April 29, 1996

David Kessler, M.D., J.D.
Commissioner, Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

Public Citizen, representing 90,000 consumers, urges the FDA to delay approval for the weight control drug dexfenfluramine (Redux, Wyeth-Ayerst/American Home Products) until questions about its effectiveness, public health benefit and most importantly its safety are resolved. It is our understanding that the FDA is about to approve this drug from an advertisement appearing in the May 1, 1996 *Annals of Internal Medicine*. FDA approval of dexfenfluramine for indefinite use would signify to consumers that dexfenfluramine is effective; has been proven safe for life time use; that dexfenfluramine reduces the health risks of obesity; and the health benefits derived from dexfenfluramine outweigh any potential risks of using the drug. Even in France and the United Kingdom where the drug is approved its use is restricted to three months. In December 1995, 22 neurologists and other neuroscientists wrote the FDA asking that the approval of dexfenfluramine be delayed until the drug's neurotoxicity had been properly evaluated (see attached letter).

Public Citizen has just learned that a year ago Health Ministers in the United Kingdom conducted an investigation into the prescribing of appetite suppressants, including dexfenfluramine.[i] Serious adverse reactions have been reported with these drugs including 15 deaths, and reports of addiction, insomnia and depression. We contacted the U.K.'s Medicines Control Agency and confirmed that there are 15 reports of deaths with these drugs, though a causal relationship has not yet been established.[1]

In light of these recent reports of severe adverse reactions including deaths from the U.K. and valid safety concerns about primary pulmonary hypertension and long term neurotoxicity we urgently request that these reports be carefully examined and any action on dexfenfluramine's approval be suspended.

Public Citizen's concern arises from the evidence showing dexfenfluramine only results in a meager weight loss[ii,iii,iv] ,a degree of loss that is of unknown value in reducing the health risks of obesity; its association with a rare but serious adverse reaction, primary pulmonary hypertension (PPH)[v], and unanswered questions about its potential to cause neurotoxicity in humans.

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[1] Personal Communication with Dr. Matthew Thatcher, Medicines Control Agency, April 26, 1996.

Dexfenfluramine has been linked to a rare and sometimes fatal adverse drug reaction, PPH.[5] An international study undertaken to assess the role of weight control drugs, including dexfenfluramine, as causes of PPH found a strong association between those who had used dexfenfluramine or other weight control drugs for more than three months and the development of PPH.[2] In France and the United Kingdom, drug regulatory authorities have restricted the use of dexfenfluramine to three months because of its association PPH.[vi,vii]

Experiments have shown dexfenfluramine to alter brain structure and function in laboratory animals.[viii,ix,x] Controversy exists in the neuroscience community and unanswered questions remain about the meaning of results seen in laboratory animals and the potential for dexfenfluramine to cause neurotoxicity in humans. Neuroscientists first wrote the FDA in 1993 declaring their concerns about the safety of dexfenfluramine with the suggestion to convene a scientific advisory committee to address the safety and public health issues surrounding this drug.[3] In response to these concerns and suggestion the FDA agreed that a special advisory committee would be of great assistance in the evaluation of dexfenfluramine.[4] Again, in December 1995 neuroscientists contacted the FDA with the same concerns and the same suggestion for the evaluation of dexfenfluramine by a special scientific advisory committee.[5] To the best of our knowledge these serious concerns have not been adequately addressed.

In light of dexfenfluramine's limited effect in reducing weight, its unknown long term benefit, if any, and its association with PPH Public Citizen strongly supports the request of neuroscientists to delay approval until the question of neurotoxicity is resolved.

Dexfenfluramine has been available in European countries for years and has not proven to be a major therapeutic breakthrough nor has it been shown to have a positive impact on the

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[2] Interoffice Memorandum: International Primary Pulmonary Hypertension Study, to Leo Lutwak, M.D., Ph.D., Medical Officer, from Bruce V. Stadel, M.D., M.P.H., Medical Officer/Epidemiology. September 8, 1995.

[3] Letter to David A. Kessler, M.D., Commissioner, Food and Drug Administration, from George A. Ricaurte, M.D.,Ph.D., Lewis S. Seiden, Ph.D., Charles R. Schuster, Ph.D., Mark Molliver, M.D., John Harvey, Ph.D., Stephen Peroutka, M.D., Ph.D. December 10, 1993.

[4] Letter to George A. Ricaurte, M.D., Ph.D., Department of Neurology, Johns Hopkins University from Solomon Sobel, M.D., Director, Division of Metabolism and Endocrine Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration. January 3, 1994.

[5] Letter to Solomon Sobel, M.D., Director, Division of Metabolism and Endocrine Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration from George Ricaurte, M.D., Ph.D. and twenty-one other neuroscientists. December 7, 1995.

public's health by reducing the health risks of obesity. Similarly, the mixture of dexfenfluramine and levofenfluramine has been sold in the United States for years as the drug Pondamin (fenfluramine) and we are aware of no scientific evidence that dexfenfluramine and levofenfluramine in combination reduces the health risks of obesity.

Manufacturers have had years to conduct the research necessary to show a benefit for dexfenfluramine and fenfluramine. This has not been done.

The following summarizes Public Citizen's concerns about dexfenfluramine:

1. On average, studies show those taking dexfenfluramine may lose up to 7.5 pounds more weight than those taking placebo after one year.[2,3,4]

2. Those who use dexfenfluramine for longer than three months are nine times more likely to have primary pulmonary hypertension than those who had never used the drug.[5]

3. Drug regulatory authorities in France and the United Kingdom have restricted the use of dexfenfluramine to three months because of its association with PPH.[6,7]

4. Members of the neuroscience community are concerned about dexfenfluramine's neurotoxic potential in humans. (footnotes c and e)

Each of these points is discussed in detail below.

THE EFFECT OF DEXFENFLURAMINE ON WEIGHT LOSS

Three studies were identified by the manufacturer as pivotal in showing the effectiveness of dexfenfluramine in reducing weight and establishing that the drug could be used indefinitely by the public. Of these three trials the longest, the International Dexfenfluramine Trial (INDEX), lasted only one year, and was originally published in 1989.[2] Two additional studies testing dexfenfluramine were located each lasting only one year.[3,4] One of these constituted the Danish study group of the INDEX Trial.4 The results of these three trials are summarized below in Table 1.

Table 1 - Summary of One Year Long Clinical Trials Comparing Dexfenfluramine Plus Diet to a Placebo Control Plus Diet

	INDEX Trial[¶]	Mathus-Vliegen et al.[3]	Andersen[§] et al.[4]
Study Duration	12 months	12 months	12 months
Study Design	Multicenter, randomized, placebo-controlled	Single Center, randomized, placebo-controlled	Single Center, randomized, placebo-controlled

	INDEX Trial[¶]	Mathus-Vliegen et al.[3]	Andersen[§] et al.[4]
Treatment Groups (numbers randomized / numbers analyzed)	Drug - 520/463 Placebo - 527/467	Drug - 36/36 Placebo - 39/39	Drug - 21/ Placebo - 21/
Dexfenfluramine Dose	15 mg twice daily	15 mg twice daily	15 mg twice daily
Diet	Restricted	Restricted	Restricted
Mean Baseline Weight	Drug - 96.8 kg or 213.4 lbs Placebo - 97.4 kg or 214.7 lbs	Drug - 111.2 kg or 245.2 lbs Placebo - 110.3 kg or 244.2 lbs	Drug - 92.5 kg or 203.9 lbs Placebo - 106.6 kg or 235.0 lbs
Mean Weight Loss from Baseline	Drug - 8.2 kg or 18.1 lbs Placebo - 4.8 kg or 10.6 lbs	Drug - 10.7 kg or 23.6 lbs Placebo - 8.0 kg or 17.6 lbs	Approximately 10 kg or 22 lbs
Absolute Difference in Mean Weight Between Groups at End of Study	3.4 kg or 7.5 lbs	2.7 kg or 6 lbs	No difference between drug and placebo groups
Statistical Significance	Statistically Different	Not Statistically Different	Not Statistically Different

¶ Data from Statistical Review and Evaluation of Dexfenfluramine Hydrochloride Capsules, prepared by Lee-Ping Pian, Ph.D., FDA Mathematical Statistician, May 6, 1994. § Danish study group of the INDEX Trial.

Excluding the 21 patients in the report of the Danish study group of the INDEX Trail a total of 499 patients have been given dexfenfluramine and a restricted diet or diet counseling for one year in controlled clinical studies.

The best estimate of the amount of weight that consumers can expect to loose at the end of one year with diet and dexfenfluramine is 6 to 7.5 pounds, and the actual contribution of dexfenfluramine is uncertain.

ADVERSE EFFECTS: PRIMARY PULMONARY HYPERTENSION (PPH)

The International Primary Pulmonary Hypertension Study (IPPHS) was undertaken to assess the role of several known or suspected risk factors in the development of PPH, including dexfenfluramine and other weight control drugs. Detailed histories of 95 persons who were diagnosed with PPH between September 1992 and September 1994 were compared to 355

persons not having PPH. Major findings of the IPPHS were:

1. Those who had used dexfenfluramine or other weight control drugs for longer than three months were about nine times more likely to have PPH than those who had never used these drugs. Odds ratio (OR) and 95% confidence interval (95% CI); OR = 9.1, 95% CI 2.6 to 31.5) There was no significant increase in the risk among those who had used the drugs for three months or less. (OR = 1.9, 95% CI 0.5 to 6.9)

2. The increased risk of PPH was concentrated in those who had used dexfenfluramine or other weight control drugs within the year before being studies (OR = 5.9, 95% CI 2.1 to 16.9) There was no significant increase in those who had stopped using the drugs more than one year before being studied (OR = 2.4, 95% CI 0.6 to 8.8).

3. These results represent the risks primarily for dexfenfluramine, as this was the principal drug used.

The FDA epidemiologist who reviewed the IPPHS found it scientifically sound and commented it provided the best source of information about the effect of using dexfenfluramine or other weight control drugs on the occurrence of PPH.(footnote b) The FDA epidemiologist concluded that the IPPHS provides strong evidence that the use of dexfenfluramine or other weight control drugs by women for over three months increases the risk of developing PPH, and that the increased risk persists for up to one year after the drugs are discontinued.

EUROPEAN REGULATION OF DEXFENFLURAMINE

European drug regulatory authorities are concerned about the association between dexfenfluramine and PPH. In the United Kingdom, the Committee on Safety of Medicines (the British equivalent of the FDA) advised doctors in 1992 not to prescribe dexfenfluramine for longer than three months. The British authorities specifically stated:

> "The serious nature of this reaction [PPH] is nevertheless cause for concern, especially in relation to the lack of evidence of long-term benefit associated with these drugs [including dexfenfluramine].[6]

The French health ministry has made similar recommendations. Appetite suppressants, including dexfenfluramine, are considered second line treatment after failure of appropriate dietary measures, and there use should be limited to three months.[7]

NEUROTOXICITY

Central to the controversy over the potential for dexfenfluramine to cause neurotoxicity is the interpretation of data from animal studies and its extrapolation to long term use in humans. Scientific consultants for the drug's manufacturer and outside experts differ on the interpretation

of these data. Dexfenfluramine has been shown in monkeys, rats and mice to cause changes in the structure and function of the brain.[8,9,10] Neuroscientific advisors invited by the FDA to evaluate dexfenfluramine's potential to cause neurotoxicity testified before the Endocrinologic and Metabolic Drugs Advisory Committee that in animals this drug has caused long lasting changes in the structure and function in the brains of experimental animals.[6]

Members of the neuroscientific community expressed concern in 1993 about the safety of dexfenfluramine.(footnote c) At that time the Director of the Division of Metabolism and Endocrine Drug Products found that their suggestion to convene a special scientific advisory committee to evaluate the unresolved issues about dexfenfluramine's neurotoxicity to be an excellent one. (footnote d) These same reservations about the safety of dexfenfluramine were repeated by neuroscientists in a letter to the FDA dated December 7, 1995.(footnote e)

In their letter to Dr. Sobel dated December 7, 1995 the outside neuroscientists outlined human clinical studies that could definitively decide the issue of dexfenfluramine's potential for neurotoxicity.(footnote e) Because dexfenfluramine has had widespread clinical use in many countries, controlled studies of individuals exposed previously to high doses of dexfenfluramine or fenfluramine may be useful in ascertaining whether human users are at risk for dexfenfluramine neurotoxicity before it is marketed in the United States.

CONCLUSION

The meager one year efficacy of dexfenfluramine versus placebo speaks for itself. This is clearly not a "breakthrough" drug nor is there any data to suggest that the approval of dexfenfluramine for life-long use will lead to a reduction in morbidity and mortality associated with obesity. Thus, there is no imperative to hurry this drug to market and risk the public's health before the question of neurotoxicity is resolved. Following the suggestions made to the FDA on two occasions by a broad segment of the neuroscience community the opportunity is now available to resolve the question of potential neurotoxicity before dexfenfluramine is marketed.

In summary, we support the suggestion of a broad section of neuroscience community. We hope that you will look favorably on their request and ours.

Sincerely,

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Public Citizen

Larry D. Sasich, Pharm.D., FASHP
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[6] Transcript of the Open Session of the Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee, September 28, 1995.

Health Research Group Health Research Group

cc: Janet Woodcock, M.D.
Director,
Center for Drug Evaluation and Research

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