

sildenafil and mild pulmonary arterial hypertension

NEW INDICATION

Unjustified risks, with no tangible benefit

Only one retrospective subgroup analysis



NOT ACCEPTABLE

For patients with mild (stage II) pulmonary arterial hypertension, two endothelin receptor antagonists are available, but neither has any proven impact on survival, clinical complications or symptoms. However, both have frequent and potentially severe adverse effects (1,2).

Sildenafil (Revatio®, Pfizer), a type 5 phosphodiesterase inhibitor, is also authorised for use in this indication. Clinical evaluation is based on a placebo-controlled trial, in 277 symptomatic patients (stage III), that was submitted in support of the marketing application (3,4). The subgroup of mildly symptomatic patients (39% of the study population) was analysed retrospectively. Only 24 patients received a dose of 20 mg 3 times a day. The mean 6-minute walking distance increased by about 50 m, a statistically significant improvement (1,4).

Adverse effects were frequent, and included headache (41.7%), dizziness (16.7%), and abdominal pain (12.5%). One patient experienced severe left ventricular dysfunction, an effect the investigators attributed to *sildenafil* (4). *Sildenafil* carries a risk of haemorrhage and neurosensory and cutaneous disorders (4). It also has a high potential for drug-drug interactions (3).

In practice, the adverse effects of *sildenafil* outweigh its documented benefits in patients with mildly symptomatic pulmonary hypertension.

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Selected references from Prescrire's literature search.



In response to our request for information, Pfizer only provided us with basic administrative documents.

- 1- Prescrire Editorial Staff "Ambrisentan" *Prescrire Int* 2009; **18** (100): 54.
- 2- Prescrire Editorial Staff "Bosentan" *Prescrire Int* 2009; **18** (100): 55.
- 3- Prescrire Editorial Staff "Sildenafil" *Prescrire Int* 2006; **15** (86): 221.
- 4- European Medicines Agency "Assessment report for Revatio. EMEA/H/C/638/II/0021" 7 July 2009: 16 pages.

sildenafil

Tablets

- 20 mg of *sildenafil* per tablet

vasodilator; type 5 phosphodiesterase inhibitor

■ New indication:

"Patients with pulmonary arterial hypertension classified as WHO functional class II, (...) to improve exercise capacity (...) in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease".

[EU marketing authorisation, centralised procedure; orphan drug status]

benfluorex

MARKET WITHDRAWAL

EU Marketing authorisation finally withdrawn

This amphetamine derivative was marketed for more than 30 years in France despite its lack of tangible efficacy in diabetes and hypertriglyceridaemia, and its potentially severe cardiovascular effects.

In late 2009 the French Health Products Safety Agency (Afssaps) suspended marketing authorisation for *benfluorex*-containing products and ordered their market withdrawal (1). This decision triggered a European reassessment intended to modify, suspend or withdraw marketing authorisation for *benfluorex*-containing products throughout the European Union (2).

In June 2010 the European Commission endorsed the opinion of the European Committee for Medicinal Products for Human Use (CHMP) and ordered that these marketing authorisations be with-

drawn (2). According to CHMP "*benfluorex is harmful (...) leading to pulmonary hypertension and cardiac valvulopathies*" (2). The risk of severe cardiovascular adverse effects with *benfluorex* had been known for many years (1).

It was high time to withdraw this amphetamine derivative, which had been sold for many years in various countries, including France, despite the lack of proven benefits in patients with diabetes or hypertriglyceridaemia (1). See the Prescrire in English website for further information (www.english.prescrire.org) (3).

This withdrawal, although welcome, is yet another example of health authorities' incapacity to protect citizens from drugs with unfavourable risk-benefit balances in a timely manner. Healthcare professionals must therefore take time to inform themselves, based on reliable and inde-

pendent sources, in order to avoid exposing their patients to a risk of potentially life-threatening adverse effects.

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Selected references from Prescrire's literature search.

- 1- Prescrire Rédaction "Benfluorex: enfin retiré du marché!" *Rev Prescrire* 2010; **30** (315): 13.
- 2- European Commission "Commission decision of 14.6.2010 concerning, in the framework of Article 107 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations for medicinal products for human use which contain the active substance "benfluorex" + "Annex" 14 June 2010: 10 pages au total.
- 3- Prescrire Editorial Staff "Benfluorex (Mediator® or other brands): marketing authorisation withdrawn throughout the European Union" 1 July 2010. www.english.prescrire.org: 1 page.