Benfluorex (Mediator®, Servier) was marketed in France in 1976 (a). Chemically speaking, benfluorex is related to other appetite suppressants like fenfluramine (Servier) (b) (1). One of its approved indications, as “an adjunct to dieting in asymptomatic overweight diabetic patients,” has regularly been promoted over the years (c) (2). To reply to readers’ questions on the possible value of benfluorex in diabetes, and to answer claims by medical representatives that benfluorex is as effective as metformin, we examined the clinical assessment file (d).

The main aims of treating diabetes are to prevent clinical complications and reduce mortality. On the basis of these criteria, the value of the various oral antidiabetics currently on the market is poorly established (3,4). Is benfluorex any different in these respects?

**Slight laboratory effects in the short term**

Most of the comparative trials mentioned in the Servier information brochure (5) are published.

**Placebo-controlled trials.** We found 6 trials comparing benfluorex with a placebo in double-blind manner in patients with non-insulin-dependent diabetes (5-10). These trials all had similar designs: after a preinclusion (placebo) phase of 1 month in most cases, aimed at checking the stability of the diabetes, patients received a three-month course of a placebo or benfluorex (450 mg/day by mouth) in double-blind manner. The only end points for efficacy were laboratory criteria (see page 109). One trial involved patients on a low-calorie diet and no other antidiabetic drugs (6); 3 trials involved overweight patients also receiving insulin (5,7-9); 2 trials involved patients also receiving a glucose-lowering sulphonamide (5,10).

According to the American Diabetes Association, the aim of treatment is to bring fasting blood glucose levels down to 6.7 mmol/l (approximately 12 g/l) and glycated haemoglobin down to 7% (11). In only two of the six trials did benfluorex show greater efficacy than the placebo in reducing fasting blood glucose, and average figures fell below 6.7 mmol/l in only one trial (7). In the five trials in which the comparison was possible, the effect of benfluorex on glycated haemoglobin was statistically superior to that of the placebo, but only in one trial did the average level of glycated haemoglobin fall below 7% (7). With the exception of one trial (7), benfluorex failed to influence fasting insulin levels relative to the placebo. Benfluorex yielded a statistically significant reduction in daily insulin requirements in only one of the three trials involving patients treated with insulin (9). None of these placebo-controlled trials showed an effect of benfluorex on morbidity or mortality, but these end points were not provided for by the protocol (e).

**Trial versus metformin.** A trial comparing benfluorex with metformin in 121 patients was published, but the results were uninterpretable because of major sources of bias (12). At baseline the patients in the metformin group had statistically lower postprandial blood glucose levels and a statistically smaller area under the curve for glucose tolerance test than the patients in the benfluorex group. Yet the main end point was changes in blood glucose in an oral glucose tolerance test. Furthermore, the trial was not blinded.

**In brief.** Available trials show that benfluorex has effects, at least in the short term (3 months), on certain indices of blood glucose balance, particularly glycated haemoglobin. Benfluorex failed to influence fasting insulin levels relative to the placebo. Benfluorex yielded a statistically significant reduction in daily insulin requirements in only one of the three trials involving patients treated with insulin (9). None of these placebo-controlled trials showed an effect of benfluorex on morbidity or mortality, but these end points were not provided for by the protocol (e).

**Licensed indication in diabetes:**

“Adjunct to dietary measures in asymptomatic overweight diabetic patients.”
Double-blind comparative clinical trials of benfluorex (B) versus placebo (P)

<table>
<thead>
<tr>
<th>Réf.</th>
<th>Number of patients</th>
<th>Other treatment</th>
<th>Fasting blood glucose (mmol/l)</th>
<th>Glycated haemoglobin (%)</th>
<th>Fasting blood insulin</th>
<th>Other results</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>32</td>
<td>no</td>
<td>B -1.3 (±1.0) P -0.5 (±1.3)</td>
<td>NS</td>
<td>p=0.024</td>
<td>B -4.9 (±4.3) P -2.7 (±5.0) NS</td>
</tr>
<tr>
<td>5.7</td>
<td>20</td>
<td>insulin</td>
<td>B -3.0 (±1.9) P -1.6 (±3.3)</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>B -0.3 (±8.5) P +0.11 (±10.1) p=0.02</td>
</tr>
<tr>
<td>5.8</td>
<td>30</td>
<td>insulin</td>
<td>B -0.5 (±2.5) P +1.7 (±3.0)</td>
<td>NS</td>
<td>p=0.006</td>
<td>B -10.2 (±12.7) P -5.0 (±6.8) NS</td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>insulin</td>
<td>B -1.45 (±5.28) P +0.15 (±3.88)</td>
<td>NS</td>
<td>heterogeneous at inclusion</td>
<td>not stated</td>
</tr>
<tr>
<td>5 (*)</td>
<td>25</td>
<td>sulphonylurea</td>
<td>B -1.6 (±1.9) P +0.2 (±2.3)</td>
<td>p=0.046</td>
<td>B -0.5 (±1.0) P +1.2 (±2.1) p=0.023</td>
<td>B -4.8 (±4.7) p=0.07 (±3.6) NS</td>
</tr>
<tr>
<td>5.10</td>
<td>68</td>
<td>sulphonylurea</td>
<td>B -1.4 (±27) P -0.3 (±27)</td>
<td>p=0.009</td>
<td>B -0.66 (±1.14) P -0.14 (±1.04) p=0.007</td>
<td>B -0.8 (±4.0) P -1.3 (±3.6) NS</td>
</tr>
</tbody>
</table>

* Study by Louvet

**Adverse effects?** Given the lack of independent data it is impossible to know the precise pattern of adverse effects on benfluorex. According to Servier “the most common adverse effects of benfluorex are gastrointestinal (nausea, vomiting, gastroparesis and diarrhea) but also include fatigue, drowsiness and dizziness. These only occur at doses of more than 3 tablets a day and vary from patient to patient” (5). These claims do not match data from four clinical trials in which benfluorex was used at a dose of 3 tablets a day (450 mg) and in which the same adverse effects were observed (10,13-15). In these small trials, involving the recommended dose of 450 mg/day, drowsiness occurred in 7 to 10% of patients on benfluorex (1), and diarrhoea was observed in 25% of patients in a non-comparative trial (13). In another trial 5 of the 34 patients stopped taking benfluorex because of adverse effects, compared to 2 of the 34 patients in the placebo group (10).

**Conclusion.** Even though it has been on the market for 20 years, it is unclear whether benfluorex benefits diabetic patients. No long-term trials with morbidity or mortality endpoints are available.

A few placebo-controlled trials lasting only 3 months and involving non-insulin-dependent diabetics showed that benfluorex alone or in combination with insulin or a glucose-lowering sulphonylamide reduced glycated haemoglobin levels. A reduction in fasting blood glucose was observed in only two of the six relevant trials. These effects were only mild, rarely returning these parameters to within “normal” limits. The only trial comparing benfluorex with metformin is uninterpretable.

Benfluorex has adverse effects at the recommended dose of 450 mg/day, including drowsiness and diarrhoea, but neither the frequency nor the type of adverse effects is correctly documented.

There is currently no basis for treating noninsulin-dependent diabetics with benfluorex. The French health authorities should reconsider their decision to license and reimburse this product.

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**References**