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Patient Health Protection

Benfluorex

Summary background on discussions at CPMP (1998), PhVWP (1998-2003) and CHMP (2009)

This document summarises the discussions on the safety of benfluorex-containing medicines by the Committee for Medicinal Products for Human Use (CHMP), which was formerly known as the Committee for Proprietary Medicinal Products (CPMP), and by the Pharmacovigilance Working Party (PhVWP), between 1998 and 2009.

The CPMP/CHMP is involved in the authorisation, maintenance and supervision of medicinal products for human use processed through the centralised procedure, as well as referrals made to the European Medicines Agency for non-centrally authorised products (nationally authorised medicinal products, authorised through the mutual-recognition procedure, decentralised procedure or national procedures).

The PhVWP's involvement in the safety monitoring of medicines reflects the operation of the European pharmacovigilance system since the creation of the Agency in 1995. Its mandate is in accordance with the duality of the system:

1. reporting to the CPMP/CHMP on centrally authorised products and nationally authorised products referred to the Agency;
2. reporting to the National Competent Authorities of the Member States for nationally authorised products not subject to a referral procedure. For such nationally authorised products, the PhVWP acts as a discussion platform for the Member States and its recommendations (including, where relevant, recommendations for regulatory action) are not legally binding on the Member States.

Chronology of discussions

- During the CPMP meeting of October 1998 a letter from the Italian CPMP member to the Agency "asking whether benfluorex can be considered as a fenfluramine containing product due to its related chemical structure was circulated and discussed. The CPMP considered that benfluorex should not be included in the scope of the new referral on anorectics (it is a mediator anorectic agent). It was agreed that the PhVWP would investigate if there is a safety issue with this compound." (extract of the minutes of the CPMP meeting of October 1998)

Explanatory note: Three referral procedures under Article 15a of Council Directive 75/319/EEC triggered by Member States for anorectic agents were ongoing at the time at the level of the CPMP.

- In November 1998 the PhVWP concluded the following (extract of the minutes of the PhVWP meeting of November 1998):

"At their meeting in October 1998, the CPMP considered a letter from ... concerning benfluorex which is an active substance used in the treatment of obesity because of its anti-hyperlipoproteinemic effect. It could possibly be metabolised to fenfluramine which is subject to an ongoing Article 15a Referral because of heart valve disorders. The CPMP agreed that the PhVWP should investigate if there is a safety issue with this active substance. Benfluorex containing products are authorised in France, Greece, Italy and Spain. A French investigation has not provided any evidence for a safety concern. In Italy, a problem of misuse might exist. The PhVWP agreed that Italy as Rapporteur will request data on metabolism and a safety update from the marketing authorisation holder. Italy will then prepare an Assessment Report for further discussion in February 1999. If necessary, a new Article 12 procedure could be initiated because benfluorex was not included in any of the previously initiated referral procedures."

- In March 1999 the PhVWP Italian Member presented the Assessment Report (dated February 1999) to the PhVWP.

This report concludes that:

"It is reasonable that ...benfluorex is referred to CPMP under art. 12 procedure for complete risk/benefit reassessment. In this respect, it should be asked to the Company to provide:

- *Preclinical and clinical studies on cardiovascular effects of repeated doses of benfluorex and toxicological studies about neurotoxicity*
- *Complete case reports for cerebrovascular, nervous, pulmonary and cardiac adverse reactions;*
- *Confidence limits of norfenfluramine plasma levels after repeated doses of benfluorex;*
- *Further data on long-term efficacy of benfluorex therapy."*

Following this presentation the PhVWP agreed that *"there was no major benefit-risk concern for benfluorex containing medicinal products. Italy is considering to withdraw the indication of obesity and to update the section on undesirable effects in their Summary of Product Characteristics with regard to potential cardiotoxicity. For June 1999, the Italian Member, in co-operation with the French colleagues, will circulate a revised Assessment Report taking into account the individual case safety reports submitted to the French authorities."* (extract of the minutes of the PhVWP meeting of March 1999)

- A further Assessment Report prepared by Italy was circulated to the PhVWP on 2 June 1999.

In this Assessment Report it is concluded that:

"We agree with French colleagues that on the basis of the data deriving from spontaneous monitoring there is no definitive evidence of neurotoxicity and cardiotoxicity of benfluorex in humans, but there are elements of suspicion to require that precautions are adopted to further monitor the issue, especially to prevent long term adverse effects. The following actions are possible:

- *Referral of benfluorex to CPMP by Italy and France;*
- *Request the company to provide preclinical and clinical studies on cardiovascular effects of repeated doses of benfluorex and toxicological studies about its neurotoxicity, further elements*

for cerebrovascular, nervous, pulmonary and cardiac adverse reactions if available, confidence limits of norfenfluramine plasma levels after repeated doses of benfluorex, further data on long-term efficacy of benfluorex therapy;

- *Ask the company to perform, as suggested by French colleagues, a pharmacokinetic study on benfluorex and its metabolites, especially norfenfluramine after a single dose and after several days of treatment.*
- *Reduction of indications of benfluorex containing medicinal products. Updating of adverse effects, contraindications and special warnings sections of SPC, with particular regard to cardiac function monitoring, possibly by echocardiography for long term use and contraindication in case of preexisting hypertension or cardiovascular and/or cerebrovascular diseases."*

During the June 1999 PhVWP meeting *"the Italian Member informed the PhVWP that, as suggested by the French colleagues, pharmacokinetic studies on benfluorex and its metabolites will be requested from the marketing authorisation holder. The Italian and French Members will prepare an updated Assessment Report for discussion by the PhVWP in September 1999."* (extract of the minutes of the PhVWP meeting of June 1999).

- In November 1999 the Italian Assessment Report prepared in collaboration with the French colleagues was presented to the PhVWP.

In this Assessment Report it is concluded that a List of Questions would be sent to the MAH by France and in case the data requested in the questions would not be available, *"the MAH should carry out a long term study (more than one year) with periodic echocardiographic, glycaemic, serum lipid levels level controls and measurement of pharmacokinetic parameters"*. In addition, changes to the Summary of Product Characteristics (SPC) were also proposed.

The minutes of the meeting state that *"together (France and Italy) they had agreed upon a List of Questions regarding efficacy and safety in drug use longer than 6 months to be sent to the marketing authorisation holder. In France, an efficacy review is currently awaited from the national advisory board. Italy and France will assess the response from the marketing authorisation holder for discussion in May 2000 when France will also report upon their efficacy review. An oral update will be provided in January 2000."*

Explanatory note: Looking at the last assessment report and the conclusions of the PhVWP, no further consideration appears to have been given to the option of making a referral under Article 12 of Council Directive 75/319/EEC.

- Further to the above discussions benfluorex appeared in the agendas of the PhVWP in January, February, July, October and November 2000 and March 2001 where oral updates were provided by France and Italy with regards to the answers provided by the marketing authorisation holder and on the progress on the study protocol requested to the marketing authorisation holder by these Member States. No further Assessment Report or protocol of the study was circulated or discussed by the PhVWP.
- In January, May, July and October 2003 benfluorex appeared in the Drug Monitor (a tool used as a sharing of information between Member States to update on the progress made on product related issues) which was routinely circulated for information at each PhVWP meeting. The Drug Monitor provides factual information on the withdrawal by Servier of the marketing authorisations for benfluorex in Italy and Spain.
- In November 2009 the CHMP became involved in the evaluation of benfluorex containing medicines in the context of a procedure under Article 107 of Directive 2001/83/EC further to the suspension

of the marketing authorisations in France. The CHMP adopted an Opinion in December 2009 recommending the revocation of the marketing authorisations.