REDACTED

Public Health Service

Food and Drug Administration
Rockville MD 20857

(3)

IND 30,673

JAN 28 1997

Abbott Laboratories
Pharmaceutical Products Division
Attention: REDACTED, Ph.D.
REDACTED
Abbott Park, IL 60064

Dear Dr. REDACT:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug and Cosmetic Act for Depakote (divalproex sodium).

Refer also to your amendment of December 10, 1996, providing for a new study, Protocol M96-491 entitled, "A Double-Blind, Placebo-Controlled, Study of Valproate in the Treatment of Behavioral Agitation Associated with Dementia."

Although the clinical investigation you plan to conduct can reasonably be deemed to pose no unreasonable risk to any human subject who is competent to give informed consent and elects to participate in it, we are uncertain, at least at this point in time, as to what inferences can reasonably and responsibly be drawn from its outcome.

We call attention to this matter because the declared aim of your study is to assess the effects of Depakote on what you characterize as "behavioral agitation in elderly patients with dementia." There is, however, no consensus among those expert in the management of patients with dementia as to the specific phenomena that comprise this putative syndrome or symptom set, let alone agreement on the nature of the beneficial actions that a product would have to possess to be granted a claim for such an indicated use. Accordingly, an assertion that the evidence adduced in your trial supports a claim for the treatment of "behavioral agitation in elderly patients with dementia" will be arguable.

Moreover, your protocol has other problematic features. The primary outcome measure employed, the BEHAVE-AD, measures a number of diverse phenomena, some of which are only arguably legitimate targets of pharmacologic intervention. For example, some of the phenomena rated, e.g., aggressiveness and verbal outbursts, may actually represent an attempt of an individual, deprived by his/her illness of the capacity for verbal expression, to communicate needs and express complaints about the conditions (not always kind or caring) under which he/she is compelled to live.

Furthermore, there is the problem of potential "pseudospecificity" of any behavioral management claim. Every behavioral sign and symptom exhibited by a patient with Alzheimer's Disease need not be Alzheimer's related. To the contrary, patients afflicted by dementia may suffer from any number of co-morbid conditions, both physical and emotional. The anxiety, agitation, or disruptive behaviors that occur in patients with Alzheimer's Disease may be only indirectly related to their status as Alzheimer's Disease patients. To be clear, you have every right to postulate that such a

syndrome exists, but your assumptions are not a sufficient basis to support a drug related claim, especially when, as noted earlier, there is no consensus on its existence, let alone identifying features, at this point in time.

Accordingly, if you intend to pursue any sort of behavioral control claim tied to Alzheimer's Disease, much work remains to be done, in particular, in regard to the reification of the entity for which product labeling will assert Depakote is an effective and safe treatment.

If you undertake such an endeavor, we would urge you to be conservative, defining carefully and narrowly, not only the entity, but the precise nature of the therapeutic effects of Depakote on that putative condition. Importantly, a clinical trial that shows that behaviorally symptomatic demented patients randomized to Depakote do better than those randomized to placebo on some multi-item measure of behavior is unlikely to prove sufficient for such a purpose.

Again, we are not implying that restriction of the scope of therapeutic target will necessarily gain you the kind of claim you want. To the contrary, if you were, for example, to conduct a clinical study showing that Depakote relieves the signs and symptoms of mania in patients with Alzheimer's, it would be unlikely that we would view its results as doing more than confirming the claim, already established, that Depakote is an effective antimanic. We would be likely, however, to allow Depakote product labeling to be modified to include a description of the study's results insofar as they could be characterized as further evidence supporting Depakote's approved indication as an antimanic.

In sum, in light of the controversies and uncertainties extant about the "behavioral manifestations of Alzheimer's Disease," any pursuit of a claim for such an indication could prove fruitless. We trust you understand that we are in no way opposed to efforts to document the existence of a behavioral syndrome and/or to develop effective treatments for its management; indeed, we would applaud such efforts.

Should questions arise concerning these comments, please contact CDR REDACTED, R.Ph., Project Manager, at (301) REDACTE.

Sincerely yours,

REDACTED

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