

**ANNEX I**

**LIST OF THE INVENTED NAMES, PHARMACEUTICAL FORMS, STRENGTH OF THE  
MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION AND MARKETING  
AUTHORISATION HOLDERS IN THE MEMBER STATES (EEA)**

<u>Member State (EEA)</u>	<u>Marketing Authorisation Holder</u>	<u>Invented Name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>
CY - Cyprus	Les Laboratoires Servier 22, rue Garnier F- 92200 Neuilly-sur-Seine France	Lipophoral Tablets 150mg	150mg	tablet	oral
FR - France	Les laboratoires Servier 22 rue Garnier F-92200 Neuilly-sur-Seine France	Mediator	150 mg	tablet	oral
FR - France	Mylan SAS 117 allée des Parcs 69800 Saint-Priest France	Benfluorex Mylan	150 mg	tablet	oral
FR - France	Qualimed 117 allée des Parcs 69800 Saint-Priest France	Benfluorex Qualimed	150 mg	tablet	oral
LU - Luxembourg	Les Laboratoires Servier 22, rue Garnier F- 92200 Neuilly-sur-Seine France	Mediator	150mg	tablet	oral
PT - Portugal	Servier Portugal - Especialidades Farmacêuticas, Lda. Av. António Augusto de Aguiar 128, 1069-133 Lisboa Portugal	Mediator	150 mg	coated tablet	oral

**ANNEX II**

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE REVOCATION OF THE  
MARKETING AUTHORISATIONS PRESENTED BY THE EUROPEAN MEDICINES  
AGENCY**

## SCIENTIFIC CONCLUSIONS

### OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING BENFLUOREX (see Annex I)

Benfluorex is used as an adjunct in the management of type 2 diabetes mellitus in overweight patients. The currently authorised therapeutic indication in France is as « *Adjuvant therapy of overweight diabetics, in combination with an appropriate diet* ». Benfluorex has an action on carbohydrate metabolism. In animals, the following effects have been observed:

- Facilitation of precipitation and use of glucose in cells (rats);
- Reduction in hyperglycaemia in diabetic rats (insulin deprived or not), decrease in hyperglycaemia (measured by the glucose tolerance test area) in rabbits.

Benfluorex has no action on insulin-secretion.

Medicinal products containing benfluorex are authorised in four EU Member States with a tablet formulation, with only 2 countries (France and Portugal) in which the product was marketed up to the suspension of the Marketing Authorisations in November 2009 (see Annex I for the list of benfluorex containing medicinal products authorised in the EU). In Cyprus and Luxembourg, medicinal products containing benfluorex were not marketed any longer.

On 25 November 2009, the French Competent Authority (Afssaps) issued a Rapid Alert informing the Members States, the European Medicines Agency and the European Commission in accordance with Article 107 of Directive 2001/83/EC, as amended, of its decision to suspend the marketing authorisations of all benfluorex containing medicinal products in France due to an increased risk of a cardiotoxicity signal (valvular heart diseases) with benfluorex.

The decision of the French Competent Authority was based on updated results of a Pharmacovigilance (PV) survey, preliminary data from 3 clinical studies (the retrospective case-control study performed in a Brest hospital, the REGULATE trial and the data from the French National Insurance Fund) and from a recent publication (K. Boutet *Fenfluramine-like cardiovascular side-effects of benfluorex*, Eur Respir. J. 2009; 33: 684-688) that have shown a risk of cardiac valve diseases and pulmonary hypertension (PHT) for patients treated with benfluorex.

Further to receipt of the Rapid Alert, the Portuguese Competent Authority also decided to suspend the marketing authorisation of all benfluorex containing medicinal products in Portugal on 30 November 2009.

The CHMP considered the matter in accordance with Article 107(2) of Directive 2001/83/EC, as amended, during a written procedure, during the December 2009 and March 2010 CHMP plenary meetings.

### Safety

Updated results of the pharmacovigilance survey regarding the risk of cardiac valve diseases with benfluorex and data from a recent publication on this subject (K. Boutet *Fenfluramine-like cardiovascular side-effects of benfluorex*, Eur Respir. J. 2009; 33: 684-688) lead to the conclusion of an existence of cardiac valvulopathy and PHT in the general population of patients using benfluorex.

In addition, the retrospective case-control study conducted in Brest in order to look for a link between exposure to benfluorex and the occurrence of unexplained mitral insufficiency, establishes an association between the exposure to benfluorex and the occurrence of valvulopathy.

Based on the aforementioned data, the CHMP considers that the link between exposure to benfluorex and the occurrence of cardiac valve diseases is confirmed. The Committee is of the opinion that the link is supported by the results shown in the REGULATE study which confirms the risk of

valvulopathy with benfluorex and reveals the occurrence of morphological and functional valve anomalies after an average of only 328 days of exposure.

Furthermore, the results of an additional study (cohort study conducted by the French National Insurance Fund) were commented upon by the MAH in their response document to the List of Questions adopted by the Committee. The imprecision regarding information about the diagnosis of cardiac valve disease and the limited number of patients identified as presenting cardiac valve disease and treated with benfluorex (35 patients) were pointed out by the MAH. However, the CHMP maintains the opinion that these data further confirm the safety signal of a risk of cardiac valve disorders with the use of benfluorex.

Finally, on the basis of the available data sources, the CHMP is of the opinion that the number of spontaneous reports of cardiac valvulopathies associated with benfluorex is significantly underestimated due to limitations of data collected from spontaneous reporting in this situation such as:

- the type of effect of benfluorex (valvulopathy which remains clinically asymptomatic for a long period of time);
- the time to event (a very long period of exposure to Benfluorex is necessary to induce valvular changes).

Therefore, the CHMP is of the opinion that aggravation of the functional anomalies in case of prolonged exposure could not be ruled out, particularly given the prolonged use of the product based on utilisation data, which showed an average exposure time of 3 years.

As stated in the MAH's written response, at the time of the national evaluation of the cardiac valvular abnormality, the MAH proposed to maintain benfluorex on the market with a restriction to the indication in patients with no ultrasound evidence of valve anomalies and the implementation of echocardiographic monitoring. The MAH projected to discontinue the treatment in the event of echocardiographic anomalies.

The CHMP did not accept this proposal. The CHMP is of the opinion that additional echocardiographic monitoring as proposed by the MAH could not solve this issue due to the fact that echocardiographic monitoring prevent the use in patients with previous valvulopathy but do not prevent the development in patients who have no previous abnormalities.

### **Benefit/risk**

Benfluorex is used as an "*Adjuvant therapy of overweight diabetics, in combination with an appropriate diet*". The MAH, in their written response, considers that there is a consistent significant clinical effect on blood glucose control in all the studies performed with benfluorex in overweight type 2 diabetic patients. However the CHMP notes that benfluorex is approved only as an adjuvant therapy in the treatment of type 2 diabetes in overweight patients: on the basis of very limited relevance of efficacy in diabetic patients, an indication as monotherapy for treatment of diabetes was never granted for benfluorex. Therefore, the CHMP, after review of the data provided by the MAH and the Member State, considers that the benefit of benfluorex is only limited in the management of type 2 diabetes.

The updated results of the second national Pharmacovigilance survey, the preliminary data from 3 clinical studies (the retrospective case-control study performed in a Brest hospital, the REGULATE trial and the data from the French National Insurance Fund) and the recent publication from K. Boutet demonstrate the serious risk of cardiac morphological and functional valvulopathies and pulmonary hypertension associated with the use of benfluorex.

The Committee noted that morphological and functional valvular heart abnormalities can be seen after an average of only 328 days of exposure. Furthermore, aggravation of the functional abnormalities in case of prolonged exposure is not ruled out; this is of particular concern given the prolonged use of the product with an average exposure time of 3 years (based on utilisation data).

Taking all these elements into account, the CHMP concluded that the medicinal products containing benfluorex are harmful under the normal conditions of use, and that the benefit/risk balance for benfluorex is not considered favourable. Therefore the Committee recommended the revocation of the Marketing Authorisations for the medicinal products referred to in Annex I.

## **GROUNDS FOR THE REVOCATION OF THE MARKETING AUTHORISATIONS**

Whereas,

- The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended, for medicinal products containing benfluorex.
- The Committee concluded, after having reviewed the available data, that benfluorex is harmful under normal conditions of use leading to pulmonary hypertension and cardiac valvulopathies. Such valvulopathies have the potential to induce progressive impairment of cardiac function and associated clinical symptoms requiring, in the severe cases, cardiac surgery.
- The Committee noted that morphological and functional valvular heart abnormalities can be seen after an average of only 328 days of exposure. Furthermore, aggravation of the functional abnormalities in case of prolonged exposure is not ruled out; this is of particular concern given the prolonged use of the product with an average exposure time of 3 years (based on utilisation data).
- The Committee considered the benefit-risk ratio of benfluorex under the normal conditions of use and considered that the aforementioned proven risk of cardiac valve disease is not acceptable, taking into account that the benefit of benfluorex is only limited in the treatment of type 2 diabetes.
- The Committee, in light of the above findings, concluded that the benefit/risk balance of benfluorex containing medicinal products is not favourable under the normal conditions of use.

Following the provisions under Article 107(2) of Directive 2001/83/EC, as amended, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommends the revocation of the Marketing Authorisations for all benfluorex containing medicinal products listed in Annex I.