

Mediator[®]: norfenfluramine at the heart of the trial

The verdict in France's Mediator[®] criminal trial is expected at the end of March 2021, twelve years after this drug, which caused several hundreds of people to die from pulmonary arterial hypertension (PAH) or heart valve disease, was withdrawn from the French market (1).

Benfluorex, a fenfluramine just like the others. One of the key questions in the trial was to establish when the company, Servier, first knew that *benfluorex* could cause PAH (a).

Benfluorex (Mediator[®] and other brands), *fenfluramine* (Ponderal[®] and other brands) and *dexfenfluramine* (Isomeride[®] and other brands) are fenfluramines developed by Servier from the 1960s onwards, and inspired by norfenfluramine, a fluorinated amphetamine derivative with mainly appetite-suppressing properties (2,3).

PAH due to appetite-suppressing amphetamines (other than fenfluramines) had been reported since the late 1960s (1,2). This effect was demonstrated with *fenfluramine* in rats by a Servier researcher in 1971 (2). Cases of PAH in patients on *dexfenfluramine* and *fenfluramine* were reported, particularly in France, and published in widely-read international journals in 1981, 1992 and 1993. A link between *fenfluramine* and *dexfenfluramine* and PAH was confirmed in 1995 by the IPPHS study, sponsored by Servier, which contributed to their withdrawal from the French market in 1997 (2).

The fact that norfenfluramine is a metabolite of fenfluramines was established in the mid-1960s (2,3). In 1972, a Servier publication mentioned norfenfluramine as a metabolite of *benfluorex*, which was actually referred to under its chemical name N-(2-benzoyloxyethyl) norfenfluramine (2).

Benfluorex is metabolised to norfenfluramine in quantities close to those found with other fenfluramines at their respective dosages, according to an internal Servier study by Gordon in 1993 (3-5). According to the company, this study was provided to the French drug regulatory agency no later than 1998, but in an incomplete form, according to the agency (4).

Was the agency misinformed? In summary, since the 1970s, data indicated that *benfluorex* had largely the same properties as other amphetamine-like drugs, including *fenfluramine*. In addition, since the mid-1990s, there were strong reasons to suspect that *benfluorex* caused PAH, just like other fenfluramines.

Nevertheless, Servier kept *benfluorex* on the market until 2009, at which time the French drug regulatory agency finally decided to withdraw it,

after the human disaster had been revealed. Some drug regulatory agency officials continued to believe the company's claim that the norfenfluramine derived from *benfluorex* was only produced in negligible quantities, or even that it was not metabolised in the same way as norfenfluramine derived from other fenfluramines (4). The "scientific absurdity" of this claim was highlighted by one of the prosecutors (b).

These facts alone are sufficient to explain why the company and the drug regulatory agency have been criticised for not withdrawing *benfluorex* from the market in the mid-1990s at the very latest (6).

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a-A link between fenfluramines and heart valve disease was discovered later (ref 1).

b- Citation from notes taken by a Prescrire editor who was present at the prosecution's closing arguments on 23 June 2020.

Selected references from Prescrire's literature search

- 1- Prescrire Editorial Staff "The Mediator[®] disaster: so much time wasted, so many lives destroyed" *Prescrire Int* 2019; **28** (210): 303-305.
- 2- Bensadon AC et al. "Enquête sur le Mediator - Rapport définitif" IGAS 2011: 261 pages.
- 3- Lechat P "Propriétés pharmacologiques du benfluorex" Afssaps 31 December 2010: 33 pages.
- 4- "Procès Mediator: l'ex-chef de la vigilance évoque une "confusion" autour des données de métabolisation du médicament" *APMnews* 20 November 2019: 3 pages.
- 5- Prescrire Rédaction "Maître Charles Joseph-Oudin: "Un procès à visée prophylactique"" *Rev Prescrire* 2019; **39** (433): 871-1-871-2.
- 6- "Mediator: Servier a manqué à son obligation de sécurité et de prudence, l'ANSM a fauté par négligence (procureur)" *APMnews* 25 June 2020: 3 pages.