CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-894

OFFICE DIRECTOR MEMO

Memorandum

Date: August 15, 2008

From: Robert Temple, MD
Director, ODE-I/HFD 101

To: Memo to File, NDA 21-894

Subject: Approval memo for NDA 21-894 for tetrabenazine (Xenazine, Prestwick) for treatment of the chorea of Huntington's Disease

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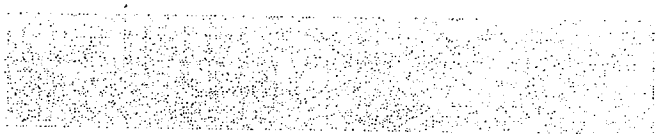
I. Background:

The effectiveness and safety concerns of tetrabenazine are well-summarized in Dr. Katz's November 7, 2007 briefing memo for the December 6, 2007 meeting of the PCNS Advisory Committee to discuss the use of tetrabenazine in treating the choreiform movements of Huntington's Disease. The issue before the AC, and the issue that has concerned FDA, has been that, despite the clear effect of tetrabenazine on choreiform movements, many other pertinent outcomes were affected adversely, including a number of safety measures (described below) and several elements of the Unified Huntington's Disease Rating Scale (UHDRS), notably, functional assessment and cognitive assessment, that were statistically significantly worse. Behavioral assessment (UHDRS Part 3), independence scale (UHDRS Part 5) and functional capacity (UHDRS Part 6) were directionally, albeit not significantly, worse.

Favorable outcomes were seen on the CGI and Total Motor Score (which, however, includes many chorea items). This bidirectional set of effects raised the question of whether there was a "net benefit." Although CGI did favor tetrabenazine, there was no patient/caregiver assessment, which might also have been useful. In all such situations, of course, average scores can mislead; that is, there may be people who have good effects on chorea without important decreases in function or adverse effects. Moreover, adverse effects often respond to dose decreases, perhaps with persistent benefit, and labeling points this out. Dealing with all this requires informed and aware patients, caregivers, and physicians, and attaining that state is what the Medguide, physician labeling, and other communications efforts are attempting to accomplish.



II. Effectiveness

Dr. Katz has described the results of 2 controlled trials

A. Study 004 randomized 84 patients on 16 US sites 2:1 to tetrabenazine (54) or Placebo (30), with 49 tetrabenazine and 29 placebo patients completing the 7 week titration and 5 week maintenance (total 12 week) study period. Titration was demanding, starting at 12.5 mg od, then increasing by 12.5 mg per week to a maximum dose of 100 mg/day. The initial dose was 12.5 mg/day with higher doses given bid and then tid. After 12 weeks the drug was stopped in all patients, who were then seen at week 13.

The primary endpoint was drug-placebo difference in change in chorea score from baseline at weeks 9 and 12. The chorea score is 7 items from the UHRDS motor score, each granted 0 (none) to 4 (marked), for a maximum score of 28. Results (ITT) were

	Baseline Chorea	Change	P-value
Tetrabenazine (N=54)	14.7	-5.04	
Placebo (N=30)	15.2	-1.52	0.0001

The results over time are shown in a figure taken from labeling, showing most of the full effect at about 5-7 weeks, with perhaps a somewhat greater effect at 12 weeks. One week off therapy led to a full return of choreiform movements to baseline values. Of interest, in the open label extension of study 004 (called study 007), in which all patients were re-titrated on tetrabenazine, results were essentially identical to the treated group in 004.

Fig 1

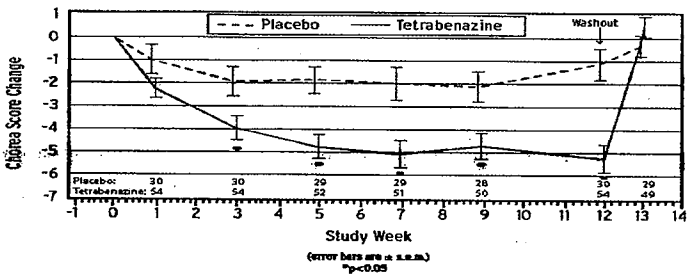
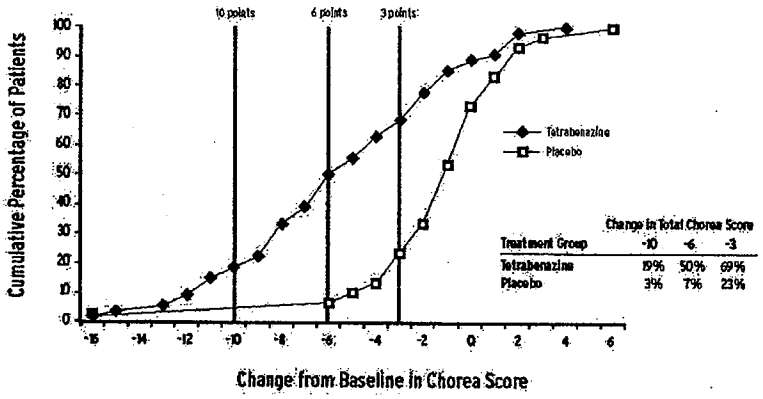


Figure 1. Mean ± s.e.m. Changes from Baseline in Total Chorea Score in 84 HD Subjects Treated with Tetrabenazine (n = 54) or Placebo (n = 30)

The cumulative distribution of results, shown in fig 2 (from labeling), is also revealing, showing that about 1/5 of patients on drug (but almost no one on placebo) had a 10 point change.

Fig 2

Figure 2 illustrates the cumulative percentages of patients from the XENAZINE and placebo treatment groups who achieved the level of reduction in the Total Chorea Score shown on the X axis. The left-ward shift of the curve (toward greater improvement) for tetrabenazine-treated patients indicates that these patients were more likely to have any given degree of improvement in chorea score. Thus, for example, about 7% of placebo patients had a 6-point or greater improvement compared to 50% of tetrabenazine-treated patients. The percentage of patients achieving reductions of at least 10, 6, and 3-points from baseline to Week 12 are shown in the inset table.



Treatment Group	Change in Total Chorea Score -10	-6	-3
Tetrabenazine	19%	50%	69%
Placebo	3%	7%	23%

B. Study 005 was a small randomized withdrawal study in just 30 patients. Dr. Katz's memo describes the travails of this study (notably a mix up on timing of

assessments). The results did not attain statistical significance but were numerically very close to 004 in the 18 patients treated correctly, so that the study provides some support for study 004.

III. Safety

Many reviews address safety issues. Dr. Katz and others have reviewed deaths, all but one of which occurred in uncontrolled studies. There was one suicide in study 004 in a patient with a history of suicidal ideation. The others include a variety of apparently non-drug-related causes (CV disease, cancer) and a number with aspiration pneumonia, a recognized consequence of the dysphagia associates with Huntington's Disease (but there is some suggestion that dysphagia may be increased by tetrabenazine).

In the controlled study 004 there were many adverse effects that occurred at far greater rates on drug than placebo, including the following over 5%, shown in labeling

	Tetrabenazine n = 54	Placebo n = 30
Psychiatric		
Sedation/Somnolence	31%	3%
Insomnia	22%	0
Depression	19%	0
Anxiety	15%	3%
Irritability	9%	3%
Central & Peripheral NS		
Akathisia, hyperkinesia	19%	0
Entrapyramidal (Parkinsonism, bradykinesia)	15%	0
Other		
Fatigue	22%	13%
Nausea	13%	7%
Vomiting	6%	3%

Of particular concern is depression and suicidality, a problem exacerbated by the presence of these occurrences as part of Huntington's Disease. There was, as noted, 1 suicide in study 004, as well as 2 cases of suicidal ideation. Depression occurred at a rate of 19% overall, vs 0% on placebo, and was seen as early as 4 days into treatment and at doses as low as 25mg/day. In the longer-term studies, depression was seen in over 40% of patients. Dose-reduction seemed effective in somewhat less than half of those. Drug-induced Parkinsonism and extra-pyramidal effects can also be hard to distinguish from progression of the underlying disease.

Sedation was a particularly common problem, affecting almost a third of patients, but generally responsive to dose reduction.

Tetrabenazine causes an approximately 8 msec prolongation of QTc, which should not be a problem if concomitant QT prolonging treatment is avoided.

The active metabolites of tetrabenazine are metabolized by CYP 2D6, with a 3 and 9-fold increase in alpha-HTBZ and beta-HTBZ (the metabolites) respectively, after inhibition by paroxetine, a strong 2D6 inhibitor. A similar increase would be expected in 2D6 poor metabolizers, about 8% of the Caucasian population. Because of this, D&A recommends genotyping for 2D6 status before use of a dose above 50mg and a maximum dose of 50mg in poor metabolizers (100mg in EMs).

IV. Risk/Benefit and Risk Management

A. Advisory Committee and Conclusions
On Dec 6, 2007, tetrabenazine was presented to the PCNS Advisory Committee. The Public Hearing included patients, caregivers, and physicians who spoke feelingly and persuasively about the life-altering effects of the chorea component of Huntington's Disease. The Committee, while concerned about the safety findings and adverse effects on secondary outcomes, clearly advised that the beneficial effect on chorea outweighed these effects. The Committee emphasized the need to alert prescribers to the need to control dosing and to consider whether adverse effects are consequences of disease progression or of treatment. The Committee did not favor a restricted distribution program that would make obtaining the drug difficult.

The Division and I agree with the Approval Recommendation. There is no internal disagreement. The Division and OSE also worked together to develop the labeling and REMS.

B. Risk Management
The combination of an important beneficial effect on chorea together with a clear ability to worsen depression and evidence of adverse effects on other aspects of functioning led us to the conclusion that tetrabenazine could be approved only with efforts to manage the risks of the drug with methods beyond drug labeling, i.e. with a REMS (Risk Evaluation and Mitigation Strategy) a step explicitly provided for under FDAAA.

1. Physician Labeling (not part of REMS)

Because of the 2005 date of submission tetrabenazine has "old style" (pre-PLR) labeling, and thus no highlights. It has a box warning about depression and suicidality that emphasizes 1) the need for particular care in people with a history of

depression or suicide attempts 2) the need to balance the depression risk and the clinical need for control of choreiform movements, and 3) the need for close observation by caregivers, patients, and families for worsening depression, suicidality, or unusual changes in behavior.

As noted, labeling shows both the mean and distribution of results, a very informative presentation, as well as the dramatic effect of drug withdrawal. Warnings point out (in dark print) that mood, cognition, rigidity and functional capacity are slightly worsened, that there are important adverse effects, and that there should be periodic reevaluation of net benefit, and also point out the need for careful titrated dosing and the possible need for dosage adjustment. Dosage and Administration provides a high level of detail on these matters. Labeling, of course, describes, in Warnings and Precautions, the risk of depression and how to assess and manage it, akathisia, Parkinsonism, dysphagia (not entirely clearly related to the drug), sedation and somnolence, and other risks.

2. REMS elements

a. Medication Guide
Emphasizes need to not use the drug if depressed and to watch for changes and indicators (listed) of depression.

b. Communication Plan
Prestwick will communicate (provide educational materials) with health care professionals, especially neurologists and movement disorder specialists, and pharmacists. Details are in the Approval letter.

c. REMS assessments: 1, 2, 3, 7 years post-approval
These will include surveys of prescribers (do they know how to titrate, monitor, and manage), patients, and caregivers.

V. Conclusion

Tetrabenazine will treat a major disability of Huntington's Disease. Care is demanded by all parties (patients, caregivers, physicians) to monitor favorable and unfavorable effects and regulate dosing. The REMS and physician labeling should assure that benefits will outweigh risks.

Approval with REMS is appropriate.

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/s/

Robert Temple
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MEDICAL OFFICER