



The Mediator° disaster: so much time wasted, so many lives destroyed

ABSTRACT

- The criminal trial of the pharmaceutical company Servier, France's national drug regulatory agency and some of their members opened in France in September 2019. The charges include delay in the market withdrawal of Mediator° (*benfluorex*), a drug with particularly serious adverse effects.
- The articles published by *Prescrire* over the years provide some insight into the key issues of this trial.
- *Prescrire* was already questioning the efficacy of *benfluorex* in diabetes back in 1986.
- *Prescrire* pointed out *benfluorex*'s anorectic (appetite-suppressing) nature in 1990, and data emerged in 1999 showing that it was being used off-label for weight loss.
- *Prescrire* criticised the fact that Mediator° was still on the market in 1997. In the late 1990s, there was mounting evidence that *benfluorex* has the same serious adverse effects as other amphetamine-like appetite suppressants: pulmonary arterial hypertension and heart valve disease.
- Since 2003, *Prescrire* has highlighted cases of heart valve disease observed in patients exposed to *benfluorex* and has drawn attention to the stubborn inertia displayed by the French drug regulatory agency in response to the dangers faced by patients.
- The French regulatory agency finally suspended the sale of Mediator° and its generic versions in late 2009, after the publication of studies showing the scale of the disaster.
- By 2015, 6743 cases of heart valve disease and 1273 cases of pulmonary arterial hypertension attributed to *benfluorex* had been reported in France. Figures from 2009 suggest a death toll of at least 1300.

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In late September 2019, the criminal trial involving Mediator° opened in France. It is due to continue for an estimated 6 months (1). In September 2019, it had been 9 years since the scale of the disaster was revealed thanks to Irène Frachon's book "Mediator°, combien de morts?", published in 2010, and 10 years since the drug was withdrawn from the market (a)(2,3).

Prescrire was already questioning the efficacy of this drug in 1986 (4). Beginning in the late 1990s, *Prescrire*'s editorial staff has issued warnings that *benfluorex* is an anorectic (appetite suppressant) with increasingly foreseeable risks of pulmonary arterial hypertension and heart valve disease (b)(5-7).

Long-time subscribers will have seen the sad tale of Mediator° unfold over the years in *Prescrire*. As a recap and to provide some insight into the key issues of the trial, this review outlines the main articles *Prescrire* published about *benfluorex*, and Mediator° in particular, before its market withdrawal.

1986-1997: what exactly is *benfluorex* used for?

One of the mysteries of Mediator° is its commercial success in multiple indications, despite its insubstantial evaluation. For example, in 1986, *Prescrire* considered its evaluation as an "antidiabetic" unconvincing (4). In 1997, the editorial team commented that "even though it has been on the market for 20 years, it is unclear whether *benfluorex* benefits diabetic patients", and called for its reimbursement and marketing authorisation in diabetes and hypertriglyceridaemia to be revoked (5,6).

The drug's success (6 million boxes reimbursed in 2006) undoubtedly had more to do with advertising than with evidence-based medicine (8,9).

1990-1999: an anorectic used for weight loss.

One aspect of the trial pertains to Servier's concealment of *benfluorex*'s anorectic properties (10).

Prescrire reported that *benfluorex* is an anorectic back in 1990 (11). In 1997, *Prescrire*'s editorial team expressed surprise that *benfluorex* was not officially classified as an anorectic in France, whereas the World Health Organization (WHO) listed it as an

a- Mediator, how many deaths?

b- Benfluorex also has neuropsychiatric adverse effects. This article only discusses the pulmonary arterial hypertension and heart valve disease it caused.

anorectic, and the inclusion of *benfluorex*, along with other anorectics, had been prohibited in extemporaneous preparations in France since 1995 (5).

Mediator^o used as an appetite suppressant? A study cited in *Prescrire* in 1999, conducted by the former Regional Union of Health Insurance Funds (Urcam) in Bourgogne, found that 35% of prescriptions for Mediator^o were off-label, and at least 15% of prescriptions were for patients also receiving treatment to help them lose weight (12).

1970-2003: foreseeable adverse effects. The association between amphetamine-like appetite suppressants and pulmonary arterial hypertension has been known since the 1970s (7). In 1997, their implication in heart valve disease led to the market withdrawal of *fenfluramine* (Pondéral^o) and *dexfenfluramine* (Isoméride^o), from the same pharmaceutical company as Mediator^o while *Prescrire* called for the market withdrawal of all anorectics (7,13-15).

In 1998, *Prescrire* suggested that the lack of reported cases of heart valve disease in France in patients exposed to anorectics was due, at least in part, to confusion with rheumatic fever (14).

Prescrire reported in 2003 that a case of heart valve disease had been attributed to Mediator^o in Spain. The same type of valve lesions were seen as with *fenfluramine* and *dexfenfluramine*, to which *benfluorex* is chemically related (16). *Benfluorex* was withdrawn from the Spanish market in 2003, at the pharmaceutical company's request (8,17).

1999-2009: the French authorities refuse to act. Those charged in the Mediator^o trial include the French drug regulatory agency (called Afssaps at the time) and some of its officials (1). *Prescrire's* repeated calls for Mediator^o to be withdrawn and its withdrawal from the Spanish market had no effect in France, where the authorities' response was to prevaricate and incessantly request new studies (18).

In 1999, a case of heart valve disease attributed to *benfluorex* was reported in Marseille, but due to dysfunctions within the French drug regulatory agency, the case was buried and then forgotten, against a background of pressure from the company (10). In 2005, the director of the agency wrote to *Prescrire* without mentioning the 1999 case and appeared to be unaware of any reports prior to 2004. He asserted that the risk of pulmonary arterial hypertension with Mediator^o was very low: "about 1 case per 55 million boxes sold" (18).

In 2006, *Prescrire* criticised the fact that the French drug regulatory agency took a decision concerning Mediator^o in the presence and with the involvement of two members of the agency who had links with Servier, including the vice-president of the pharmacovigilance committee (19). Such conflicts of interest will occupy an important place in the trial; indeed, both the concept and the reality of conflicts of interest have received a great deal of attention in the aftermath of the Mediator^o disaster.

Also in 2006, the French drug regulatory agency launched a new study after learning that 17 cases

of pulmonary arterial hypertension had been reported. But there were still no reports of heart valve disease. *Prescrire's* reaction was that "while preparations are made for the studies, *benfluorex* continues to be sold and patients remain exposed to an unjustified risk of adverse effects" (20).

A study published in 2006 showed that the symptoms of pulmonary arterial hypertension can develop years after taking an anorectic (21).

In 2007, after examining the data again, the French drug regulatory agency simply narrowed the indications for Mediator^o (8).

2006-2019: heart valve disease demonstrated. After the "forgotten" case of heart valve disease reported in Marseille in 1999, a case observed in Toulouse in a patient exposed to Mediator^o was published in 2006. The French national pharmacovigilance committee expressed reservations about Mediator^{o's} harm-benefit balance in 2007 (22).

More and more cases of pulmonary arterial hypertension were reported (20,22). Another case of heart valve disease was published in 2009, yet there was still no mention of the risk of pulmonary arterial hypertension or heart valve disease in the French summary of product characteristics (SPC) (23). The Besançon Pharmacovigilance Centre identified about 30 cases of heart valve disease reported in France between 1998 and 2009 (24).

Despite these reports, generic versions of Mediator^o were authorised in 2008 (25).

It was not until November 2009 that the French drug regulatory agency suspended the marketing authorisations for Mediator^o and its generic versions and withdrew them from the market. Their withdrawal was prompted in particular by the conclusion of a study from Brest, conducted by Irène Frachon, which showed a link between *benfluorex* and heart valve disease (2,10,26). In late October, a study by the national health insurance fund CNAM, designed and conducted by Alain Weill's team, had also shown a four-fold risk of valve replacement in patients exposed to Mediator^o (c)(10,26).

In 2010, a study by the CNAM estimated that Mediator^o had caused 500 deaths through heart valve disease in France (27). A study by two scientists from the French National Institute of Health and Medical Research (Inserm) estimated that over 1300 such deaths occurred between 1976 and 2009 (28). A total of 6743 cases of heart valve disease and 1273 cases of pulmonary arterial hypertension reported in France between 1976 and 2015 were attributed to *benfluorex* (29).

Denial. Knowledge of the drug class to which *benfluorex* belonged and analysis of the clinical results of its evaluation enabled *Prescrire* to urge readers to

c- Irène Frachon is a pulmonologist at Brest Hospital; Alain Weill is a member of the studies and statistics division at the French national health insurance fund CNAM.

avoid this drug at a very early stage due to its foreseeable harms and lack of tangible efficacy.

For years, the French drug regulatory agency and many healthcare professionals failed to recognise the adverse effects of *benfluorex* for what they were, leading to underreporting and underestimation of the drug's harms. For years, *benfluorex*-induced heart valve disease was attributed to supposed rheumatic fever, without considering that a useless drug might be responsible.

Fortunately, while reading *Prescrire*, Irène Frachon made the link between Mediator[®] and the disorders she had observed, and then showed great tenacity in the face of the influences at work to discredit her (1,2). Thankfully, the scale of the disaster and the scandal were eventually revealed.

**Review produced collectively
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First sanctions against companies for drug shortages in France

● Companies failing in their duty to supply drugs of "major therapeutic interest".

Since January 2017, in France, companies have been required to submit a management plan to deal with potential shortages of drugs deemed to be of major therapeutic interest, for which supply interruptions would present a "serious and immediate risk" to patients (1,2). Along with other measures, this involves planning other manufacturing sites, or identifying products which could constitute an alternative. Failure to comply with this requirement could render companies liable to financial penalties (1,2).

Following a ruling in December 2018, the French National Health Products Agency (ANSM) has for the first time sanctioned a company, MSD France, for not meeting its obligations (up to October 2018), in the face of a shortage of Sinemet[®] (*levodopa + carbidopa*), used in the treatment of Parkinson's disease (2,3). The ANSM imposed a fine of 348 623 euros, in line with the scales provided for failings of this type (2).

Subsequently, other penalties linked to the fight against drug supply disruption have been made public (4,5). It remains to be seen whether their on-line publication on the ANSM website, for just one month (or until the situation is rectified), and the penalty amounts, will turn out to be a sufficient deterrent for companies (6).

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