28 cases of pulmonary hypertension in patients using *benfluorex* were reported in France, including 4 apparently idiopathic cases in patients who were not using other appetite suppressants.

Cardiac valve disorders. About 30 cases of valve disorders were reported between 1998 and 2009, in 24 women and 6 men who had been taking *benfluorex* for an average of 5.3 years (1). One valve was involved in 6 cases, two in 16 cases, and three in 8 cases. There were 28 cases of mitral regurgitation (17 severe cases), 24 cases of aortic regurgitation, and 11 cases of tricuspid regurgitation (4 severe cases). Pathology reports on the affected valves were available for 6 patients.

A team of clinicians in Brest conducted a detailed study of 15 cases of valve disorders associated with *benfluorex*, including 4 recent cases that were not included in the pharmacovigilance review (1). The cases were directly identified by Brest clinicians or, in 11 cases, by searching a medical database. The patients were 12 women and 3 men, with an average age of 58 years, who had been using *benfluorex* for a mean duration of 53 months. Five patients had also been exposed to other appetite suppressants. Seven patients had ultrasound scans before *benfluorex* exposure, and they were normal in 5 cases. All of the patients had both mitral and aortic valve involvement. The tricuspid valve was impaired in 7 patients and the pulmonary valve in 1 patient. Eight patients underwent heart valve replacement.

Similar adverse effects to those that led to fenfluramine withdrawal. *Benfluorex* has the same type of adverse effects that led to the withdrawal of other amphetamine appetite suppressants such as *fenfluramine.* They include neuropsychological disorders such as agitation, confusion and delirium, as well as pulmonary arterial hypertension and valve disorders (4,5).

In addition, *fenfluramine* derivatives are produced during *benfluorex* metabolism (1).

In practice: patients remain exposed to a risky drug. Despite these findings, the French Pharmacovigilance Committee simply recommended "*waiting for the results of planned or ongoing studies before taking any necessary measures*" (1).

However, *benfluorex* has no proven beneficial impact on morbidity or mortality, despite being on the market for over 30 years, and its risk-benefit balance is clearly unfavourable (2). The risk of pulmonary arterial hypertension linked to appetite suppressants has been known since the 1960s. It is well known that cases reported to pharmacovigilance organisations only represent the tip of the iceberg.

While waiting for the French regulatory agency to come to a decision, sales of *benfluorex* continue and patients remain exposed to an unjustified risk of serious adverse effects. Worse yet, generic versions of *benfluorex* have been authorised in France, even though this drug was withdrawn from the Spanish market in 2003.

It is up to healthcare professionals to warn patients of these risks; patient safety must come before drug company profits.

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News update

The French drug regulatory agency has decided to withdraw **benfluorex**-based products as of 30 November 2009.

More on Prescrire website at http://english.prescrire.org

Selected references from Prescrire's literature search.

1- Agence française de sécurité sanitaire des produits de santé "Enquête sur les HTAP/valvulopathies et benfluorex, Mediator°, benfluorex Mylan°, benfluorex Qualimed° – Commission nationale de pharmacovigilance du 7 juillet 2009" 29 September 2009. afssaps.sante.fr accessed 22 October 2009: 4 pages.

2- Prescrire Editorial Staff "Benfluorex: negative data in France, but still on the market" *Prescrire Int* 2009; **18** (101): 214.

3- Prescrire Rédaction "Benfluorex interdit en Espagne" *Rev Prescrire* 2005; **25** (264): 589.

4- Prescrire Editorial Staff "Hidden amphetamines: from smoking cessation to diabetes" *Prescrire Int* 2004; **13** (69): 18-20.

5- Prescrire Rédaction "Benfluorex: hypertensions artérielles pulmonaires et troubles neuropsychiatriques" *Rev Prescrire* 2006; **26** (273): 427.

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