2.24 Insomnia, nervousness, anorexia, and weight loss.

Unlike standard tricyclic antidepressants, fluoxetine's profile of adverse effects more closely resembles that of a stimulant drug than one that causes sedation and gain of weight. Among treatment emergent signs and symptoms, the most common effects produced by fluoxetine included nausea, insomnia, and nervousness. Indeed nervousness was the most common adverse symptom cited by long-term fluoxetine patients who eventually discontinued therapy due to an adverse reaction. (See Section 3.1 of this review, and Appendix Tables XIV through XIX.) In addition, fluoxetine is known to suppress appetite and produce loss of weight as demonstrated in one double-blind study of obese patients. (See Section 3.23 of this review.).

It is possible that these adverse effects of fluoxetine treatment may negatively affect patients with depression. Since depressed patients frequently suffer from insomnia, nervousness, anorexia, and weight loss, it is possible that fluoxetine treatment might, at least temporarily, make their illness worse. Among elderly, cachectic, anorexic, or physically ill patients, reduction of nutritional intake may have serious consequences; and perhaps such an effect is related to the decrements of hemoglobin discussed above.

Nevertheless the severity of the risk posed by these effects does not appear great. Among patients who terminated fluoxetine studies prematurely (presumably the ones who had the most severe negative reactions) no patient was reported to have suffered loss of weight. Moreover no patients in the study of geriatric patients suffered weight loss. However, 25% of fluoxetine patients who terminated prematurely did report nervousness, while 20% reported insomnia, and 5% complained of poor appetite (see Appendix Table II). At the present time, it does not appear that any serious risk results from these adverse effects, and such risk as does occur may be easily managed by discontinuing or changing the treatment.

From a regulatory point of view, it would appear that no stringent action is required to deal with this problem. However it may be appropriate to develop advisory labelling warning the physician that certain signs and symptoms of depression may be exacerbated by this drug. If the drug is marketed, post-marketing studies should be required to determine the frequency with which fluoxetine may cause intensification of these specific signs and symptoms of depressive illness.

2.25 Summary of Section 2.2

In conclusion, it appears that there may be three possible safety risks and one possible benefit associated with fluoxetine. Patients exposed to this drug show higher rates of reduced hemoglobin than do patients on placebo or imipramine, and there may also be a fluoxetine-induced elevation of LDH. It is not clear whether any of these alterations reflect clinically significant [illegible] possible that adverse effects