

FACTS

The decision memo on amphetamines and other anorectics initiated by the Commissioner took a stand to the efficacy of the various drugs marketed or proposed for marketing as anorectics. It did not go into most special claims for specific drug products, e.g., claims for individual formulations. A group of special claims requiring further decision is that of the "sustained-action" formulations.

A number of anorectic drugs are in formulations associated with claims for sustained action or something similar. Examples are:

- (1) Diethylpropion in "Dospans" or "Ten-Tabs", the former being a hydrophilic matrix, carboxypolymethylene;
- (2) Phentermine or amphetamine (Ionamin or Biphetamine, respectively) as a resin complex;
- (3) Amphetamine or dextroamphetamine as a "Spansule";
- (4) Phenmetrazine as an "Enduret", containing aluminum tristerate and silica gel to slow dissolution; and
- (5) Methamphetamine as a "Gradumet", an insoluble plastic matrix from which the drug is leached.

A brief survey of NDA's for these products yields the attached blood level curves. (Attachments—Tab A, Dexedrine;—Tab B, Tenuate). It appears that, with the possible exception of phenmetrazine the "sustained-action" formulation does not produce blood levels which differ substantially from those produced by the same dose of drug in a non-"sustained-action" formulation. Other differences exist for phenmetrazine, so that in each case examined, any practical difference or special therapeutic benefit of the "sustained-action" formulation appears unlikely, and is not supported by these studies.

Efficacy trials have by and large been done with the "sustained-action" formulations, with a demonstrated drug-placebo difference, so that general efficacy is not a question. Therapeutic (as opposed to blood-level) comparisons of the special formulations with conventional tablets or capsules have not been done; the slowness of weight loss, i.e., days to weeks, and the large inter-subject variations makes it appear impractical to do such trials. (Short-term trials of food consumption by mealtimes might be practical, however.) The SKF studies suggest less jitteriness with the "Spansule" which would be consistent with the lower, slower peak.

Administrative deadlines for decisions of two sorts exists. First, a number of New Drug Applications include claims for "sustained action" for single-entity drugs, and our conclusions on these claims should be communicated to the sponsors; our reservations may be indicated in a general way for now, and a final conclusion left until later. Second, follow-up DESI notices are due on Tenuate Dospen, Diphetamine, Ionamin, Desoxyn, and some less known amphetamines. These Notices should include our definitive conclusions.

DISCUSSION

It appears that claims for "sustained action" for current formulations of anorectics are not justified. On this basis we have incorporated the following form paragraph in letters to sponsors of NDA's.

We have serious reservations as to any labeling claims for sustained action. We request that you either delete such claims or state in more precise language any possible therapeutic difference of the sustained release formulations from an equal dose of tablets.

We hope you concur with this; if you have reservations, the language of the paragraph will permit future revision of our stand.

Assuming that "sustained-action" claims are considered inadequately supported, further questions arise, for example, what future studies and results might the firms attempt to achieve. Two pressing and visible decisions are required now however.

The first involves publishing follow-up notices for sustained-action anorectics, for which "possibly effective" notices were published over two years ago. We believe we can go ahead on these; they would require deletion of claims for sustained action, so placing the burden on the firms to support any special claim other than general efficacy.

The second involves formulation brand names. The proprietary names, "Dospans" and "Enduret" imply prolonged action, and we suggest these names be deleted or replaced by a neutral name such as "matrix formulations" or