

**MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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HFD-120

**SUBJECT:**    January 14 & 15, 2001 Meeting of the Psychopharmacological Drugs Advisory  
Committee

**TO:**        Members of the Psychopharmacological Drugs Advisory Committee (PDAC)

A number of antipsychotic drugs have been available in the US, beginning in the early 1950s with chlorpromazine, and these drugs have proven to be immensely useful in the treatment of various psychotic illnesses, in particular schizophrenia. Several of these drugs are available in parenteral form, e.g., haloperidol and chlorpromazine, for intramuscular (IM) use. Many clinicians have found these parenteral formulations of considerable clinical value, particularly in the management of patients during acute exacerbations of their illness. For this reason, there seems to be little controversy in principle regarding the importance of finding a way to provide for parenteral formulations of the newer antipsychotic agents approved over the past decade.

One approach to gaining approval for parenteral formulations of these newer agents would be to rely on pharmacokinetic (PK) studies characterizing the PK profile for these parenteral formulations, along with sufficient safety data to provide reassurance of the safety of these formulations. The problem with this approach, from FDA's perspective, is that parenteral formulations are almost certainly not going to be bioequivalent with the immediate release formulations, i.e., equivalent regarding both rate and extent of absorption. Thus, relying on this approach would necessitate assuming that either rate or extent of absorption is not pertinent to efficacy, and this is not an assumption the agency has been willing to make for other formulations. For example, sustained release formulations have been proposed for a number of psychotropic products, and at the current time, the requirements for approval of these formulations include a demonstration of efficacy based on at least one adequate and well-controlled clinical trial. It should be noted that, at the time the parenteral formulations of the older antipsychotics were approved, there was not a requirement for efficacy data to support such approvals.

Thus, as we have been approached by sponsors of more recently approved antipsychotic drug products seeking to develop parenteral formulations for their products, we have had to confront the issue of how best to develop these formulations. In designing a clinical program, the first question to address is what clinical entity to target in the program. Depending on how this

question is answered, two alternative approaches for developing parenteral formulations has emerged.

One approach to targeting a clinical entity is to take the view that the clinical entity being treated with the parenteral formulation is the identical entity for which the antipsychotic drug product has an approved indication, i.e., schizophrenia. In fact, this is consistent with the view of many clinicians who consider the use of parenteral antipsychotic drugs as the only practical way to initiate treatment for some acutely exacerbated schizophrenic patients. Thus, they view the use of an IM antipsychotic agent as the initiation of the treatment of a schizophrenic episode, with the understanding that a switch to oral immediate release medication will occur very quickly. Furthermore, it is understood that the antipsychotic effect will most likely not be achieved until well after the switch to oral medication is made.

A clinical trial to demonstrate the effectiveness of a strategy of initiating treatment with an IM formulation and then rapidly switching to oral medication could be done and would simply be a slight modification of a typical short-term antipsychotic trial. The modification would be that, rather than getting oral medication from day 1, patients would get IM medication for some fixed time period, e.g., the first 2 days, and would then be switched to oral medication. Assessments of antipsychotic effect would still focus on the later time points in the trial, since the expected time frame for antipsychotic response would not be changed. However, this does raise the interesting question of whether or not initiation of treatment with IM medication would hasten the antipsychotic response. This question could also be studied, but would involve a more complex design.

An alternative view is that the use of IM antipsychotic medication is not really intended to treat the psychosis per se, but rather, is intended to have a more general calming effect, related to properties of the drug other than its specific antipsychotic effect. The clinical targets in this case might be considered to be the "agitation" that is often observed in exacerbated schizophrenic patients. This approach to gaining approval of IM formulations of these products has the advantage of focusing on a clinical target for which a very rapid response could be expected and, thus, an effect would be fairly easy to demonstrate. This approach is also appealing from the standpoint of what the drugs may actually be used for, i.e., initial rapid control of patients, rather than a longer-term antipsychotic effect.

The question then becomes, "What is agitation?" Dorland's Medical Dictionary defines "agitation" as "exceeding restlessness associated with mental distress." It defines "agitated" as "marked by restlessness and increased activity intermingled with anxiety, fear, and tension." DSM-IV defines "psychomotor agitation" as "Excessive motor activity associated with a feeling of inner tension. The activity is usually nonproductive and repetitious and consists of such behavior as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still." These are fairly general definitions that might apply to patients with very different underlying diagnoses. They are consistent with a definition that appeared in a recent paper in the psychiatric literature, i.e., "motor restlessness such as fidgeting and pacing associated with an inner tension..."(Phenomenology and Treatment of Agitation, Alan Schatzberg, J Clin Psychiat, Monograph on "Phenomenology and Treatment of Aggression Across Disease States," Vol 17, Monograph 2, 1999, pp.12-14).

One distinction worth noting is between what might be considered acute agitation and chronic agitation. Acute agitation might be considered the restlessness associated with an acute illness, e.g., exacerbation of schizophrenia. Chronic agitation might be considered a more chronic pattern of behavior associated with a chronic disease state, e.g., Alzheimer's disease. In fact, there was considerable discussion of the concept of "agitation" at a March 9, 2000 meeting of the PDAC focused on behavioral and psychological symptoms associated with various dementias. The chronic agitation associated with an illness like Alzheimer's disease is generally viewed as including a much broader set of behaviors than usually considered to comprise acute agitation.

At the March 9, 2000 meeting of the PDAC, there was no general consensus regarding agitation, either how to define it, or how to think of it in terms of it being either a disease specific entity or a nonspecific symptom. Some members and guests considered agitation of Alzheimer's disease a syndrome distinct to that illness, while others viewed it as an entity that might be considered nonspecific and occurring in a similar form in association with different disease states. In either case, there were widely varying views on how to define the entity. Thus, no agreement was reached at the March 9th meeting on whether or not and how to develop drug treatments for "agitation" in association with Alzheimer's disease.

The committee should be aware that two types of clinical entities are considered appropriate targets for new claims. Specific diseases or syndromes are the usual focus of a drug claim, e.g., congestive heart failure or rheumatoid arthritis. Nonspecific signs or symptoms not unique to a single disease or syndrome, e.g., pain or fever, may also be the focus for a claim. Antipyretics and analgesics are approved for these nonspecific symptoms on the basis of studies involving different "models" for each such symptom, e.g., headache pain and dental pain as different pain models. The basis for accepting this nonspecific approach to indications is the view that, while the disease states leading to these nonspecific symptoms may differ markedly, the symptoms themselves are: (1) universally defined, in whatever disease context they occur; (2) readily measured, using commonly accepted assessment methods; (3) ideally have a well understood pathophysiologic basis; (4) and respond similarly to drug treatment for that symptom, quite apart from the diverse disease states that may lead to the nonspecific symptom. Of course, we do not understand most psychiatric illnesses at a pathophysiological level, and this would not be an absolute requirement for a nonspecific symptom; however, this is a reasonable goal to strive for in this instance, since an understanding of mechanism may help to establish such a symptom as really independent of the underlying specific disease state in which it happens to occur. Critical to this approach to gaining a new claim is the concept of pseudospecificity. In this context, since the essence of this type of claim is that the symptom is nonspecific, i.e., to any one disease, it is essential that efficacy be demonstrated in several different disease models. To attempt to obtain a claim for a nonspecific symptom in a single disease model would, by definition, be pseudospecific, since such a claim would give the impression that the symptom is specific to that disease.

In considering new claims, whether for a specific disease/syndrome or a nonspecific sign/symptom, it is important to understand that similar criteria are used by FDA to evaluate the proposed clinical entity as an appropriate target for a new claim. The proposed clinical entity must be accepted in the relevant clinical/academic community, it must be operationally

definable, and it must identify a reasonably homogeneous patient group. The latter two criteria are important to ensure the validity of the clinical trials supporting the claim and to make it possible to inform clinicians in labeling about the use of the proposed treatment.

Despite the questions about how best to develop parenteral formulations of antipsychotics, two sponsors of antipsychotic drug products have completed programs for such formulations and have submitted marketing applications, and these are the subject of this two-day meeting of the PDAC.

On the first day, we will consider an application by Lilly (NDA 21-253) for a parenteral formulation of olanzapine (Zyprexa). Prior to the development of this product, we advised Lilly that they would need efficacy studies, and discussed the options of targeting schizophrenia or agitation. They chose to study IM olanzapine for agitation, and we subsequently advised them that we considered agitation likely to be a nonspecific symptom, and therefore, advised that it would likely be necessary to study it in several different disease models. They chose to study agitation in three disease models: schizophrenia; bipolar mania; dementia. They conducted 4 placebo-controlled trials, 2 in schizophrenia and 1 each in bipolar mania and dementia. In all cases, the primary outcome was change from baseline in the excited component of the PANSS. The excited component consists of 5 items: poor impulse control; tension; hostility; uncooperativeness; and excitement. Also in all cases, the time point for comparison of drug and placebo was 2 hours after the first IM injection.

In addition to efficacy, we will want the committee to address the safety of Zyprexa IM. In particular, there were 64 of 850 individuals exposed to olanzapine in this development program who met criteria for experiencing bradycardia (see Lilly's Addendum to Zyprexa IM Briefing Document). Twenty-eight of these cases occurred among the 64 normal volunteers in this program, and the rest among patients. Forty of the 64 cases of bradycardia were associated with either a drop in resting blood pressure or an orthostatic drop. Among the normal volunteers having bradycardia, 3 subjects (2 exposed to olanzapine IM and 1 to oral olanzapine) experienced sinus pauses of 5-6 seconds duration. There will be discussion of the significance of these cases by FDA consultants as well as by consultants from Lilly.

On the second day, we will consider an application by Pfizer (NDA 20-919) for a parenteral formulation of ziprasidone (Zeldox). Prior to the development of this product, we advised Pfizer that they would need efficacy studies, and discussed the options of targeting schizophrenia or agitation. They chose to study IM ziprasidone for agitation. Our discussions with Pfizer regarding this product occurred approximately two years prior to our discussions with Lilly regarding olanzapine, and prior to our reaching a view that agitation would likely be considered a nonspecific symptom. Consequently, we did not advise them of the necessity of studying agitation in several different disease models. Pfizer conducted 2 controlled trials, both in schizophrenia, and both comparing a low ziprasidone dose (2 mg) against a higher dose (10 mg in one study and 20 mg in the other). In both cases, the primary outcome was AUC (0 to 2 hours for one study and 0 to 4 hours for the second) for the Behavioral Assessment Scale (BAS) after the first dose. The BAS was developed by Pfizer specifically for these 2 trials, and consists of a 7-point scale targeting both agitation and level of consciousness. As with Zyprexa IM, we will want the committee to address both the efficacy and safety of Zeldox IM.

Before the committee considers these specific applications, we would like to have some discussion by the committee on the first morning of the meeting of the general issues pertinent to developing parenteral formulations of antipsychotic drugs for IM use. We would hope that the discussion would address, but need not be limited to, the following questions:

-Are effectiveness data needed to support the approval of a parenteral formulation of an antipsychotic for IM use, or is it sufficient to rely on the efficacy data available for the orally administered immediate release formulation?

-If effectiveness data are needed, what should be the clinical target that is the focus of the required effectiveness studies?

-In particular, should the focus be on schizophrenia, the approved indication for the oral formulation, or on some other clinical findings present during an acute episode of illness that are deemed to require the use of IM medication?

-If schizophrenia is considered to be the appropriate clinical target for the development of IM formulations of antipsychotic drug products, what study designs would be optimal to support a claim for these products?

-Is "agitation" an acceptable clinical target for the development of IM antipsychotic drug products?

-If so, how should "agitation" be defined?

-What outcome measures are optimal for the assessment of "agitation?"

-What study designs are optimal for the study of "agitation?"

-Is it worthwhile distinguishing between what might be considered "acute agitation" and "chronic agitation?"

-Is "agitation" a phenomenon that is specific to different disease states or can this be considered a nonspecific symptom that occurs in identical form in association with different disease states?

-If "agitation" can be considered a nonspecific symptom, is it necessary to study it in different disease models in order to gain a claim?

-If so, in what disease models should it be studied?

After considering the specific programs conducted by each of the two sponsors represented at this meeting, we would like you to vote on the usual questions regarding safety and efficacy, i.e.,

-Has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that (olanzapine IM/ziprasidone IM) is effective for the treatment of agitation?

-Has the sponsor provided evidence that (olanzapine IM/ziprasidone IM) is safe when used in the treatment of agitation?