

side effects attributable to the dextroamphetamine component. Lederle also argues that Bamadex Sequels must be found effective because meprobamate and dextroamphetamine have each been found by the FDA to be effective as single entities, and that its product must be found safe because Bamadex Sequels were approved on the basis of safety in August 1960 and there has been no clinical experience to the contrary since that time. Lederle contends that the addition of meprobamate, a schedule IV controlled substance under the Controlled Substances Act (21 U.S.C. 801 et seq.) to dextroamphetamine, a schedule II substance under the same act, results in a combination with significantly lower potential for abuse than dextroamphetamine alone, within the meaning of 21 CFR 3.86(a)(2).

Finally, Lederle claims that the FDA interpreted certain data in its investigations in a manner contrary to the observations and reports of the investigators who conducted the studies.

The Commissioner has considered all of the material submitted by Lederle and has concluded that there is no genuine issue of material fact requiring a hearing and that the legal objections offered are insubstantial. A full discussion follows:

I. The drug

Bamadex Sequels contains (each capsule) a fixed combination of milligrams dextroamphetamine sulfate and 300 milligrams meprobamate.

II. Recommended uses and dosage; rationale for the combination

The labeling reviewed by the NAS/NRC, Drug Efficacy Study Group, claimed that Bamadex Sequels was useful in the management of obesity, curbed appetite with minimal overstimulation of the central nervous system, and provided a sustained release of active ingredients. Lederle's present labeling retains the claims with respect to sustained release and minimal overstimulation of the central nervous system, but incorporates the changes required by 21 CFR 310.504 and recommends Bamadex only for use in exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. The usual adult dosage of Bamadex Sequels is one capsule daily in the morning.

Lederle's rationale for the combination is twofold: (1) The dextroamphetamine results in a drug with a lower abuse potential than dextroamphetamine counteracts the overstimulation which frequently accompanies the use of dextroamphetamine sulfate, and (2) the addition of meprobamate to dextroamphetamine results in a drug with a lower abuse potential than dextroamphetamine alone.

III. Data submitted to support claims of effectiveness

A. Bamadex Sequels studies.—Lederle submitted three clinical studies in support of the claimed effectiveness of Bamadex Sequels. These studies, with the exceptions noted below, followed substantially identical protocols; they are evaluated as follows:

1. Noble, Rudolph E., "A Comparison of Bamadex Sequels (15 mg dextroamphetamine and 300 mg meprobamate), Bamadex Sequels Minus Meprobamate (15 mg dextroamphetamine) and Placebo on Weight Loss and Side Effects in 90 Overweight Patients," unpublished study, 1971. In an attempt to establish, *inter alia*, that patients on Bamadex Sequels experience fewer adverse reactions than those who receive dextroamphetamine alone (i.e., that meprobamate reduces the side effects attributable to dextroamphetamine), the investigator selected 90 patients who were 20 percent overweight according to Metropolitan Life Insurance Company standards. These were divided into three equal groups and randomly assigned to one of three treatment regimens of Bamadex Sequels, dextroamphetamine, or placebo. The first group received Bamadex Sequels for 21 days, placebo for 21 days, and then Bamadex Sequels for the final 21 days; the second received dextroamphetamine for 21 days, placebo for 21 days, and dextroamphetamine for 21 days; the third received a placebo for the entire 9-week period. Each patient was instructed to take one capsule each day at least 1 hour before breakfast. Male patients were placed on a 1,500 calorie daily diet; females on a 1,200 calorie daily diet. Prior to entrance in the study and at 3, 6, and 9 weeks after entry into the study, patients' height, weight, pulse, and blood pressure were recorded and compared.

This study is not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii)(a)(2)(iii) in that it fails to assure that test and control groups were comparable with respect to the use of drugs other than the test drug. Thus, although the investigator undertook statistical analysis to assure the