

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-894

MEDICAL REVIEW(S)

Review of Clinical Data

NDA:	21-894
Product name:	Tetrabenazine (Xenazine®)
Dosing regimen:	25 to 100 mg daily, oral formulation
Applicant:	Prestwick Pharmaceuticals
Indication :	Chorea of Huntington's Disease
Subject:	Complete response to Approvable letter of 12/26/07
Submission date:	June 13, 2008
PDUFA date:	August 16, 2008
Review date:	August 8, 2008
Reviewer:	Lourdes Villalba, MD, DNP Safety Team

1. Background

Xenazine® (tetrabenazine) inhibits the central nervous system (CNS) specific vesicular monoamine transporter-2 (VMAT-2) leading to CNS monoamine depletion, in particular, dopamine depletion (with resulting reduction of chorea), and to a lesser extent, serotonin and norepinephrine depletion. These pharmacologic effects explain common adverse effects observed with TBZ (somnolence, insomnia, anxiety, restlessness/akathisia, depression and parkinsonism). Prestwick Pharmaceuticals Inc. is requesting approval of Xenazine for the treatment of Chorea of Huntington disease at the dose of 25 to 100 mg daily.

Regulatory History:

NDA 21-894 (Xenazine®) was submitted on September 23, 2005. On March 24, 2006, the FDA issued an Approvable (AE) action to this application. The DNP felt that despite the documented efficacy of TBZ in the chorea component of the disease (based on Part 1 [Motor Assessment] of the Unified Huntington Disease Rate Score [UHDRS] in study 004, supported by study 005, "troubling questions remained regarding the utility and ultimate approvability of the application." There was no evidence of improvement on the behavioral/cognitive components of the disease. Additionally, some of the adverse reactions associated with TBZ use might have not been adequately distinguished from the underlying disease. Serious risks associated with its use include the occurrence of depression and suicidality. Other adverse events associated with Xenazine are akathisia, parkinsonism, neuroleptic malignant syndrome and small QTc interval prolongation. Patients requiring dosing above 50 mg daily should be genotyped for CYP2D6. The maximum recommended dose for poor metabolizers is 50 mg daily. For intermediate and extensive metabolizers it is 100 mg daily. For additional details about the safety of Xenazine, the reader is referred to my review dated December 13, 2007.

A Complete Response to the March 24, 2006 approvable letter was submitted on April 10, 2007 (& Major Amendment August 9, 2007). The application was discussed at the FDA Peripheral and Central Nervous System Advisory Committee on December 6, 2007.

The panel unanimously voted in favor of approving Xenazine. It also favored the development of a Risk Minimization Action Plan for this drug, emphasizing that such a plan should not be burdensome for patients and physicians. On December 26, 2007, the FDA issued another AE action to this application. The AE requested a revised RiskMAP and a Medication Guide to address adequate dosing and to emphasize the risk of suicidality. A response to the FDA AE letter was submitted by the sponsor on January 18, and amended on February 26, 2008. The submitted RiskMAP addressed most of the issues raised by the FDA, however, some materials had not been submitted by the time of the PDUFA date. Moreover, the Food and Drug Administration Amendment Act of 2007 (FDAAA), which provides the FDA with authority to require sponsors to develop and comply with Risk Evaluation and Mitigation Strategies (REMS), was to take effect on March 25, 2008. On March 18, 2005 this application was granted another AE action requesting resubmission of the RiskMAP materials under a REMS.

2. Review of the Current submission

The current submission of June 13, 2008 (NDA 21-894/s0072) is the Complete Response to the AE letter of March 18, 2008. Minor edits to some of the documents were submitted on July 7, and August 6, 2008. The AE letter did not request, and the current application does not provide, any new efficacy or safety data. The submission includes:

1. A proposed REMS
2. REMS-related documents
 - a. Package insert (PI)
 - b. Medication Guide (MG)
 - c. Dear Healthcare Professional Letter
 - d. Dear Pharmacist Letter
 - e. Healthcare Professional Guide
 - f. Patient/Caregiver Counseling Guide
 - g. Initial Dosing Plan
3. Proposed postmarketing studies

All submitted documents have been extensively discussed between the FDA and the sponsor prior to their submission and are considered to be acceptable by the DNP. The proposed REMS is included in Appendix 1 of this review. The MG is in Appendix 2. The other documents are consistent with the PI and MG. They inform physicians, patients and caregivers of the risks associated with Xenazine and emphasize proper dosing. The postmarketing studies are five non-clinical studies and one in vitro clinical pharmacology study. They have also been previously agreed upon by the FDA and the sponsor.

4. Recommendation for Regulatory Action

Xenazine has been shown to reduce the chorea of Huntington's disease. Serious risks associated with its use include the occurrence of depression and suicidality. Patients requiring dosing above 50 mg daily should be genotyped for CYP2D6. The sponsor's proposed REMS adequately addresses the risk of depression and suicidality as well as other risks associated with the use of Xenazine and emphasizes proper dosing.

This application should be Approved.

4 Page(s) Withheld

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/s/

Maria Villalba
8/8/2008 11:31:41 AM
MEDICAL OFFICER

Alice T. Hughes
8/8/2008 11:36:09 AM
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Memorandum

DATE: March 17, 2008

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-894

SUBJECT: Recommendation for action on NDA 21-894, for the use of Xenazine (tetrabenazine) in the treatment of the chorea of Huntington's Disease (HD)

NDA 21-894, for the use of Xenazine (tetrabenazine) in the treatment of the chorea of Huntington's Disease (HD), was submitted by Prestwick Pharmaceuticals on 4/22/05. The application was subsequently withdrawn and re-submitted on 9/26/05.

The application contains reports of two randomized controlled trials, Studies 004 and 005, as well as safety data. The safety database is quite small, and much of the data were obtained by the sponsor from Dr. Jankovic, an HD expert at Baylor College of Medicine in Texas, who has been treating patients with tetrabenazine for years under his own IND.

The Agency issued an Approvable letter on 3/24/06. Although the Agency had determined that tetrabenazine was considered effective in the treatment of the chorea of HD, we noted several issues that raised significant concern about the ultimate approvability of the application.

Specifically, although analyses of the primary outcomes (measures of chorea) yielded statistically significant between-treatment differences favoring drug, analyses of numerous other secondary outcomes (including measures of functionality and cognition) tended to favor placebo, some reaching nominal statistical significance. In addition to the obvious concerns raised, we were concerned that if the drug actually caused deterioration in these domains, it would be difficult for the practitioner to recognize these clinical changes as being drug-related, given that deterioration of function and cognition are symptoms of HD itself.

Further, we noted the clear drug-related increase in significant adverse events, including parkinsonism, akathisia, depression, and dysphagia, the latter possibly being associated with aspiration pneumonia. Here, too, we were concerned that practitioners might not be able to identify some of these events as being drug related, again because several of these are symptoms of HD. In particular, if these events were drug related, but were not considered as such, it is possible

that they could continue to increase in severity, perhaps becoming irreversible and resulting in significant clinical sequelae. For these reasons, we informed that sponsor that we were unsure that the potential benefit of tetrabenazine on chorea could be justified, and this overarching issue motivated the division to bring the application to the PCNS Advisory Committee.

The application was presented at a public meeting of the PCNS AC on December 6, 2007. The committee recommended that the application be approved. They acknowledged that there were significant adverse events associated with the use of tetrabenazine, but that safe use of the product did not require a restricted distribution program (which the sponsor had proposed), although they recommended that the sponsor should undertake educational efforts to inform prescribers and patients about these risks. They also concluded that the findings on the secondary outcomes were of little clinical consequence (see below).

The division agreed that the data supported approval, and the Agency issued an Approvable letter on December 26, 2007. In that letter, we asked the sponsor to submit a revised Risk Minimization Action Plan (RiskMAP), a Medication Guide, and a revised package insert. Further, we had enumerated several potential post-marketing commitments that we wanted the sponsor to agree to. These will be described below. The sponsor responded to this second Approvable letter with a submission dated January 18, 2008.

I will give a relatively brief description of the effectiveness and safety data submitted in the original application, a summary of the sponsor's response to the Approvable letter, and the issues we raised with the Advisory Committee. The sponsor's response to the 12/26/07 Approvable letter consisted of numerous documents reviewed by members of the staff of the Office of Surveillance and Epidemiology (OSE) as well as by the staff of DNP. Finally, I will offer the division's recommendation for action in response to the sponsor's 1/18/08 re-submission.

Effectiveness

Study 004

This was a randomized, parallel group, double-blind trial in which patients not previously treated with tetrabenazine were randomized to receive either active drug or placebo in a 2:1 ratio, respectively. The study involved a 7 week titration phase, followed by a 5 week maintenance phase. Treatment was initiated at 12.5 mg once a day, then titrated by 12.5 mg/day increments per week to a maximum dose of 100 mg/day (the 12.5 and 50 mg/day doses were given qd and bid, respectively; higher doses were given in a qid regimen). Patients were to be titrated to the dose felt to offer the best control of their chorea and adverse

events. Patients were to be seen after a one week period off of drug at the end of the trial, on week 13.

The primary measure of efficacy was the difference between drug and placebo on the mean change from baseline in the Chorea Score for the average of Weeks 9 and 12. The Chorea Score is a subset of the Motor Assessment Scale of the Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS consists of 6 subscales:

- 1) Motor Assessment
- 2) Cognitive Assessment
- 3) Behavioral Assessment
- 4) Functional Assessment Checklist
- 5) Independence Scale
- 6) Functional Capacity (TFC)

Part 1 consists of 15 items, 7 of which constitute the Chorea Score; these 7 items are each graded 0 (chorea absent)-4 (marked/prolonged), for a maximum score of 28.

Part 2 consists of 5 timed items: verbal fluency, digit symbol substitution test, Stroop color naming test, Stroop word reading test, and the Stroop interference test.

Part 3 consists of 11 behavioral items, rated each for frequency and severity.

Part 4 consists of a list of 25 activities, each rated as 0 (cannot perform activity) or 1 (can perform activity).

Part 5 is an examiner rated assessment of the patient's level of independence, ranging from 10 (tube feeding, total bed care) to 100 (no special care needed).

Part 6 consists of 5 items (occupation, finances, domestic chores, ADL, and care level). Zero represents the lowest level of functioning, 13 represents normal functioning.

The following measures were secondary outcomes that were to be analyzed in the following order:

CGI, part 2: A 7 point scale, ranging from 1 (Very Much Improved) to 7 (Very Much Worse)

Mean Change from Baseline in the total Motor Score (UHDRS, Part 1)

Mean Change from Baseline in the Functional Assessment (UHDRS, Part 4)

Mean Change from Baseline in the Gait Score (UHDRS, Part 1, Item 13)

Results

A total of 84 patients were enrolled at 16 centers in the US. The following chart displays patient flow in the study:

	Drug	Placebo
Randomized	54	30
Completed	49	29
Withdrew AEs	5	0
Withdrew consent	0	0

The following chart displays the results of the primary analysis for the intent-to-treat population (ITT):

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

The following results were seen for the secondary outcomes:

	Change From Baseline	P-value
CGI		
Tetrabenzine	2.99	
Placebo	3.73	0.0074
Total Motor Score		
Tetrabenzine	-6.84	
Placebo	-3.51	0.0752

	Change from Baseline	P-value
Functional Assessment		
Tetrabenzine	-0.81	
Placebo	0.37	0.0183*
Gait		
Tetrabenzine	0.0001	
Placebo	0.11	0.2410

*-favors placebo

Other endpoints were evaluated:

Behavioral Assessment (UHDRS Part 3)

Tetrabenzine	-0.96	
Placebo	-2.22	0.355*

In this subscale, one of 11 items, the Anxiety item, reached nominal significance (P=0.03) in favor of placebo.

Cognitive Assessment (UHDRS Part 2)

Tetrabenzine	-7	
Placebo	5	0.025*

All 5 items of this scale favored placebo numerically, with the Stroop Word and Interference items reaching nominal statistical significance (0.012 and 0.053, respectively).

Independence Scale (UHDRS Part 5)

Tetrabenzine	-1.98	
Placebo	0.55	0.135*

Functional Capacity (UHDRS Part 6)

Tetrabenzine	-0.43	
Placebo	-0.03	0.29*

Further examination of the effect on Chorea

Because the effect on chorea seemed so robust, the following additional analyses were performed.

As can be seen from Figure 1 in Dr. Massie's review (page 14), the between treatment comparisons on the mean chorea score becomes statistically significant at Week 3, and was also significant at Weeks 7 and 12.

Most patients in the tetrabenazine group received maintenance doses of either 50 or 100 mg.day (18.5% and 41%, respectively). In these groups, 90% and 64%, respectively, had a 3 point or more improvement in the chorea score. For the entire tetrabenazine group, a total of 69% of patients had an improvement of at least 3 points. In the placebo group, almost all patients received the maximum number of pills (94%), and a total of 21% of these had an improvement of at least 3 points (a total of 23% of placebo patients had an improvement of at least 3 points). The difference between the overall rates of improvement of at least 3 points (69% tetrabenazine vs 23% placebo) was highly statistically significant ($p < 0.0001$).

The following distribution of improvements in chorea score between the treatment groups was seen:

	10 points	6-9	3-5	0-2	Worsening
Tetrabenazine	19%	31%	19%	20%	11%
Placebo	3%	3%	17%	50%	27%

Finally, an examination of the results by individual centers revealed a numerical difference in favor of tetrabenazine in 14/15 centers, with the difference at one center, Center 5 (Rush Presbyterian), reaching near nominal significance ($p = 0.056$).

In addition, other analyses document the robustness of this finding.

Specifically, upon drug withdrawal at Week 12, patients' chorea scores returned to baseline levels by Week 13, confirming the drug effect seen over the previous 12 weeks. In addition, exploratory analyses document that the pattern of response of patients during the first 11 weeks of Study 007, the open-label extension to Study 004, during which all patients were re-titrated, were essentially identical to the responses seen in the drug treated patients during the titration period in Study 004. This effect in Study 007 was seen in both patients who had previously received active treatment in Study 004 as well as in those who had previously received placebo.

A similar effect was seen for patients enrolled in Study 006, the open-label extension to Study 005. That is, although patients (after their participation in Study 005) were placed back on their best dose in Study 006 (as opposed to being re-titrated, as were the patients in Study 007), their responses over the first 12 weeks in Study 006 were also essentially identical to those of the drug-treated patients in Study 004.

Further, the drug effect is relatively independent of the baseline degree of severity of the chorea.

Finally, although patients were not randomized to fixed dose in Study 004, PK/PD analyses strongly suggest a dose response relationship in this study.

Study 005

This was a study in which patients already receiving tetrabenazine for at least 2 months were randomized in a five day randomized phase to one of three groups in a 2:2:1 ratio:

Group 1-to receive placebo for all 5 days

Group 2-to receive tetrabenazine until after the assessment on Day 3

Group 3-to receive tetrabenazine for all 5 days

The primary outcome was to be a comparison of the mean change from baseline (Day 1 of the randomized phase) in the chorea score between Group 1 and the combined Groups 2 and 3 on Day 3.

A total of 24 patients were randomized into Groups 1 and 2 (12 patients in each group) and 6 patients were randomized into Group 3.

The mean daily dose of tetrabenazine in the three groups was 50 mg, 37.5 mg, and 62.5 mg, respectively.

The following chart displays the chorea scores for each group, and the results of the primary analysis:

	Baseline Chorea	Change Day 3	Change Day 5
Group 1	9.4	5.3	5.3
Group 2	9.1	3.6	5.5
Group 3	11.2	1.7	4.0
Group 2/3	9.8	2.9	

The p-value for the primary comparison (Group 1 vs Group 2/3 on Day 3) was 0.078.

After the study was completed and analyzed, the sponsor learned that the protocol had not been followed. Specifically, although the protocol stated that the Day 3 assessment was to be made after the morning dosing on Day 3, the investigator actually treated patients in Group 2 with placebo in the morning. As a result, presumably, the change in the scores for the Group 2 patients was smaller than expected. In an attempt to address this problem, the sponsor performed several post hoc analyses.

For example, given that the scores in Group 2 were intermediate between those for Groups 1 and 3 on Day 3 (again, presumably as a result of the specifics of the study conduct), the sponsor performed a trend test; this yielded a p-value of 0.048.

Another analysis combined Groups 1 and 2 and compared this combined group to Group 3. The rationale for this analysis was that Group 2 was, as the study was conducted, similar to Group 1, in that patients were off treatment for a reasonable duration (about 12-18 hours in Group 2) that would be expected to be sufficiently similar (pharmacodynamically) to the duration that Group 1 patients had been off treatment (about 3 days in this latter group).

Another analysis compared the results in Group 1 and Group 3 at Day 3. The rationale for this analysis was that Group 3 patients clearly were treated as per protocol (that is, they received drug on Day 3 prior to the assessment), and this keeps faith with the intent of the original protocol (that is, Groups 2 and 3 were to be combined because they both were to have been treated on Day 3 prior to the assessment).

The results of these two analyses are displayed below:

	Change at Day 3	P-value
Group 1 and 2 (N=24)	4.45	
Group 3 (N=6)	1.67	0.138
Group 1 (N=12)	5.33	
Group 3 (N=6)	1.67	0.11

SAFETY

The sponsor submitted safety data from several sources, which they denote as primary and secondary.

Primary

A total of 651 unique individuals received tetrabenazine in this database.

A total of 150 subjects received tetrabenazine in Phase 1 studies.

A total of 514 patients received tetrabenazine in controlled and open-label Phase 2/3 studies.

Specifically, in Study 004, the only study in which treatment-naïve patients were exposed to tetrabenazine in a controlled setting, 54 patients received drug.

An additional 27 unique patients (who had been randomized to placebo in the controlled phase) received tetrabenazine in the open-label extension (Study 007) to Study 004 (a total of 75 patients received tetrabenazine in Study 007).

Study 011 was an open-label titration study in patients with Chorea. A total of 123 patients received drug in this study; 76 had HD, 47 had chorea not associated with HD.

In Study 005, 30 patients received tetrabenazine; 29 of these continued drug in an open-label extension (Study 006).

Finally, in Study H-721, a total of 280 patients without chorea (but with hyperkinetic movement disorders) received drug in a "compassionate" use protocol at Baylor College of Medicine.

Secondary

Nitoman 003

This was an open-label study in 757 patients with hyperkinetic movement disorders conducted by Roche in Canada between 1989-1995. Records were available for 541 patients. Of these 541, 66 patients had HD.

Deaths

A total of 69 patients died in the studies described above.

Study 004

One 40 year old man committed suicide; he had been treated for 65 days, and was receiving a dose of 87.5 mg/day at the time of his death. This patient had a history of suicidal ideation.

Study 007

One 55 year old woman died of metastatic breast cancer after 451 days of treatment.

Study 011

A total of 18 patients died in this study. Very little documentation or description of these patients is available. The data submitted by the sponsor for this study were taken from patient records and transcribed onto CRFs years after the patient records had been created. Of these 18 deaths, 9 were considered due to "end-stage" HD (2 with aspiration pneumonia), 2 were due to MIs, 3 were related to either pneumonitis or pneumonia (one explicitly stated to be due to dysphagia and aspiration), 2 were related to "unknown" causes, and one each due to lung carcinoma and peptic ulcer with hemorrhage. Two of the pneumonia deaths occurred at 20 and 36 days of treatment. A total of 9 of the deaths occurred after at least 1000 days of treatment. Of the remaining 7 deaths, the duration of treatment in 6 varied from 193-884 days; duration of treatment was not available for one patient.

Of particular note, an inspection of this site by the Agency's Division of Scientific Investigations revealed that Dr. Jankovic, the investigator, did not record all cases of dysphagia, because he considered it related to the underlying HD; therefore, how many cases of dysphagia occurred (with resultant aspiration pneumonia) is unknown.

Study H-721

A total of 4 patients died in this study.

A man with Tourette's syndrome had a suicidal gesture consisting of an overdose of tetrabenazine. However, his death was related to a suicide more than a month after discontinuing the drug.

Three women died of cardiovascular disease from months to years after discontinuing treatment with tetrabenazine.

Nitoman 003

A total of 45 patients died in this study, 10 of whom had HD. Data are relatively incomplete for these patients as well.

Of the 10 patients with HD who died, 6 died of aspiration pneumonia secondary to dysphagia, 3 died of "end-stage" HD, and 1 died of a subarachnoid hemorrhage.

Of the 35 deaths in patients with other movement disorders; 10 were related to dysphagia/aspiration pneumonia, 4 each were related to CVA and MIs, and the cause for 11 was unknown.

Serious Adverse Events (SAEs)

The following were the SAEs that led to discontinuations.

A total of 12 patients suffered SAEs that led to discontinuation of treatment with tetrabenazine.

Study 004

One patient, described above, committed suicide. Another patient fell with a resultant subarachnoid hemorrhage. A third experienced restlessness (which decreased after a decrease in dose) and suicidal ideation (presumably secondary to the resultant increase in chorea related to the decrease in dose), and a fourth patient discontinued due to a diagnosis of breast cancer.

No placebo patients reported an SAE.

Study 006

One woman discontinued secondary to nausea and dehydration.

Study 007

One woman died from breast cancer. One man discontinued because of depression, agitation, anxiety, and akathisia.

Nitoman 003

A total of five patients discontinued secondary to an SAE.

The one patient with HD had aspiration pneumonia, GI hemorrhage, and dehydration. The other four patients had dystonia, confusion, depression, and "intercurrent illness".

A total of 41 patients experienced SAEs that did not result in discontinuation.

Study 006

A total of 6 patients experienced SAEs that did not lead to discontinuation of treatment.

One woman had a fall, one woman had diarrhea and depression, two men had infections (pneumonia; UTI), one man had chest pain (presumably non-cardiac), and one woman developed hallucinations and suicidal ideation (she had a history of depression, and in this case had discontinued her antidepressants).

Study 007

A total of 6 patients had SAEs that did not lead to discontinuations.

Three (3) patients suffered falls that led to hospitalization. Two were noted to have pneumonia (one was noted to have dysphagia). Two other patients were diagnosed with cancer. One other patient had an elective hip replacement.

Study 011

A total of 23 patients experienced SAEs without discontinuing treatment.

A total of 7 patients had pneumonia (6 described either as aspiration pneumonia or associated with dysphagia), 5 patients had dehydration, 3 had suicidal ideation. No other specific event was present in more than one patient.

Nitoman 003

A total of 8 patients had an SAE that did not lead to discontinuation. The one patient in this group with HD experienced "over sedation". One patient had pancreatitis and renal and hepatic failure. The other events listed were insomnia, sedation, and dysphagia.

Discontinuations

Several patients discontinued from Phase 1 studies, none related to drug treatment, almost all for protocol violations.

Study 004

One placebo patient discontinued. A total of 5 drug-treated patients discontinued treatment. The patient who died and the patient who fell and suffered a subarachnoid hemorrhage have been described.

Another patient discontinued after 71 days of treatment (final dose 12.5 mg) due to psychosis and paranoia. Another patient discontinued after a breast mass was found, and another developed akathisia after 50 days of treatment (final dose was 37.5 mg).

Studies 006,007

One patient from Study 005 did not continue into open-label because of inability to travel to the investigational site.

One patient discontinued because of nausea and dehydration 27 days after initiating treatment in Study 006, and another discontinued from the same study upon placement in a nursing home.

A total of 2 placebo patients from Study 004 did not enter Study 007, and 2 patients who received tetrabenazine in Study 004 did not enter Study 007; no reasons were given.

A total of 19 patients discontinued treatment with tetrabenazine in Study 007.

Two of these patients have previously been described (death from breast cancer; depression, anxiety, akathisia [this last patient was listed as "consent withdrawn"]).

One other patient developed suicidal ideation after 145 days of treatment. Two patients developed akathisia (one after 175 days of treatment [this patient also developed depression that did not remit with discontinuation], one after 153 days [this latter patient was described earlier]). One patient developed unsteady gait, two others were lost to follow-up, 6 patients were listed as "consent withdrawn" (see above; one other in this group experienced severe anxiety at the time of discontinuation).

One patient had abnormal liver function tests (maximum ALT of 289 IU/L, AST of 76 IU/L, GGT 131 IU/L about 2 months after enrollment in Study 007; ALT was 83 [2X ULN] at the end of Study 004). Three weeks after discontinuation of treatment, his ALT was normal, with a residual GGT of 131 IU/L.

One had an abnormal bilirubin (1.42 mmol/ml at the end of 004; bilirubin of 1.75 mmol/ml after 6 months in Study 007 [ULN 1.2], one met an exclusion criterion, one was considered to have had disease progression, and one patient had vocal tics (after 140 days of treatment; the tics did not resolve when tetrabenazine was discontinued).

Study 011

Of the 145 patients in this study who were treated for chorea at Baylor, 27 are still being treated in Study H-721. Of the remaining 118, 22 went into Study 005. Fourteen of the remaining patients died and twelve discontinued due to financial/travel difficulties. A total of 10 patients discontinued because of inadequate symptom control.

A total of 33 other patients discontinued for "other" reasons (including placement in a nursing home, lost to follow-up [6], disease progression, and transfer to another physician). A total of 28 other patients discontinued for reasons that were not entirely clear, but who reported adverse events at the time of discontinuation. Some of these events included 8 patients with depression, 6 patients with somnolence, 2 with parkinsonism, 2 with akathisia, (2 others with "restlessness", and one other with "movement disorder").

Study H-721

For these patients who were treated at Baylor and who did not have chorea, the sponsor cannot confirm which specific adverse events were responsible for discontinuations. The following partial list describes the AEs in the 45 patients who discontinued, excluding deaths:

Drowsiness/fatigue:	20
Parkinsonism:	13
Depression:	10
Nausea/vomiting:	9
Akathisia:	6

The sponsor presented analyses of specific adverse events of interest in the initial submission. I will briefly describe these analyses.

Sedation

A total of 19 (15%) of the 125 subjects in Phase 1 studies reported sedation. In single dose studies, 11% reported sedation after 12.5 or 25 mg, and 25% of subjects receiving a 50 mg dose reported sedation. In repeat dose studies, over 50% of patients receiving 25 mg/day reported sedation.

In Study 004, a total of 15 (28%) of patients receiving tetrabenazine had to have their dose decreased or did not have a scheduled increase in dose because of sedation; in almost all patients, the sedation resolved. No placebo patients complained of sedation. In Study 006, 28 patients (37%) experienced sedation.

A total of 3 (10%) of patients in Study 007 reported sedation.

In Study 011, 37 (38%) of HD patients reported sedation, and 28 (60%) of patients with non-HD related chorea experienced sedation. A total of 74 (26%) of patients with other hyperkinetic movement disorders also complained of sedation.

Depression

Study 004

In this controlled trial, 56% of the tetrabenazine and 67% of the placebo patients were being treated with anti-depressants. During the study, an additional 3 drug and 1 placebo patient started anti-depressant therapy. There was a statistically significant difference in the mean HAM-D between placebo and drug ($p=0.003$), in favor of placebo. A total of 8 drug (15%) and 0 placebo patients reported depression as an adverse event.

Across all HD studies, 15-30% of patients reported depression as an adverse event. In patients with non-HD chorea, 21% reported depression as an adverse event, and in patients with movement disorders other than chorea, 9% reported depression as an adverse event. In Study 007 (the extension of Study 005), 24% of patients reported depression.

Suicide/suicidal ideation

In Study 004, two drug-treated patients were reported as having either suicidal ideation or suicide. The sponsor conducted an analysis using the "Columbia" classification developed for use with the anti-depressants (in which patient narratives are reviewed in a blinded manner and classified into categories that define potential suicidal thinking and/or behavior); they determined that these were the only patients in this study who could reasonably be considered to have had "real" events, although the initial screen revealed a total of 12 patients who were considered to have had possibly suicide related adverse events (the other 10 were classified as Code 8, Other [i.e., whether or not these events represented true suicidality could not be determined]).

Insomnia

In Study 004, 12 patients (22%) reported insomnia; no placebo patients reported this event. A similar number of patients (21%) reported insomnia in Study 007, the extension phase of Study 004, and in Study 011 (28%).

Parkinsonism

In Study 004, 1 patient (2%) reported parkinsonism as an adverse event, but 6 patients had their dose reduced or titration curtailed because of parkinsonism. A

total of 2 patients (3%) reported parkinsonism as an adverse event in Study 007, and 14% reported parkinsonism in Study 011.

In Study 004, a total of 5 patients (9%) experienced akathisia, compared to 0 placebo patients. In Study 007, 11 patients (15%) reported akathisia; a similar number (12%) reported akathisia in Study 011.

Dysphagia/Pneumonia

In Study 004, 1 patient (2%) reported dysphagia. In Study 007, 2 patients (3%) reported dysphagia. In Study 011, 15% of patients reported dysphagia.

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On Original

Common Adverse Events

In Study 004, the only controlled trial in naïve patients, the following incidences of adverse events were seen in at least 2 patients on tetrabenazine and at a frequency greater than in the placebo group:

Event	Tetra (N=54)	Placebo (N=30)
Somnolence	31%	3%
Insomnia	26%	0%
Fatigue	24%	13%
Nausea	17%	0%
Fall	17%	13%
Agitation	15%	0%
Anxiety	15%	3%
Depression	15%	0%
URI	13%	7%
Irritability	9%	3%
Ataxia	9%	0%
Akathisia	9%	0%
Diarrhea	7%	10%
Cough	7%	10%
Headache	6%	3%
Bradykinesia	6%	0%
Abnormal gait	6%	0%
Apathy	6%	0%
Anorexia	6%	0%
Vomiting	6%	3%
Dizziness	4%	3%
Hypertonia	4%	0%
Abdominal pain	4%	0%
Aggression	4%	0%
Confusion	4%	0%
Dysuria	4%	0%
Bronchitis	4%	0%
Dyspnea	4%	0%
Back pain	4%	0%
Obsessive compulsive Behavior	4%	3%

Laboratory findings

There were no important changes in routine laboratory findings, save for a mean change from baseline in ALT of 12 compared to 2 in the placebo group. This

change was largely accounted for by 3 patients whose maximum ALTs were 145, 447, and 174 IU/L.

Vital signs

There were no important changes in vital signs.

EKGs

In Study 004, there were no important EKG changes, including changes in the QT interval duration.

However, the sponsor also performed a "thorough" QT study in which the effects of single doses of 25 and 50 mg of tetrabenazine on the QT interval were compared to single doses of moxifloxacin 400 mg (active control) and placebo. Dr. Yasuda has performed a detailed review of this study. In brief, according to Dr. Yasuda, the maximum mean change from baseline drug-placebo difference occurred at 2.5 hours after dosing for all 3 active treatments; this difference was about 12 msec for moxifloxacin, and about 7.5 msec (upper bound of the 95% CI 10 or slightly greater, depending upon the correction used) for the tetrabenazine 50 mg single dose. As she notes, the 50 mg dose is greater than any single dose recommended for a 100 mg/daily dose (to be given in a tid regimen).

COMMENTS

The sponsor submitted the results of two randomized controlled trials that, as noted earlier, the Agency concluded establish the effectiveness of tetrabenazine in the treatment of the chorea of HD. The results of Study 004 are quite robust in this regard, with the primary analysis yielding an extraordinarily low p-value, with extraordinary consistency of the finding across 14/15 centers, and with other ancillary analyses (including an examination of response by dose, withdrawal data, and the pattern of response in patients re-treated in Studies 006 and 007) yielding very positive results.

Study 005, on the other hand, did not meet the usual standard ($p=0.05$) for being a "positive" study; the p-value for the between-treatment comparison was 0.078. The sponsor suggested that this result was related to a study conduct issue, specifically that patients inappropriately had their morning dose of active drug withheld on the morning of Day 3, making Group 2 patients more like placebo patients (Group 1) than like patients who were, by protocol, to be continued on treatment (although these patients were not identical to Group 1 patients, in that the latter were off drug for three days, and the Group 2 patients had been off drug for 12-18 hours). In order to address this issue, the sponsor performed numerous post hoc analyses, which are described above.

We concluded that the most reasonable way to analyze this study was to compare Group 1 patients to Group 3 patients at Day 3. Although this was clearly a post hoc analysis, this analysis keeps complete faith with the protocol specified analysis, which was to compare patients off drug for 3 days to patients still on drug. This analysis yielded a p-value of 0.1 (relatively close to 0.05, given the very small numbers of patients in the analysis), and, importantly, the estimate of the treatment effect in this study was essentially identical to that seen in Study 004; about 3.5 points on the Chorea items of the Motor scale of the UHDRS (although it is true that there were baseline differences in the mean Chorea scores between these 2 groups; 9.4 in Group 1 and 11.2 in Group 3).

Although we did not conclude that the sponsor had submitted data that established substantial evidence of effectiveness under the typical requirement of evidence from at least two independent adequate and well-controlled trials, we did conclude that the evidence was consistent with the statutory standard of substantial evidence derived from a single adequate and well controlled trial plus confirmatory evidence.

In particular, Agency guidance describes the elements that could serve to support the use of single trial as providing substantial evidence of effectiveness, and many of these elements are present here, including a very small p-value, equivalent effects in sub-groups of different disease severity, and numerical superiority of drug compared to placebo in 14/15 study sites. Further, there is evidence of dose response, and the data from the withdrawal week in this study, as well as the pattern of responses in patients whose treatment was re-initiated (or initiated) in Studies 006 and 007 provide powerful confirmatory evidence of effectiveness. Although this language (confirmatory evidence) is not used in the Agency guidance, these sorts of findings are described in that document to serve exactly the same ends as confirmatory evidence; that is, to support the use of a single adequate and well controlled trial as providing substantial evidence.

Further, we did consider the results of Study 005 as being confirmatory.

Specifically, as noted earlier, we concluded that the Group 1 vs Group 3 analysis was an appropriate analysis, given the error in the study conduct. The results of this analysis yielded an estimate of the treatment effect essentially identical to that seen in Study 004; further, although the between-treatment contrast did not achieve statistical significance, this is not unexpected, given the very small number of patients included. Ordinarily, it should be noted, a "failed" second study should not be considered to "confirm" another, "positive" study. However, for the reasons stated above, we concluded in this case that it was reasonable to consider the elements described above in Study 004, together with the results of Study 005, to constitute "confirmatory evidence". For these reasons, we concluded that the sponsor had provided substantial evidence of effectiveness for tetrabenazine as a treatment for the chorea of HD.

The PCNS AC was clearly in agreement that the sponsor had provided substantial evidence of effectiveness for tetrabenazine as a treatment for the chorea of Huntington's Disease.

However, examination of several of the secondary outcomes in Study 004 revealed results that we found troubling.

Specifically, on the components of the UHDRS other than the motor score (which numerically favors drug, largely related to the effect on chorea), patients receiving placebo performed better than those on tetrabenazine, with several of these differences achieving nominal statistical significance. Specifically, patients on placebo performed superiorly on the Functional Assessment, the Behavioral Assessment, the Independence Scale, the Functional capacity, and the Cognitive Assessment.

These sorts, and frequency, of differences favoring placebo are unusual (for an effective drug). These findings do not undermine the effects on chorea, but they did raise significant questions about the approvability of the application. Study 004 did not include a patient/caregiver assessment of the utility of the treatment; it is possible that the effects on the chorea did not compensate, in the patient's/caregiver's mind, for any of these potentially negative effects that the drug seems to be associated with (assuming any of these negative findings on these scales have detectable clinical consequences). Indeed, it may be difficult to assess in this population any (subtle) deleterious effects of the sorts suggested by these negative findings, although they may be present (and possibly progressive).

In addition to the (potentially adverse) findings described above, it appears that the use of tetrabenazine is associated with the occurrence of several significant safety issues, including parkinsonism, depression, EPS, somnolence, and dysphagia resulting in aspiration pneumonia (with potential significant underreporting of this event). Although the incidence of a number of these events was not greater in the drug-treated patients than in the placebo-treated patients in Study 004, in some cases they were (for example, depression 15% on drug, 0 on placebo; akathisia 9% vs 0), and these events were seen in considerable numbers in open-label experience.

It is important to point out that, with regard to these findings (both the findings on the UHDRS and the frank adverse events), their (potential) drug-relatedness may be confounded with the progression of HD. That is, with progressive disease, patients develop cognitive and behavioral changes, as well as parkinsonism, dysphagia, depression, etc. This raised the concern that, even if these findings may be drug-related in any given case, the prescriber might be likely to attribute them to progressive disease, and not drug treatment (especially if the chorea continues to be well-controlled). In such a case, it might further be likely that the drug will be continued, and, at least theoretically, these findings may convert

from being reversible (there is some evidence that this might be true for some of these events with short term treatment) to becoming irreversible (again, we have no reliable information, given the open-label nature of the long-term experience, about either the incidence of these events, or their reversibility with long durations of exposure).

The interpretation of the safety data was also complicated by some methodological difficulties, as described above. For example, there is little information presented about the cause of death in many of these patients, and, as noted, the true incidence of dysphagia in the Baylor experience is unknown, given that Dr. Jankovic attributed this event to progressive disease, and therefore did not record it in all cases. Further, the results of the thorough QT study strongly suggest that, at least at a single 50 mg dose, there is the potential for a significant prolongation of the QT interval.

Drs. Carol Davis and Lourdes Villalba reviewed the sponsor's response to the Approvable letter in detail. As Dr. Davis has noted, although it is true that most of the between-treatment comparisons favoring placebo were not statistically significant and the differences were small, there seem to be no compelling reasons to conclude that the original directionality of the differences (i.e., favoring placebo) was inaccurate, or as the result of inappropriate analyses.

As Dr. Villalba notes, most of the adverse events of concern (depression, parkinsonism, akathisia) appear to be dose related, and in most cases, when the dose was decreased, the symptom resolved, if not entirely, at least to a large degree. It appeared that after the decrease in dose in many cases, there was still an important beneficial effect on the chorea, albeit often a smaller effect than at the higher doses (Dr. Atul Bhattaram's pharmacometrics review clearly establishes a dose response for the effect on chorea, although a dose response for the adverse effects was more difficult to show formally). Nonetheless, there were cases of adverse events (especially depression) that appeared to not resolve with drug discontinuation, or to resolve very slowly of time (of course, in any given case, it is difficult to discern if depression was drug related, given the high prevalence of depression in patients with HD). Whether or not tetrabenazine is associated with dysphagia is difficult to tell; there was no increased incidence in Study 004 compared to placebo, but there were numerous cases in the open-label experience (again, dysphagia occurs spontaneously in patients with HD). As noted earlier, in a significant subset of the patient experience presented, not all cases of dysphagia were recorded, making an accurate assessment of the occurrence of this event problematic.

At the 12/6/07 PCNS AC meeting, we asked the sponsor to answer the following questions:

- 1) Do the findings on the secondary efficacy outcomes (lack of a beneficial effect of tetrabenazine on numerous measures of function and cognition and/or numerical superiority of placebo on some measures) by themselves raise sufficient concerns about the utility of tetrabenazine's effect on chorea to justify not approving the application?
- 2) If not, is the panoply of adverse effects associated with tetrabenazine use sufficient to justify not approving the application? When considering this question, we are particularly interested in hearing the committee's views about any maneuvers that might mitigate these risks sufficiently to justify approval (e.g., reducing the dose, discontinuing the drug, instituting concomitant treatments [e.g., antidepressant therapy]). Further, we are also interested in the committee's views of the aforementioned Agency concerns that it might be difficult for the practitioner to discern if clinical worsening in various areas (e.g., cognition, depression, etc.) is drug related or not, with the possibility that, if drug related, the adverse events could become severe and/or irreversible.
- 3) If the committee determines that, for any reason, the application should not be approved, what studies (if any) could the sponsor perform to establish the necessary substantial evidence of effectiveness and/or safety in use?

The Committee clearly did not consider the findings on the secondary outcomes of concern. In particular, the Committee was convinced that the differences favoring placebo on various measures were quite small and of uncertain clinical meaning. Also, the sponsor presented data that suggested that long-term changes in functional measures in treated patients in the application were very similar to those seen in placebo patients in a large previously performed study of HD patients (CARE-HD). Further, the sponsor presented evidence that tetrabenazine patients in Study 004 were significantly worse than placebo patients on a particular cognitive measure at baseline (Symbol Digit Modalities Test) which they believed accounted for a major portion of the variance in the between-treatment difference on the Stroop, and that an absence of an effect on Verbal Fluency and the Stroop Interference score was evidence that there was no adverse effect on executive function. Also, on the Functional Assessment, the sponsor noted a (nominally) statistically significant increase in the number of placebo patients who filled out the check list by themselves; the company asserted that this could have resulted in an under-estimate of their impairment. When they examined the results of questionnaires which were completed by both patients and caregivers, the results quite clearly favored tetrabenazine.

These considerations led the committee to the conclusion that the small changes on those measures favoring placebo were of no clinical consequence.

Regarding adverse events, although the committee took note of the findings, they did not consider any of the adverse events as posing a bar to approval. They were convinced, on the whole, that the adverse events could be managed successfully with dose reduction and/or institution of appropriate concomitant medication (e.g., anti-depressants). With regard to the question of the difficulty of attributing causality to the treatment given the background rate of some of these events in this population, the committee was convinced that appropriate labeling directing the prescriber's attention to the issue would suffice to ensure (as much as possible) appropriate clinical behavior.

The committee did not believe any additional studies would be necessary.

We did not ask the committee to formally consider the question of whether or not the sponsor has established that tetrabenazine has a beneficial effect on chorea. As noted earlier, the Agency had concluded that they had. As noted earlier, the Committee clearly agreed that the sponsor had done so.

The sponsor submitted numerous documents in relation to their proposed RiskMAP, including educational materials and a detailed plan for their program. These have been reviewed, but agreement has not been reached with the sponsor about the specific content. Further, several documents we had requested have not yet been submitted. These include:

- 1) survey instruments (intended to assess the success of the educational program)
- 2) a final version of a proposed titration card
- 3) copies of the Dear Health Care Provider and Dear Pharmacist letters
- 4) timelines for re-assessment of the program
- 5) details of the plans for the continued assessment of the program

It has been determined that the RiskMAP will, instead, be considered a Risk Evaluation and Mitigation Strategy (REMS) as described under FDAAA. It should be noted also that the sponsor had proposed a restricted distribution program that the committee, and we, felt was unnecessary. As a result, the sponsor has withdrawn that proposal.

Finally, as noted earlier, the sponsor has agreed to perform the following studies in Phase 4 (again, under FDAAA, these are likely to be considered Post Marketing Requirements [PMRs]):

- 1) an in vivo metabolism study to examine the effects of the major metabolites on CYP2D6
- 2) complete the 2 year carcinogenicity study in male rats
- 3) conduct a 2 year carcinogenicity study in female rats
- 4) conduct a study of fertility and early embryonic development
- 5) submit in vivo metabolism in animals

6) conduct a neurotoxicity study in animals

We have largely agreed with the sponsor on the language for the package insert, but, as noted above, we have not agreed on the content of the elements of the REMS that they have already submitted, and the sponsor has not yet submitted all of the elements of the REMS. Because, under FDAAA, all elements of the REMS need to be in place prior to approval, we recommend that the Agency issue a third Approvable letter.

Russell Katz, M.D.

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/s/

Russell Katz
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MEDICAL OFFICER

Vol 2, Series

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 21-894

Drug: Tetrabenazine (Xenazine)

Route: oral

Indication: Chorea of Huntington's Disease

Sponsor: Prestwick Pharmaceuticals

Review date: March 18, 2008

Reviewer: Alice Hughes, M.D.

In this memorandum, I will discuss selected clinical safety issues addressed in responses to two approvable letters for the tetrabenazine NDA. First, I will discuss Prestwick's April 10, 2007 response to the first approvable letter for the tetrabenazine NDA, which was issued on March 24, 2006. Safety reviewer Dr. Lourdes Villalba has reviewed the sponsor's responses pertaining to safety issues in detail in a memorandum dated November 9, 2007, focusing on the safety issues of major concern that were not considered to have been adequately addressed in the original NDA submission: akathisia, depression, dysphagia, and parkinsonism. In this memorandum, I will briefly review and comment on Dr. Villalba's key findings and recommendations pertaining to each of these topics and offer my own comments.

After reviewing Prestwick's response, tetrabenazine's risk-benefit profile was presented and discussed at a Peripheral and Central Nervous System Drug Advisory Committee Meeting on December 6, 2007. Although the Advisory Committee unanimously recommended approval of tetrabenazine, they considered the development of a risk minimization plan that focused on education pertaining to the important risks of tetrabenazine, while at the same time not making drug acquisition too burdensome (e.g., by means of a restricted distribution program), to be important. The FDA considered the prescribing information and risk minimization plan submitted by the sponsor in their complete response to the March 24, 2006 approvable letter to be insufficient to insure safe use of tetrabenazine, and issued another approvable letter on December 26, 2007.

The sponsor submitted a complete response to this second approvable letter on January 18, 2008, which I will review briefly in this memorandum. The sponsor's complete response is discussed in greater detail in a memorandum by Dr. Villalba dated March 17, 2008. Here, I will focus on modifications to the risk minimization plan that were negotiated with the sponsor subsequent to the submission of the initial complete response, and make a recommendation for regulatory action from the perspective of clinical safety.

1 Review of key clinical safety issues addressed in response to March 24, 2006 Approvable letter

1.1 Depression

In the 12-week placebo-controlled Study 004, 19% (10/54) of tetrabenazine-treated patients had an adverse events of depression or worsening depression compared to no (0/30) placebo-treated patients. In all tetrabenazine-treated patients in Prestwick-sponsored studies, 42% (47/111) of patients had new or worsened depression. There was one case of completed suicide in the placebo-controlled study 004 and two cases of suicidal ideation. Depression was reported as early as four days into tetrabenazine treatment, and occurred at doses as low as 25 mg/day. Approximately 40% of the cases of new or worsening depression were treated with dose reduction (+/- antidepressant medication), and approximately 40% of these cases had resolution of depression 1-7 months after dose reduction. One of the three patients who underwent dose reduction relapsed and attempted suicide in the subsequent open-label study 007. In her review, Dr. Villalba addresses potential imbalances in baseline measures of depression in Study 004; of note, more patients in the placebo-treated group were treated with antidepressants at study entry (67% vs. 56%), and more patients in the tetrabenazine-treated group had a previous history of depression (63% vs. 47%).

1.1.1 Team Leader comment

Depression and suicidality were markedly more frequent among tetrabenazine-treated patients compared to placebo-treated patients in the placebo-controlled Study 004, providing strong evidence that depression, although also associated with Huntington's disease itself, is a drug-related adverse event. Depression is a potentially life-threatening adverse event; indeed, there was one completed suicide in a controlled study in addition to cases of suicidal ideation and suicide attempt. Although some of the difference between rates of depression in tetrabenazine- and placebo-treated patients may have been due to baseline imbalances between treatment groups (more tetrabenazine-treated patients had a history of depression, and more placebo-treated patients were taking antidepressants at study entry, thereby potentially protecting them from new or worsening depression), these differences are unlikely to account for the striking difference observed between the treatment groups.

Depression in tetrabenazine-treated patients may be challenging to manage in a real world clinical setting if tetrabenazine is approved. Because depression is associated with Huntington's disease itself, it may be very difficult to distinguish drug effect from disease effect. In addition, the response to dose reduction is questionable. Dr. Villalba argues, based on the course of patients with depression who underwent dose reduction in clinical studies, that decreasing the tetrabenazine dose is beneficial and should be the first course of action if a patient develops depression while being treated with tetrabenazine. In my view, although this could be a reasonable approach, it is possible that the response to dose reduction that was evident for some patients with depression in clinical trials could have been due to the natural waxing and waning course of depression. Moreover, it must be kept in mind that over half of the tetrabenazine-treated patients with depression did not

have a favorable response to dose reduction. Even for those patients who do improve following dose reduction, depression may take a long time to abate (up to several months in the clinical studies).

Evidence from the clinical studies suggests that depression may occur at any dose and at any time on treatment. Although the sponsor has proposed slow titration as a strategy for minimizing the risk of depression, they have presented scant evidence that slow titration is beneficial in reducing the risk of depression.

Because of the risk for depression and suicidality with tetrabenazine, I think extreme caution should be exercised in treating patients with a history of depression with tetrabenazine.

The prescribing information should include a Black Box Warning pertaining to the risks for depression and suicidality, and these risks should be a primary focus of the risk minimization plan. Patients with active _____ suicidality should not be treated with tetrabenazine, and if depression occurs on tetrabenazine therapy, the dose should be reduced, and consideration should be given to initiating antidepressant treatment. Tetrabenazine should be stopped if depression continues despite these measures.

1.2 Dysphagia

In her analysis of dysphagia with tetrabenazine, Dr. Villalba included cases of both dysphagia and choking, given that dysphagia is a likely contributor to choking events. In the 12-week placebo-controlled Study 004, 3.7% (2/54) of tetrabenazine-treated patients had an adverse event of dysphagia or choking compared to 3.3% (1/30) of placebo-treated patients. In all tetrabenazine-treated patients in Prestwick-sponsored studies, 10% (11/111) of patients had dysphagia or choking. Dysphagia was reported as early as 3 to 4 weeks into tetrabenazine treatment, and occurred only at doses ≥ 50 mg/day. Four of the eleven tetrabenazine-treated patients who developed dysphagia underwent dose reduction; all had resolution of their dysphagia within one day to six months. Dysphagia was rarely considered by investigators to be a drug-related adverse event.

1.2.1 Team Leader Comment

Dysphagia is a potentially life-threatening adverse event. Aspiration pneumonia, which occurred in one patient with dysphagia in Study 007 and four patients with dysphagia in Study 011, is one of the more ominous complications of dysphagia. The data in the tetrabenazine database do not, however, provide definitive evidence that tetrabenazine causes dysphagia (as opposed to it being an event related to the underlying disease process). The risk and rates of dysphagia in tetrabenazine-treated patients in Study 004 were very similar, although higher than the rate of dysphagia is the CARE-HD study. It is possible that dysphagia is a drug-related adverse event that requires a certain amount of exposure time to become manifest, although this is speculative. This potential risk, and the uncertainty surrounded this risk, should be addressed with a Precautions statement in labeling.

1.3 Akathisia

In her analysis of akathisia with tetrabenazine, Dr. Villalba included cases of both akathisia and restlessness, because she does not think that akathisia can be reliably distinguished from restlessness. In the 12-week placebo-controlled Study 004, 20% (11/54) of tetrabenazine-treated patients had an adverse events of akathisia or restlessness compared to no (0/30) placebo-treated patients. In all tetrabenazine-treated patients in Prestwick-sponsored studies, 23% (26/111) of patients had akathisia or restlessness. Akathisia or restlessness was reported as early as 19 days into tetrabenazine treatment, and occurred at a range of doses. In Study 004, all cases of akathisia or restlessness occurred at doses ≥ 50 mg/day and the median dose at first onset was 75 mg/day. Three cases occurred at doses < 50 mg/day in Study 007. Akathisia was not consistently reported to be a drug-related adverse event. In 20 cases of akathisia or restlessness, patients underwent dose reduction. In 13 of these cases, the akathisia/restlessness resolved (within 2 days to 11 months after the dose reduction).

1.3.1 Team Leader comment

Akathisia is an expected adverse event associated with dopamine antagonist therapy (it stands to reason that dopamine depletors would also share this risk). The tetrabenazine database provides strong evidence that tetrabenazine causes akathisia. Akathisia and restlessness were markedly more frequent among tetrabenazine-treated patients compared to placebo-treated patients in the placebo-controlled Study 004. I think that Dr. Villalba's approach of combining akathisia and restlessness in her analysis of akathisia is reasonable; even using a more conservative approach of counting only those adverse events that were coded as akathisia, there is strong support for a causal effect. The data suggest that there may be a relationship between the development of akathisia and higher tetrabenazine doses, although the occurrence of akathisia at lower doses in Study in 007 suggests a relationship between akathisia and exposure time, rather than dose per se. This, however, is speculative.

The risk for akathisia should be addressed in a Precautions statement and should also be addressed as part of a risk minimization plan.

1.4 Parkinsonism

In the 12-week placebo-controlled Study 004, 15% (8/54) of tetrabenazine-treated patients had an adverse event of parkinsonism compared to no (0/30) placebo-treated patients. In an analysis of all potential extrapyramidal symptoms in Study 004, Dr. Villalba found that 40% (22/54) of tetrabenazine-treated patients had adverse events in this category compared to 3.3% (1/30) of placebo-treated patients. In all tetrabenazine-treated patients in Prestwick-sponsored studies, 12% (13/111) of patients had parkinsonism. Parkinsonism was reported as early as 17 days into tetrabenazine treatment (mean time to onset 29 days; range 17 to 50 days). All new (vs. recurrent) cases occurred at doses ≥ 50 mg/day (median dose at time of onset was 62.5 mg/day). Approximately half (5/9) of the patients who underwent dose reduction or discontinuation of tetrabenazine had resolution of their parkinsonism within 1 day to 3 months after dose reduction, and two additional patients had improvement of parkinsonism following dose reduction.

1.4.1 Team leader comment

The tetrabenazine database provides strong evidence that tetrabenazine causes parkinsonism and other extrapyramidal symptoms, which are adverse events given tetrabenazine's mechanism of action. These adverse events were markedly more frequent among tetrabenazine-treated patients compared to placebo-treated patients in the placebo-controlled Study 004. As with akathisia, the facts that no cases occurred for the first time at doses <50 mg/day, and favorable responses to dose reduction/discontinuation in the majority of cases, provide some support for a dose-response relationship.

The risk for tetrabenazine-induced parkinsonism should be addressed in a Precautions statement and should also be one of the safety issues addressed with a risk minimization plan.

2 Review of response to December 26, 2007 approvable letter

In addition to revised prescribing information, the sponsor's complete response contained a proposal for risk minimization plan with an educational focus, which the Agency had requested in order to insure the safe use of tetrabenazine. In this section of my memorandum, I will briefly discuss both the revised prescribing information as it pertains to clinical safety issues as well as the sponsor's proposed risk minimization plan.

2.1 Prescribing information

The sponsor agreed with all key sections of the prescribing information pertinent to clinical safety that were requested by the Agency in the December 26, 2007 approvable letter. These included a Black Box Warning for depression and suicidality, as well as contraindications for patients with — inadequately treated depression or active suicidality, patients with impaired hepatic function, and patients taking concomitant monoamine oxidase inhibitors. The sponsor agreed to Warnings statements describing the risks of depression and suicidality and the risk of Neuroleptic Malignant Syndrome (the latter is discussed in greater detail in Dr. Villalba's March 17, 2008 memorandum). In addition, the sponsor agreed to Precautions statements describing the following risks: akathisia, restlessness, and agitation; parkinsonism; dysphagia; sedation and somnolence; QTc prolongation, concomitant use of neuroleptic drugs; interaction with alcohol; hypotension and orthostatic hypotension; hyperprolactinemia; and tardive dyskinesia.

The prescribing information also includes dosing recommendations tailored to CYP2D6 metabolizer status, recommending CYP2D6 genotyping for patients requiring daily doses greater than 50 mg (which is the maximum recommended daily dose for patients who are poor metabolizers or who are taking concomitant strong CYP2D6 inhibitors, whereas 100 mg is the maximum recommended dose for normal- and extensive-metabolizers).

Although agreement has been achieved on key labeling issues relevant to clinical safety, some modifications have been and will be requested of the sponsor. Notably, the

Division, in negotiations subsequent to receiving the Complete Response, requested that concomitant reserpine use be added as a contraindication (the sponsor has agreed to this). The Division will also request modifications to the Black Box Warning.

The most recent draft version of prescribing information (reflecting negotiations with the sponsor as of February 26, 2008) is affixed as an appendix to the end of this memorandum.

The sponsor also submitted a Medication Guide, as requested in the approvable letter, which required extensive modifications, which in principle have largely been agreed to by the sponsor. A recent draft version of the Medication Guide (also reflecting negotiations with the sponsor through February, 2008) is affixed as an appendix to the end of Dr. Villalba's memorandum.

The Medication Guide focuses on the risk of depression, stating that the risk of depression is the most important information to know about Tetrabenazine, but also describes the other important risks of tetrabenazine (including neuroleptic malignant syndrome, parkinsonism, restlessness and agitation [akathisia], trouble swallowing, irregular heartbeat, and dizziness upon changing positions), discusses contraindications, and dosing, and lists common side effects.

In terms of depression, the Medication Guide states that tetrabenazine may increase the chance of depression, suicidal thoughts, or suicidal actions in some patients, and that patients should not start taking tetrabenazine if they are depressed or have suicidal thoughts. Patients are admonished to pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts or feelings. Patients are counseled to contact their doctor immediately if they have any symptoms of depression or suicidality (which are listed).

Some aspects of the Medication Guide still need to be negotiated with the sponsor, including how best to describe the potential risk for tardive dyskinesia (this risk is discussed in detail in Dr. Villalba's memorandum).

2.2 Risk minimization plan

The cornerstone of sponsor's proposal in their January, 2008 complete response was a

While potentially useful in terms of ensuring dissemination of educational materials, this plan had the potential to be too restrictive and burdensome and is not necessary to ensure safe use of tetrabenazine. Subsequent to the submission of their January, 2008 Complete Response, the sponsor retooled their educational plan, eliminating the _____ component of the plan and focusing on education. The sponsor submitted revisions to their plan in February and March, 2008, which are still being reviewed by the Division. Some elements of the plan still need to be submitted. The educational plan as submitted focuses on the risks of

depression and suicidality but the sponsor also plans to educate patients and prescribers regarding dosing and other important safety issues related to tetrabenazine.

In addition to prescribing information and the Medguide, the plan includes:

- A Healthcare Professional Guide
- A Patient and Caregiver Guide
- A Dosing and Titration Guide
- A Dear Healthcare Professional Letter
- A Dear Pharmacist Letter (which, in addition to safety, dosing, and drug interaction issues, discusses the need to give out Medication Guides with each filled prescription)
- Unit of use packaging
- Ongoing Healthcare Professional education (not described in detail, but to include annual mailings to prescribers and potential prescribers)
- Patient, caregiver, and prescriber knowledge surveys (not described in detail)

3 Concluding comments

The core structure and principles of the educational plan most recently submitted by the sponsor are acceptable to adequately communicate the risks of tetrabenazine, including the risks of depression and suicidality as well as the other serious risks (described in this review and in FDA reviews done during prior review cycles). Prescribing information, including the Medication Guide, is largely adequate at this point in its description of the major clinical safety issues (see Appendix I).

The risk minimization plan as submitted, however, remains inadequate. Critical components of the plan have not yet been submitted. All elements of the plan should be submitted and fully reviewed prior to approval of tetrabenazine; otherwise, we cannot have adequate certainty that tetrabenazine can be prescribed appropriately by adequately informed physicians and used safely by patients and caregivers who have been adequately educated about all of tetrabenazine's known serious risks, including but not limited to the risks of depression and suicidal thoughts and behavior.

In addition, educational materials need to describe dosing as it relates to CYP2D6 metabolizer status in more detail, as the recommendation for genotyping when doses over 50 mg are required are novel and both physicians and patients/caregivers will likely need more explanation than is currently provided in the educational materials.

Because tetrabenazine would meet the requirements for needing a required Risk Evaluation and Mitigation Strategy (REMS) under the provisions of Food and Drug Administration Amendments Act of 2007 that go into effect on March 25, 2008, elements required under a REMS should also be requested at this time.

Including these elements, the following items are outstanding and preclude approval at this time:

- Prescriber/patient knowledge survey methods and tools
- Dosing titration card
- Full-color mock-ups of a completed Medication Guide, Healthcare Professional Guide, Dear Healthcare Professional letter, Patient and Caregiver Guide, and Dear Pharmacist letter (the Division has reviewed drafts of the first three items and has comments for the sponsor; the remaining items still need to be reviewed at this time)
- Timeline for re-evaluation and assessment of the risk mitigation plan that is consistent with the relevant new regulations
- Final prescribing information that has been agreed to by both the FDA and the sponsor

I therefore recommend an approvable action.

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Alice T. Hughes
3/18/2008 12:28:40 PM
MEDICAL OFFICER

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: March 6, 2008

To: Russell Katz, M.D., Director
Division of Neurology Products (HFD-120)

Through: Michael Klein, Ph.D., Acting Director
Controlled Substance Staff (HFD-009)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff (HFD-009)

Subject: Label review
Xenazine (tetrabenazine)
NDA 21-894
Treatment for Huntington's Disease
Sponsor: Prestwick Pharmaceuticals, Inc.

Background:

The Division of Neurology Products (HFD-120) consulted CSS regarding the abuse potential of tetrabenazine (Xenazine). Tetrabenazine acts as an inhibitor of the brain vesicular monoamine transporter type 2 (VMAT2), which induces the depletion of monoamines such as dopamine, norepinephrine, and serotonin. It is being reviewed for the indication of Huntington's Disease, under Orphan Drug status. The initial proposed therapeutic dose is 25 mg (p.o.), with increases in dose each week by increments of 12.5 mg (p.o.) up to 100 mg/day until satisfactory control of chorea is attained or until adverse events become intolerable.

The Sponsor proposes that the drug label state under the *Controlled Substance Class* subheading of *Drug Abuse and Dependence* that "tetrabenazine is not a controlled substance". In the *Physical and Psychological Dependence* subheading, the Sponsor proposes language stating that tetrabenazine "

_____ / / / / /

Conclusions and Recommendations:

Based on information provided by Prestwick Pharmaceuticals, Inc. in the NDA, CSS concludes that tetrabenazine is unlikely to have sufficient abuse potential that would warrant scheduling.

This conclusion is based on the following:

- * Central nervous system (CNS) adverse events observed in clinical efficacy trials do not include euphoria or other positive subjective effects indicative of abuse potential.
- * The clinical profile of patients who experienced overdose with tetrabenazine at doses up to 750 mg orally is typically limited to somnolence and cognitive impairment.
- * Adverse events with tetrabenazine observed during post-marketing experience in countries other than the U.S. over the past 30 years are similar to those seen during the clinical trials for Huntington's Disease in the present NDA.
- * Abrupt discontinuation of tetrabenazine did not produce adverse events other than a re-emergence of Huntington's Disease-associated choreas. This suggests that tetrabenazine does not produce a withdrawal syndrome.
- * Tetrabenazine acts as a monoamine depletor because of its ability to block the vesicular monoamine transporter type 2 (VMAT2). Given that increases in dopamine are associated with abuse potential, the decrease in dopamine produced by tetrabenazine suggests a lack of abuse potential.
- * Animal behavioral studies suggest that tetrabenazine does not produce effects similar to those produced by known drugs of abuse.

CSS recommends that the *Drug Abuse and Dependence* section (LINES 1054 – 1067) of the proposed label be revised according to the above conclusions, to read as follows:

LINE 1054 – 1067:

Clinical trials did not reveal any tendency for drug seeking behavior, though these observations were not systematic. Abuse has not been observed from the postmarketing experience in countries where tetrabenazine has been marketed. Abrupt discontinuation of tetrabenazine from patients did not produce symptoms of withdrawal or a discontinuation syndrome; only symptoms of the original disease were observed to re emerge. As with any CNS-active drug, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of tetrabenazine misuse or abuse (such as development of tolerance, incrementation of dose, drug-seeking behavior).

I. Summary of Information Related to Abuse Potential from Clinical Studies

A. Clinical Studies Assessing Safety and Efficacy of Tetrabenazine

Clinical Adverse Events Indicative of Abuse Potential

The most frequently observed CNS-associated adverse events that differentiated from placebo included insomnia (22%), depression (15%), sedation (15%), restlessness aggravated (13%), irritability (9%), anxiety (7%), and somnolence (7%). There were no reports of euphoria or other adverse events that would suggest that the sedation observed during clinical trials represents an abuse potential signal.

During clinical trials, 15 of 54 patients (28%) cited sedation as the reason for limitation of upward titration or a decrease in dose. Sedation and somnolence are stated to be observed primarily during periods of dose increases.

Overdose Experience

The label notes that 8 cases of tetrabenazine overdose are reported in the scientific literature in the past 35 years since tetrabenazine was first marketed in countries outside the U.S. The doses in these cases ranged up to 1000 mg. The adverse events observed during overdose were similar to those observed in clinical trials in the present NDA, including somnolence and cognitive impairments.

Post-Marketing Experience in Foreign Countries

Tetrabenazine has been marketed in countries other than the U.S. for over 30 years as a treatment for chorea. The CNS adverse event profile observed in this post-marketing experience is parallel to that seen in the clinical trials for Huntington's Disease in the present NDA. These include: drowsiness, depression, movement disorder, anxiety, insomnia, irritability, confusion, and dizziness. This CNS profile is not associated with abuse potential in the absence of positive subjective effects such as euphoria.

Physical Dependence and Withdrawal Syndrome

A prospective study evaluated the adverse events associated with abrupt discontinuation of tetrabenazine in patients with chorea. Although there was a re-emergence of the chorea symptoms, there were no other signs or symptoms reported that the investigators associated with a withdrawal syndrome. Thus, it appears tetrabenazine does not produce physical dependence.

II. Summary of Information Related to Abuse Potential from Preclinical Studies

A. Receptor Binding

Tetrabenazine is described as an inhibitor of vesicular monoamine transporter type 2 (VMAT2). The functional effect of this pharmacological activity is to preferentially reduce the release of dopamine, as well as other monoamines such as norepinephrine and serotonin. A reduction in these monoamines is not associated with increased abuse potential.

Additionally, tetrabenazine is described as being a weak antagonist at dopamine D2 receptors. The D2-type receptors in the brain are associated with abuse potential, so antagonism at this site suggests that tetrabenazine does not have abuse potential through this dopaminergic mechanism.

Most drugs with abuse potential increase dopaminergic transmission in the brain, and this dopamine signal is associated with pleasurable subjective responses. In contrast, drugs that reduce dopaminergic transmission (such as antipsychotics) typically produce flattening of affect and other negative subjective responses. Thus, it is unlikely that tetrabenazine, a drug that reduces dopaminergic transmission, would produce positive subjective responses in humans that would lead to abuse of the drug.

B. Animal Behavioral Studies

Two behavioral studies that relate to the assessment of abuse potential. In a rat intracranial self-stimulation test, administration of tetrabenazine was found to suppress self-stimulation. Typically, drugs with abuse potential increase self-stimulation in this test. Tetrabenazine also was able to block the effects of amphetamine on self-stimulation. In a separate study, tetrabenazine decreased the rate of responding in rats trained to press a lever to obtain water reinforcement. These results contrast with those produced by the stimulants amphetamine and methylphenidate, in which the two drugs increased the rate of response for water reinforcement.

Both of these rodent studies indicate that tetrabenazine does not produce behavioral responses similar to those produced by drugs with known abuse potential.

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/s/

Katherine Bonson
3/17/2008 09:52:23 AM
PHARMACOLOGIST

Michael Klein
3/17/2008 10:05:39 AM
PHARMACOLOGIST
Acting Director - Controlled Substance Staff

Review and Evaluation of Clinical Data – Efficacy Review

NDA (Serial Number):	NDA 21-894
Sponsor:	Prestwick Pharmaceuticals
Drug:	Xenazine® (tetrabenazine)
Proposed Indication:	Chorea of Huntington Disease
Material Submitted:	Clinical Response to Approvable
Submission Date:	April 5, 2007
	Letter
Review Date:	January 6, 2008
Reviewer:	Carole L. Davis, DO, MPH
	Medical Reviewer, DNP, ODE 1

1. Introduction

The submission, by Prestwick Pharmaceuticals, is a Clinical Response to the Approvable Letter for tetrabenazine (TBZ) issued March 34, 2006 (NDA 21-894, tetrabenazine for the treatment of the chorea of Huntington's disease). The Approvable Letter expressed Agency concern about several of the outcomes in the pivotal study (TBZ103,004; Study 004). Of primary concern was the consistent tendency of multiple secondary outcomes of the study to favor placebo. Also, some adverse events (AEs) observed in the clinical trial could possibly be attributed to the underlying disease rather than recognized as drug-related events, and might progress to a severe stage, or result in a serious outcome.

The only endpoint on which the application was able to show convincing statistical results was on chorea scores (the primary endpoint). The initial assumption that improvement of chorea control would result in improvements in gait safety and functional activities (activities of daily living) was not substantiated in the clinical trials. An additional concern was the lack of ratings by the subjects on whether the study drug affected their functioning or quality of life.

An End-of-Review meeting was held May 25, 2006 and the sponsor proposed to reexamine endpoints of Study 004 to determine if alternative explanations such as between-group differences at baseline, chance findings, or treatment emergent AEs could explain the observed treatment group differences in function, cognition and behavior.

2. Executive Summary

The efficacy review is only a part of the complete review for NDA 21-894. The problems encountered with the NDA review of Xenazine have been discussed with the Advisory Committee on December 6, 2007. Based on the efficacy review, I concur with the Advisory Committee recommendations to approve the drug for the indication of the chorea of Huntington's disease.

The sponsor's re-analysis of the data in the Clinical Response to Approvable did not reveal any substantial changes from the original review cycle of the NDA. The difficulty of proving a benefit to the management of chorea, the tendency of the secondary and exploratory endpoints to favor the placebo group, and safety concerns still remain, however, the differences in efficacy endpoints, although consistent, are generally not large. These concerns are consistent with similar drugs in this class, and could be addressed by labeling, and with physician and patient/caregiver education for monitoring. Also, the length of use in the drug in other countries for multiple hyperkinetic movement disorders without the emergence of serious adverse events patterns is rather reassuring.

On balance, I feel that tetrabenazine should be an available option for the HD patients that may benefit from management of chorea. Labeling and post-marketing recommendations are on-going, and those affecting efficacy claims are included in this review.

3. Brief Background

Tetrabenazine (TBZ) is as an oral medication currently marketed overseas with the trade name of Xenazine or Nitoman. It is a centrally-acting catecholamine depleting drug with two modes of action: depletion of pre-synaptic stores of monoamines, and a postsynaptic blocking action. The result is a selective depletion of brain amines, especially dopamine. Tetrabenazine was submitted by Prestwick Pharmaceuticals, Inc. for the indication of chorea associated with Huntington's disease (HD). It was approved in the United Kingdom in 1971 for the treatment of chorea, and is currently available there in addition to Australia, Canada, Denmark, Ireland, Israel, New Zealand, and Portugal.

Tetrabenazine was introduced by Hoffmann-LaRoche. In the 1950s, it was shown to have use in the treatment of schizophrenia. It was approved for that indication in Europe, but later withdrawn for the indication because of the entry of more efficacious psychiatric drugs.

Prestwick Pharmaceuticals, Inc. submitted the NDA application (NDA 21-894, tetrabenazine for the treatment of the chorea of Huntington's disease) to the Agency for review on September 23, 2006. They presented a clinical development program including:

Phase I Studies – six in healthy volunteers, and one in liver-impaired subjects

Phase II/III Studies – the pivotal efficacy and safety studies consisted of:

- (a) two randomized, double-blinded, placebo-controlled clinical studies of efficacy involving HD subjects for the indication of chorea: the Prestwick Tetra HD Study and the Prestwick Tetra Withdrawal Study,
- (b) interim reports of two open-label safety studies which are extension studies of the two controlled trials.

(c) additional submissions included in the application as safety studies were the Baylor Chorea Database, and the Baylor Non-Chorea Database. These were not conducted by the Sponsor, but based on the assessment of patients previously treated by Dr. J. Jankovic, under IND 16,161 for tetrabenazine at Baylor College of Medicine, Houston, Texas.

Also submitted was a review of previously published literature citing studies done on the use of tetrabenazine for chorea and non-chorea movement disorders.

A total of 114 HD subjects were enrolled in the two pivotal efficacy trials. Upon the completion of those trials, subjects that qualified could be enrolled in the matching open-label extension studies. The Sponsor also submitted information on 145 chorea patients (including 98 with HD) in the Baylor Database study for safety review.

The two primary efficacy studies were done for the chorea indication. These were randomized, double-blinded, placebo-controlled trials, consisting of:

(a) Prestwick Tetra HD Study (TBZ 103,004)/Study 004).

Objective: Evaluate the change in chorea of HD subjects newly started on TBZ or placebo. Primary endpoint: change in Total Maximal Chorea Score (TCS) for the TBZ group compared to the placebo group

Important secondary endpoints: change in scores from baseline on the Total Motor Score (TMS), the Functional Assessment (FA) Checklist, and Gait on the UHDRS, and change in the Clinical Global Impression, Part II.

(b) Prestwick Tetra Withdrawal Study (TBZ 103,005)/Study 005.

Objective: Evaluate the return/increase of chorea in HD subjects following TBZ discontinuation

The primary endpoint: change in Total Maximal Chorea Score (TCS) of the first group withdrawn from TBZ compared to the other 2 groups still receiving the drug

Important secondary endpoints: change in the Total Functional Capacity (TFC) score of the UHDRS from Day 1 to Day 3 comparing Group 1 to the combined average scores of Group 2 and Group 3.

Both of the efficacy studies used the Unified Huntington's Disease Rating Scale (UHDRS), copyright 1999, Huntington's Study Group. The scale has Parts I – VII rating motor (including chorea and gait), cognitive, behavioral, and functional areas. Both studies used changes in the Total Maximal Chorea Score (TCS), Item 12 a-g (a sub-part of Part I - Motor Assessment) as the primary objective measurement. The secondary or exploratory objectives used were the Parts I, II, III, IV, V, and VII of the UHDRS, along with the physician-rated Clinical Global Impression Scale (CGI). The same rating scales were used to evaluate either secondary or exploratory analysis of efficacy in each of the follow-on studies (Protocol TBZ 103,007 and Protocol TBZ 103,006).

The primary study upon which demonstration of the efficacy of tetrabenazine for the treatment of chorea relied was the Prestwick Tetra HD Protocol TBZ 103,004. It enrolled HD patients that had not previously used tetrabenazine, randomized at a ~2:1 ratio of

drug:placebo. The study was conducted with 84 subjects at 16 sites in the US over a 12 week treatment period, followed by a follow-up assessment after a 1-week drug withdrawal at the end of the study.

Primary Endpoint:

The primary endpoint in Protocol TBZ 103,004 was the change in the Total Maximal Chorea Score (TCS) from baseline to the maintenance phase (average of the Week 9 and Week 12 scores) The mean TCS for the tetrabenazine group was 14.69 (± 3.84) UHDRS points at baseline, and 9.41 (± 4.45) points at the End of Week 12. This gave them a change in score of -5.04 (± 0.49) points. This was compared to the placebo group's mean TCS decrease of 1.52 UHDRS points (15.20 ± 4.41 at baseline, and 14.07 ± 4.72 at End of Week 12). The resulting mean decrease in the TCS attributable to the drug treatment for the TBZ Group was 3.52 UHDRS points (ANCOVA p-value = <0.0001) favoring the TBZ group. Since the Steering Committee for the study had established a decrease of 3 chorea points on the TCS scale as clinically significant, the treatment result met their criteria for clinical significance as well as statistical significance.

The criterion for efficacy was met; there was a significant reduction in the observed chorea of the subjects receiving tetrabenazine compared to the placebo group. The results were consistent across population subgroups based on gender, age, length of illness, severity of disease, and use of concomitant medications, and were consistent at the various study sites. The small number of non-white subjects limited generalization by race or ethnic group.

The reduction in the chorea scores followed the anticipated curve showing a steady increase over the first 5 weeks while doses were being titrated upward, and a fairly steady level throughout the maintenance phase. The study also found that there was a larger effect of TBZ treatment on the scores of the subjects that had higher baseline chorea scores. This observation had been suggested in previous studies.

At the Week 13 evaluation, which was to be done one week after withdrawal from the drug, the mean TCS for the TBZ Group was 15.08 (± 4.21) UHDRS points, only slightly higher than their baseline score of 14.69 (± 3.84) points. The placebo group had a baseline TCS of 15.20 (± 4.41), and a Week 13 TCS of 14.90 (± 4.47).

Secondary Endpoints:

Evidence of efficacy was supported in only the first of the four secondary endpoints.

- The Clinical Global Impression (CGI) Part 2 is an investigator assessment of whether total improvement is due entirely to drug treatment. A rating of 1 = very much improved, 4 = no change, and 7 = very much worse. A significant number of the TBZ subjects were rated by the investigators as "much" or "very much" improved by Week 12, compared to the placebo group. The difference at Week 12 between groups was 0.75 (± 0.26) point on the 7-point scale. Although not a full point difference, it was statistically significant favoring TBZ treatment (p-value = 0.0074).

The next three secondary outcome measures failed to show a statistically significant treatment effect. These evaluated changes in the Total Motor Score, the Functional Assessment Checklist, and the Gait score:

- The second endpoint, Total Motor Score (TMS), (UHDRS Part I questions 1 – 17), included the Chorea Score (UHDRS question 12 – the primary endpoint of the study), and the Gait score (UHDRS question 13). Scores could range from 0 (best) to 124 (worst), and the average baseline score was 46 points. The mean change from baseline to maintenance (Week 9 + 12 averaged) was -6.84 points for the TBZ group and -3.5 points for the placebo group, giving a group difference of 3.3 (± 1.9) points. The TBZ scores were better than placebo, but did not reach statistical significance (p-value = 0.075). Evaluating the TMS for the non-chorea items (all the items except # 12), the difference between the groups was lower at 1.5 (± 1.5) points (p-value = 0.32) suggesting that the significance of the TMS was due mainly to the change in the chorea score which had already been evaluated separately. Since this endpoint did not reach the pre-specified p-value of 0.05 for significance, the lower priority endpoints could not be accepted for support of the application without inflating the type I error rate, but they have been included in this review.
- The Functional Assessment Checklist (UHDRS Part IV) scores were rated by the subjects and/or caregivers, and ranged from 0 (worst) to 25 (best). The average baseline score was 19 points. The difference between groups from baseline to maintenance phase was 1.18 (± 0.49) points which was statistically significant (p-value = 0.018), but favored the placebo group. The Sponsor attributed the lack of treatment benefit to the “ceiling effect” since most of the subjects had high functioning (and gait) scores at baseline.
- The Gait score (UHDRS sub-section TMS, question 13) used a 5-part rating of 0 (normal) to 4 (cannot attempt). The change from baseline to Week 12 for the TBZ group was -0.03 (± 0.06) point indicating trace improvement, and 0.11 (± 0.06) point for the placebo group suggesting slight worsening. The ANCOVA p-value of 0.2410 does not show a statistically significant difference. The difference in the baseline-to-endpoint change of only a fraction of a point for either group shows virtually no change occurred and makes clinical comparisons meaningless.

Exploratory Endpoints:

Due to the prioritization of endpoints for significance, none of the results of the exploratory endpoints were submitted for support of the application. The study included 10 exploratory endpoints, and the Functional Impact Scale.

- Only in the investigator-rated CGI Part 3 (the Efficacy Index), matching therapeutic effect to side effects, did TBZ treatment show statistical significance

(p-value = 0.001). The score was an assigned number, not a change from baseline. By the end of the study, 51% of the subjects on TBZ were judged to be a “treatment success”, compared to 7% of the subjects on placebo.

The rating for the placebo treated subjects was 11.41 (+2.88) at Week 12 (11=slight improvement with side effects significantly interfering with functioning), compared to the TBZ score of 8.22 (+4.00) at Week 12 (8=moderate improvement but side effects outweighs therapeutic effect, and 9=slight improvement not altering status of care, with no significant side effects)

The other exploratory endpoints included CGI Part 1, behavioral and cognitive assessments and three additional functional assessments.

- In the CGI Part 1 (Severity of Illness), investigators rated each subject from 1 (normal) to 7 (among most severely ill). Both groups showed virtually no change between baseline and maintenance phase (p-value = 0.9186).
- The Behavioral Assessment (BA, UHDRS Part III) included 11 items scored from 0 (best) to 4 (worst) on both the frequency and severity of various behaviors such as depressed mood, suicidal ideation, compulsive behavior, delusions, apathy, etc.). The information was given by the subject or subject and caregiver, with 5 additional assessments done by the investigator. Both groups had a nominal decrease in scores suggesting slight improvement. The mean difference between the groups was -1.2 points (p-value = 0.363) favoring the placebo group. The only behavioral item that had group differences reaching significance was on the anxiety rating. At Week 12, 70% of the TBZ group had no evidence of anxiety, compared to 90% of the placebo group. Both anxiety items statistically favored the placebo group (frequency p-value = 0.028, and severity p-value = 0.040).
- Each question of the Cognitive Assessment (UHDRS Part II) was analyzed individually as an exploratory endpoint assessing change from baseline to Week 12. These included Verbal Fluency, Symbol Digit Modalities, and the 3 Stroop Interference Tests (Color Naming, Word Reading and Interference). All of the items at least nominally favored placebo, the Stoop Interference – Words reached statistical significance (p-value = 0.0123), and Stoop Interference – Interference nearly did (p-value = 0.0532). The sum of the Total Cognitive Assessment Score showed TBZ group worsened by 7.7 (± 3.3) points from its mean baseline of 156 (± 56) points, while the placebo group improved by 5.1 (± 4.5) points from a baseline of 172 (± 55) points. The estimated difference of 12.8 (± 5.6) points was statistically significant, at ANCOVA p-value = 0.025, favoring placebo.
- The 3 additional functional assessments looked at mean change scores from baseline and Week 12. These are additionally notable for being rated by the subject and/or caregiver. The Independence scale (INS, UHDRS Part V) is a one-score rating between 100 (no special care needed) and 010 (tube fed, total bed care). The Total Functional Capacity (TFC) scale (UHDRS Part VI) rates the areas of occupation, finances, chore, ADLs on a 0 (unable) to 3 (normal) scale, and care level at 0 (full time skilled nursing) to 2 (home). Both scales nominally

avored placebo ($p=0.135$, and $p=0.291$ respectively). The Functional Impact Scale was a new test piloted on this study. It addressed 4 basic ADL items (bathing, dressing, feeding and toileting) and a social isolation item all on a scale of 0 (best) to 3 (worst). Baseline scores for both groups were 1.3 points and showed no noticeable change by Week 12 ($P\text{-value} = 0.970$).

The tetrabenazine application had been granted a priority status review on the expectation that gains in chorea control might improve the walking safety, daily functional activities, or quality of life of HD patients. The secondary and exploratory endpoints failed to establish any connection with these measures for the drug. The 10 exploratory endpoints included additional assessments of functional status (change in the Independence Scale and in Total Functional Capacity), and in these, placebo showed superiority over the TBZ group, but did not reach statistical significance.

After the 12 week study was underway, there was a change in protocol to accommodate the FDA recommendation of videotaping of the subjects for rating of the chorea score (TCS) by an outside expert blinded as to drug treatment and study week. The outside ratings showed some variation from the site investigator scores. There was a difference in chorea scoring between the site investigator and the outside reviewer of ≥ 5 points on the TCS for 20.5% (9 of 44 Week 12 and Week 13 videotapes reviewed). Overall, the outside ratings support the primary endpoint of chorea reduction with TBZ treatment ($p\text{-values} = <.0001$ at Week 12, and $.0004$ at Week 13). However, due to a lack of consistency in implementation, they are limited in their ability to support the application. Only 21 of the subjects on the study (27.4%) had both the Week 12 (on TBZ) and Week 13 (off TBZ) videotapes evaluated. Two of the 23 videotaped subjects lacked either a Week 12 or Week 13 rating by the outside reviewer. The first videotape of a subject was done on October 3, 2003, but only 44% of the subjects enrolled after that date had videotapes made. At some sites, subjects did not have videotapes done despite being enrolled later than other subjects that were taped.

4. Organization of Review

The second pivotal trial, the withdrawal study (study 005), showed a trend suggestive of effectiveness, but was not statistically significant. It experienced major implementation flaws, and other problems that limited its usefulness in support of the application. The concern that the Agency has with the clinical data regards measurements (of function, cognitive and behavioral changes and AEs) that were used primarily in the longer trial (Study 004). The CR re-analyses by Prestwick addressing these issues uses the data from Study 004 and the open-label extension, Study 007, so the Study 005 is not included in this review.

In their Response to Approvable Letter, Prestwick has re-examined the data from Study 004 to consider possible alternative explanations for the findings of the secondary and exploratory endpoints. The company acknowledges that due to the retrospective nature of the analyses, their interpretations are exploratory. The re-analyses by the company focused on whether the between group differences in endpoints might be attributable to:

- Between-group differences in baseline demographics (such as disease severity, length of diagnosed disease, functional level, cognitive level, and behavioral status).
- Possible chance findings in a relatively small single study
- Known/predictable pharmacologic effects of TBZ
- The natural history and progression of Huntington's disease

This review focuses on the sponsor's Response to Approvable Letter for the sections of effectiveness of tetrabenazine in relation to chorea, functional activities, cognitive aspects, and quality of life issues. Full review of the clinical trials applicable to the NDA application is contained in the Clinical Review of March 23, 2006. The following sections address the sponsor's re-examination of the Study 004 data and exploratory analyses submitted for the CR regarding the cognitive and functional assessments:

The usefulness of chorea management is addressed in section 5.

The incidence of functional changes associated with TBZ vs placebo is addressed in Section 6.

The incidence of cognitive changes associated with TBZ vs placebo is addressed in Section 7.

The discussion of the sponsor's comparison of the databases of Study 004 to the CARE-HD Study is addressed in Section 8.

Table 1. UHDRS Components, Clinical Global Impression and Functional Impact Scale from Study 004: Adjusted Mean Change (\pm s.e.m.) from Baseline to Week 12

Assessments	Endpoint	TBZ (N= 54)	Placebo (N=30)	p-value ANCOVA	Difference Numerically Favors
UHDRS Components:					
I. Total Motor Score (Part 1; items 1-15)	2°	-7.37 \pm 1.20	-2.08 \pm 1.62	0.010	TBZ
Total Chorea Score (Part 1, item 12a-g)	1°	-5.41 \pm 0.51	-1.03 \pm 0.70	< 0.001	TBZ
Gait Score (Part 1, item 13)	2°	0.05 \pm 0.07	0.10 \pm 0.09	0.659	TBZ
II. Cognition (Part 2; items 19-23)					
Total Cognition Score		-0.60 \pm 1.35	2.10 \pm 1.83	0.240	Placebo
Verbal Fluency	Exp.	-2.61 \pm 0.77	-1.27 \pm 1.05	0.305	Placebo
Symbol Digit Modalities Test	Exp.	2.15 \pm 0.76	3.02 \pm 1.05	0.509	Placebo
Stroop Interference Test	Exp.	-0.28 \pm 0.87	0.43 \pm 1.20	0.630	Placebo
III. Behavioral Assessment (BA) (Part 3; items 25-35)	Exp.	-0.70 \pm 0.91	-2.05 \pm 1.23	0.377	Placebo
IV. Functional Assessment Checklist (Part 4; items 43-67)	2°	-0.89 \pm 0.32	0.30 \pm 0.43	0.027	Placebo
V. Independence Scale (IND) (Part 5; item 69)	Exp.	-2.42 \pm 1.08	0.73 \pm 1.45	0.085	Placebo
VI. Total Functional Capacity (TFC) (Part 6; items 70-74)	Exp.	-0.43 \pm 0.21	-0.06 \pm 0.28	0.291	Placebo
Functional Impact Scale (FIS)	Exp.	0.11 \pm 0.17	0.13 \pm 0.23	0.970	Unchanged
Clinical Global Impression:					
CGI-1	Exp.	-0.03 \pm 0.07	-0.02 \pm 0.09	0.970	Unchanged
CGI-2	2°	3.00 \pm 0.16	3.75 \pm 0.21	0.005	TBZ

CGI-3	Exp.	8.25 ± 0.52	11.43 ± 0.70	<0.001	TBZ
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Source: CSR TBZ 103,004, Tables 14.2.1, 14.2.16, 14.2.19, 14.2.21, 14.2.22, 14.3.5.2, and 14.3.5.5

Missing scores were replaced by last available assessment.

ANCOVA = analysis of covariance; TBZ = tetrabenazine; UHDRS = Unified Huntington's Disease Rating Scale; Exp.=exploratory endpoint

Note: Higher scores on Functional Assessment, TFC, IND, and lower scores on Chorea and Total Motor Score are associated with better function. Higher scores on cognitive tests and lower scores on BA are associated with improvement.

Table 1 shows the results of the re-analysis of LOCF mean change from baseline to maintenance (average of Weeks 9 and 12) and the observed case mean change at Week 12 for many of the functional, cognitive and behavioral measures listed in Table 21. There were no meaningful differences in treatment effects between the LOCF re-analysis compared to the original LOCF analysis presented in the NDA. Findings from observed case analyses are used for the CR re-analysis. It's not always appropriate to exclude a week 12 measurement as they did if the patient had stopped taking drug. It seems to violate the ITT principle, but it's adequate for a sensitivity analysis, and it doesn't show much of a statistical difference here. The change made no significant difference in the CR review, since in the review of the initial NDA submission, the Agency did an analyses of both the baseline to the averaged Week 9 +12 scores, and the baseline to Week 12 scores during the initial review. It was on the assumption that AEs and dosage adjustment were most likely to have been resolved by the end-of-study, and the Week 12 measurements the mostly to be accurate for the treatment effect. For all the endpoints, the difference between the two scores were minor and did not change the interpretation of the data.

5. Utility of Reducing Chorea

There is some evidence in the literature that chorea is not perceived as problematic by the HD patients. There is also concern that patients would be started on a drug for the chorea, and be left on it, although chorea is characteristic of the middle course of Huntington's disease and usually diminishes or disappears in the later stage. The Agency queried the usefulness of chorea management. Prestwick was asked to analyze the rationale for chorea management and address the benefit/risk ratio.

Supporting Analyses submitted by sponsor:

- Clinical Global Impression-Part 2 (CGI—2) at end of treatment
- Responder analysis (i.e., reduction of chorea \geq 3 points)
- Patient rated measure of benefit
- Patients with substantial clinical benefit (narratives)

Evidence of efficacy was supported in only one of the four secondary objectives. Using the Clinical Global Impression Part 2 (CGI-2) endpoint (see Appendix 1), a significant number of the TBZ subjects were rated "much" or "very much" improved compared to the placebo group. The CGI-2 is a subjective assessment, by the physician/investigator of the subject's symptoms. There is no actual baseline assessment with which to

compare it, so the number listed is an assigned score, not a difference in points that occurred. Sixty-nine percent (69%, 31/51) of the TBZ-treated patients compared to 24% (7/29) of the placebo patients were assessed as improved by the investigator at the end of treatment ($p=0.0063$). The score of 2.99 on the scale for the TBZ-treated group is closest to the score of 3 = "minimally improved". The placebo group had a mean score of 3.73 which is only slightly improved from 4 = "no change". At Week 12, the difference in scores between the groups was statistically significant, but not large (less than one point). There are several weaknesses in this measurement. Although the intent was an assessment of "overall status" the responses were nearly identical to the change in chorea score, so it is possible, given the focus of the study, only chorea change was assessed by the question. This possibility is suggested in the next analysis (Responder Analysis).

Responder Analysis was defined as the pre-specified reduction in the total maximal chorea score (UHDRS question 12,) by ≥ 3 points. The total score is 0 to 28; 0 (absent) to 4 (marked/prolonged) for each extremity, face & bucco-oral. The reduction of chorea by ≥ 3 points was pre-determined by the Study 004 Steering Committee as the "clinically significant level of change. Analysis of this primary endpoint showed that 69% of the TBZ-treated subjects compared to 23% of the placebo-treated subjects had reduction in chorea that was statistically significant ($p<0.0001$). Analysis of the subject data shows the same subjects rated "decreased chorea" and improved in CGI-2. Interpretation could be that they were improved on always improved on both measures, or that it was only one measure that was assessed (chorea change).

Patient-rated measure of benefit: Response to question 79 of the UHDRS at Week 13 (washout). "Since your last assessment, does the participant feel improved, worsened, or about the same?" A higher percentage of the tetrabenazine-treated subjects reported feeling worse at Week 13 ($p\text{-value} = 0.005$), (See Table 2). Meaningful responses are difficult to interpret since there is no possible comparison to baseline. As with many of the questions, it is not even clear, or consistent, if the responses were provided by the subject, or the caregiver. Unfortunately, this was the closest the study came to providing a subject-rated "benefit to the subject" assessment. The question was asked on Week 13, so on average, the subjects had discontinued the drug the previous week. Assumption is made that if subjects respond as "feeling worse" that it confirms the benefit of the drug treatment. However, possible rebound effect cannot be ruled out since the follow-up chorea scores were higher for TBZ-treated subjects than at baseline, although not reaching a statistically significant level.

Table 2. Study 004: UHDRS item 79 at Week 13 (Visit # 7)

Visit Number	Treatment Name											
	Tetrabenazine						Placebo					
	"Since last assessment/participant feels..."						"Since last assessment/participant feels..."					
	improved		worsened		stayed about the same		improved		worsened		stayed about the same	
	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent
7 (week 13)	1	4.1	34	69.4	13	26.5	2	3.4	9	31.0	19	65.5

Patients with substantial clinical benefit: Investigators were asked to identify subjects with improvements in HD symptoms with clinical improvement unlikely to occur spontaneously. Narrative reports of improvement were obtained for 13 subjects (from Study 004 and the follow-on open-label study). Two of the subjects that related improvement in functional levels while receiving tetrabenazine in the Study 004 were reported in the CR. No formal analysis of these reports was done by the sponsor. Again, the way the reports read, it is not clear if the subject, caregiver or investigator is supplying the information, so it does not provide the subject-rated assessments that the studies needed.

The sponsor feels that the analyses listed above, when taken together, confirm meaningful benefit associated with chorea reduction from TBZ. The review dilemma is that the "analyses" are based on a) subjective assessments of investigators that may have been rating the primary endpoint characteristic rather than a vague "overall" assessment, b) reference to the primary endpoint (chorea change) which in no way addresses the utility, c) a subjective patient assessment unlinked to a baseline, no reliability of whether the subject or caregiver was the responder, and with possible confounding effects such as drug withdrawal, or d) subjective narratives by a few subjects (or, probably their caregivers). None of these directly address the utility of chorea treatment or could be used for a benefit/risk analysis.

6. Functional changes associated with tetrabenazine vs. placebo

Relationship between Chorea and Function

As previously noted, in the Study 004, nearly all the functional assessments favored the placebo-treated group. In the CR, the sponsor responds that since "HD is a multimodal disease, it is difficult to isolate the effect of reducing chorea on function using instruments that were not designed for this specific purpose". They feel that the

functional scales employed in Study 004 lack specificity for assessing changes solely due to chorea reduction and do not ascertain whether impairment results from chorea or another deficit of HD which may not be affected by treatment with TBZ. Any changes in the chorea scale “may be confounded by impairments in other domains, which if unaddressed by treatment, may contribute to the lack of measurable functional improvement”. Based on the Pearson correlation coefficients between baseline UHDRS measures, the sponsor feels that the correlation between Functional Assessment Checklist scores and the cognitive measures of the Stroop word Reading and Symbol /Digit is greater ($r = 0.56$ and 0.66 respectively) than the correlation between baseline Functional Assessment Checklist scores and chorea scores ($r = -0.35$) suggesting that the functional scores of the Functional Assessment Checklist are more closely associated with cognitive levels than with chorea.

Table 3. Pearson Correlation Coefficients (r) Between Baseline UHDRS Measures

	Functional Assessment Checklist	Independence Scale	Total Functional Capacity	Functional Impact Scale
CGI-1	-0.39‡	-0.43‡	-0.41‡	+0.47‡
Chorea	-0.35‡	-0.38‡	-0.19*	+0.21*
Behavioral Assessment	-0.02	-0.06	-0.18	+0.11
Stroop Word Reading	0.56‡	0.45‡	0.49‡	-0.43‡
Symbol Digit	0.66‡	0.57‡	0.56‡	-0.42‡

Source: CR Table 1.4 in Appendix 2

* $p < 0.10$ and > 0.05

‡ $p < 0.01$

The response doesn't adequately address why with the use of multiple functional scales, the secondary functional endpoints nearly all favored placebo. Four functional scales were used in Study 004 and re-analyses provided opportunities to delve into additional analyses of items or factors that the sponsor considered essential for extra scrutiny. However, not much emerged that was relevant for the efficacy review of the CR.

Agreeing with the sponsor's conclusions still does not resolve the question of whether a recommendation of approval should be made for a drug with known risk of adverse reactions since the scales in the clinical trials are considered lacking specificity, and the functional changes of the disease syndrome are more closely tied to factors other than chorea.

Effect of Baseline Differences

The sponsor posed the possibility that between-group differences in baseline demographics or disease severity that could explain the differential decline in functional measures between the tetrabenazine and placebo groups during the treatment period.

In the comparison of baseline demographics and disease characteristics between treatment groups, the sponsor notes that TBZ-treated subjects were more affected in functional, cognitive and behavioral domains at baseline than were placebo-treated

subjects. These differences (see Table 4) were generally slight but consistent, and had statistical significance only for the FIS and the Symbol Digit Modalities test.

Table 4. Baseline Demographic and Clinical Characteristics of Patients in Study 004

Variable	Tetrabenazine (N=54)	Placebo (N=30)	p-value (t-test)
Disease duration, yr	8.68	7.47	0.25
CGI-1*	3.98	3.83	0.36 **
Total Maximal Chorea Score (TCS)	14.69	15.20	0.57
Total Functional Capacity (TC)	8.28	8.60	0.56
Functional Assessment Checklist	18.80	19.63	0.38
Independence Scale (IND)	76.94	80.17	0.20
Functional Impact Scale (FIS)*	1.28	0.40	< 0.01*
Stroop - Word Reading	53.83	56.27	0.61
Symbol Digit Modalities Test	18.07	24.37	0.02
Behavioral Assessment(BA)*	7.39	6.60	0.62 *

* Lower numbers indicate less severe disease or better function

** Favored placebo

The differences noted raise the question - Did the between-group differences in baseline demographics or disease severity account for the differential decline in FA between treatment groups?

The sponsor computed the mean and mean change in the Functional Assessment Checklist scores for the treatment groups by baseline severity (tertile) of the variable of interest (Functional Assessment Checklist, chorea, CGI-1, Stroop Word, Symbol Digit and Behavioral Assessment [BA] score). Similar analyses were also conducted for IND, TFC and FIS with baseline tertiles of the above variables of interest. The result was that re-analysis of these variables did not identify any clear confounding of the treatment effect by baseline levels. The between-group difference in the Functional Assessment Checklist was generally independent of the baseline severity of the Functional Assessment Checklist, chorea, CGI-1, Stroop Word, Symbol Digit and Behavioral Assessment scores. Likewise, no baseline measure was found to be associated with the results for IND, TFC and FIS (Table 5).

Sponsor Conclusions from the baseline data and analyses:

- Baseline data illustrate that HD is a multi-dimensional disease that affects numerous cognitive, behavioral and motor domains on the UHDRS.
- As HD is a multimodal disease, it is difficult to isolate the effect of reducing chorea on function using instruments that were not designed for this specific purpose. Indeed, all functional scales employed in Study 004 lack specificity for assessing changes solely due to chorea reduction.
- Any observed changes in the scales may be confounded by impairment in non-motor domains that, if unaddressed by treatment, may contribute to the lack of measurable functional improvement.

Table 5. Mean and Mean Change in Functional Assessment (FA) Checklist score by Baseline Functional Assessment Severity

Change in F at:	Mean (N) at Corresponding Week†		Mean Change from Baseline (N) at Corresponding Week†		Unadjusted Effect Size
	Tetrabenazine	Placebo	Tetrabenazine	Placebo	
Week 7					
Tertile 1 (≤ 17)	13.83 (18)	15.14 (7)	0.11 (18)	1.00 (7)	-0.89
Tertile 2 (18-21)	18.83 (18)	20.00 (11)	-1.06 (18)	0.27 (11)	-1.33
Tertile 3 (≥ 22)	23.33 (15)	23.18 (11)	-0.33 (15)	0.18 (11)	-0.51
Week 12					
Tertile 1 (≤ 17)	13.58 (19)	15.14 (7)	-0.26 (19)	1.00 (7)	-1.26
Tertile 2 (18-21)	19.40 (15)	20.00 (11)	-0.47 (15)	0.27 (11)	-0.74
Tertile 3 (≥ 22)	22.92 (13)	23.00 (11)	-0.54 (13)	0.00 (11)	-0.54

Source: CR Table 2.6 in Appendix 2

† At either Week 7 or Week 12 as labeled in the left-most column

Note: Higher scores on Functional Assessment Checklist are associated with better function.

It can be concluded that there was no clear evidence of confounding of the treatment effect by baseline levels. For example, for the Functional Assessment Checklist score, Table 4 shows that the mean change was better for placebo in each of the tertiles of the baseline score. So the baseline imbalance where it exists doesn't necessarily explain the unexpected observed differences in cognitive and functional endpoints.

Possibility of a Chance Finding

The sponsor analyzed the possibility that the differences in functional scores between groups resulted from a chance finding. Table 6 shows the change in scores by functional test.

Table 6. Mean Change in Functional Parameters from Baseline to Week 12 (Observed Cases)

Functional Scale (Range of Scores)	Δ Score with Improvement	Change (N)		p-value t-test	Unadjusted Effect Size	Difference Numerically Favors
		Tetrabenazine	Placebo			
Functional Assessment Checklist (FA) (0*-25)	↑	-0.40 (47)	0.34 (29)	0.0485†	-0.74	Placebo
		-0.89	0.30	0.027		
Independence Scale (IND) (10* -100)	↑	-1.17 (47)	0.34 (29)	0.3976	-1.51	Placebo
Total Functional Capacity (TFC) (0* -13)	↑	-0.25 (48)	-0.03 (29)	0.5074	-0.22	Placebo

Functional Impact Scale (FIS) (0-15*)	↓	-0.21 (47)	0.14 (29)	0.1757	-0.35	TBZ
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Source: CR Tables 2.3, 2.4, 3.3, 3.4, 4.3, 4.4, 5.3 and 5.4 in Appendix 2

* Score associated with maximal impairment or deterioration

† Unequal variance t-test

How strong is the evidence that the observed differential decline in FA in Study 004 is due to tetrabenazine rather than a chance finding in an otherwise small clinical trial? The sponsor's re-analysis states that "Although a nominally significant differential decline in Functional Assessment Checklist scores was noted in the tetrabenazine group in, the treatment effect was numerically quite small. The degree to which this effect may be explained by the observed improvement in the placebo group (a finding inconsistent with the natural history of HD) is not known. In contrast, ADLs, as assessed by the FIS and TFC, trended in favor of tetrabenazine suggesting that significant daily tasks may be improved with tetrabenazine use. Thus, the balance of evidence does not suggest that tetrabenazine has a clinically relevant or consistent adverse effect on function."

The sponsor feels that the individual items (FA, TFC, and FIS) that deal most directly with ADLs show an advantage favoring the tetrabenazine-treated group. They have submitted the following conclusions:

- The treatment-associated difference in Functional Assessment (FA) Checklist scores between tetrabenazine and placebo is small and unlikely to be clinically relevant.
- None of the changes observed on the individual items of the Functional Assessment Checklist are large enough to be clinically significant.
- On several scales, changes from baseline in the items evaluating daily functioning, typically referred as ADLs, favor tetrabenazine.

The statement about Activities of Daily Living (ADLs) as assessed by the TFC on page 87 of the clinical response seems a little misleading: TFC trended in favor of placebo overall, and only one of the five items trended in favor of tetrabenazine. This was the ADL item but the other four, as well as overall, trended in favor of placebo.

The individual items dealing most directly with ADLs were evaluated separately by the FDA (see Statistical Review and Evaluation by Tristan Massie, Ph.D.), part of the September 23, 2006 NDA review for tetrabenazine. In it, he states his conclusions of the analysis of individual ADL questions of the UHDRS (see Table 7):

"Since there was a significant difference favoring placebo in the change from baseline to week 12 in the sum of the functional assessment checklist item responses (UHDRS items 43-67) this reviewer investigated the results on the individual items that comprise the functional checklist. Each item is answered either yes or no. The items are presented in the table sorted by the size of the group difference in percentages that answered yes at week 12. The p-values should be considered exploratory since the tests were not pre-planned or adjusted for other analyses. It is important to note that at week 12 there was a difference in Item 68 of the UHDRS which identifies whether the patient or the patient and

caregiver filled out the functional assessment checklist. More placebo patients filled out the checklist by themselves (47% vs 26% p=0.04). This may raise the question of whether the group difference may be attributable to the differences in who was filling out the checklist rather than the treatment. This is not a randomized subgroup so we can't be sure but the difference on the change from baseline to week 12 in the sum of all items was still nominally significant in the larger subgroup of patients that filled out the checklist with their caregiver. The difference on item 68 was smaller and not significant at earlier weeks.

Six of the items had group differences greater than 15% in the percentage of patients that were able to do the item. Note that there were group imbalances at baseline on some of these items although none were significant at the nominal level. Most of the differences on individual items at week 12 were less significant after adjusting for the baseline responses. Item 52, related to doing laundry, has a p value of 0.051 after adjusting for the baseline responses. This was the smallest baseline adjusted p-value among the individual functional checklist items."

Table 7. Week 12 (or LOCF) Responses on Individual Items of UHDRS Part IV Functional Assessment Checklist

UHDRS FUNCTIONAL CHECKLIST ITEM	LEVELS	BASELINE			WEEK 12 OR LAST OBSERVATION				
		TBZ (N=54)	PLACEBO (N=30)	CHISQ P-VALUE	TBZ (N=54)	PLACEBO (N=30)	PERCENT DIFFERENCE	UNADJUSTED CHISQ P-VALUE	BASELINE ADJUSTED P-VALUE
68 Obtained from Participant only	N(%) YES	18 (33.3)	10 (33.3)	1.000	14 (25.9)	14 (46.7)	-20.8 %	0.053	0.043
47 Shop for Groceries	N(%) YES	36 (66.7)	24 (80.0)	0.195	28 (51.9)	22 (73.3)	-21.4 %	0.055	0.159 *
49 Supervise children	N(%) YES	28 (51.9)	20 (66.7)	0.189	25 (46.3)	20 (66.7)	-20.4 %	0.073	0.227 *
52 Do Laundry	N(%) YES	44 (81.5)	26 (86.7)	0.541	38 (70.4)	27 (90.0)	-19.6 %	0.039	0.051 *
51 Do Housework	N(%) YES	35 (64.8)	22 (73.3)	0.423	31 (57.4)	23 (76.7)	-19.3 %	0.078	0.089 *
59 Public transport	N(%) YES	37 (68.5)	23 (76.7)	0.428	35 (64.8)	25 (83.3)	-18.5 %	0.072	0.096 *
55 Take meds w/o help	N(%) YES	44 (81.5)	28 (93.3)	0.137	42 (77.8)	28 (93.3)	-15.5 %	0.067	0.265 *
46 Manage Finances	N(%) YES	16 (29.6)	11 (36.7)	0.508	12 (22.2)	11 (36.7)	-14.5 %	0.155	0.170 *
50 Operate Auto	N(%) YES	20 (37.0)	14 (46.7)	0.389	19 (35.2)	14 (46.7)	-11.5 %	0.302	0.570 *
60 walk in neighborhood	N(%) YES	48 (88.9)	27 (90.0)	0.875	43 (79.6)	27 (90.0)	-10.4 %	0.222	0.205 *
58 Bathe self	N(%) YES	49 (90.7)	29 (96.7)	0.312	49 (90.7)	30 (100.0)	-9.3 %	0.086	0.941 *
44 Engage in any gainful employment	N(%) YES	11 (20.4)	7 (23.3)	0.751	10 (18.5)	8 (26.7)	-8.2 %	0.383	0.326 *
57 Dress self	N(%) YES	46 (85.2)	29 (96.7)	0.103	48 (88.9)	29 (96.7)	-7.8 %	0.217	0.935
45 Engage in volunteer or non gainful work	N(%) YES	30 (55.6)	17 (56.7)	0.922	31 (57.4)	19 (63.3)	-5.9 %	0.596	0.502 *
48 Handle purchase	N(%) YES	49 (90.7)	26 (86.7)	0.563	46 (85.2)	27 (90.0)	-4.8 %	0.531	0.273 *
54 Use telephone	N(%) YES	52 (96.3)	28 (93.3)	0.541	48 (88.9)	28 (93.3)	-4.4 %	0.506	0.380 *

56 Feed self	N(%) YES	51 (94.4)	30 (100.0)	0.189	50 (92.6)	29 (96.7)	-4.1 %	0.450	0.892
63 Comb hair w/o help	N(%) YES	54 (100.0)	30 (100.0)	.	52 (96.3)	30 (100.0)	-3.7 %	0.286	0.953 *
53 Prepare meals	N(%) YES	39 (72.2)	20 (66.7)	0.594	38 (70.4)	22 (73.3)	-2.9 %	0.773	0.378 *
43 Engage in accustomed gainful employment	N(%) YES	6 (11.1)	4 (13.3)	0.763	4 (7.4)	3 (10.0)	-2.6 %	0.680	0.782 *
61 walk w/o falling	N(%) YES	51 (94.4)	27 (90.0)	0.449	49 (90.7)	28 (93.3)	-2.6 %	0.680	0.433 *
67 Care provided at home	N(%) YES	54 (100.0)	30 (100.0)	.	53 (98.1)	30 (100.0)	-1.9 %	0.453	0.950 *
64 Transfer between chairs	N(%) YES	54 (100.0)	30 (100.0)	.	54 (100.0)	30 (100.0)	0 %	1.000	0.953
65 Get in/out of bed	N(%) YES	54 (100.0)	29 (96.7)	0.177	54 (100.0)	30 (100.0)	0 %	1.000	0.953 *
66 Use toilet	N(%) YES	54 (100.0)	29 (96.7)	0.177	54 (100.0)	30 (100.0)	0 %	1.000	0.953 *
62 walk w/o help	N(%) YES	53 (98.1)	29 (96.7)	0.670	54 (100.0)	29 (96.7)	3.3 %	0.177	0.809

* = favored placebo

The following items most directly deal with the ADLs (on the UHDRS Part IV FA Checklist) that determine whether a patient could remain unsupervised in the home for periods of the day (i.e., prevent or postpone nursing home placement). These are listed along with the number of subjects improved, declined or no change between baseline and Week 12:

Immediately evident is that the actual number of subjects reporting change in each of these categories is very small (Table 8 provides the percentages these represent in each group). The placebo group did not show a robust improvement that would have significantly skewed the analysis of the treatment group. Although again, it is difficult to account for the gains in the placebo group in view of the progressive nature of the illness. However, this group of essential ADLs does show that although changes were slight, they did not favor the tetrabenazine-treated group. The selection of these "daytime-independence" essential ADLs also addresses the concerns of the sponsor that too many of the functional tests were evaluating the more complex issues such as employment, driving, managing finances, etc... that would be unlikely to change during the duration of a 12-week study.

Table 8. Change from Baseline to Week 12 (or LOCF) in Selected Functional Assessment Checklist ADL Items.

ADL	TBZ			PLACEBO		
	Declined N (%)	Unchanged N (%)	Improved N (%)	Declined N (%)	Unchanged N (%)	Improved N (%)
Prepare meals	4 (7.4)	47 (87.0)	3 (5.6)	1 (3.3)	26 (86.7)	3 (10.0)
Use telephone	6 (11.1)	46 (85.2)	2 (3.7)	0 (0.0)	30 (100)	0 (0.0)
Take meds without help	4 (7.4)	48 (88.9)	2 (3.7)	0 (0.0)	30 (100)	0 (0.0)

Feed self	2 (3.7)	51 (94.4)	1 (1.9)	1 (3.3)	29 (96.7)	0 (0.0)
Walk without falling	3 (5.6)	48 (88.9)	3 (5.6)	0 (0.0)	29 (96.7)	1 (3.3)
Walk without help	0 (0.0)	53 (98.1)	1 (1.9)	0 (0.0)	30 (100)	0 (0.0)
Transfer between chairs	0 (0.0)	54 (100)	0 (0.0)	0 (0.0)	30 (100)	0 (0.0)
Get in/out of bed	0 (0.0)	54 (100)	0 (0.0)	0 (0.0)	29 (96.7)	1 (3.3)
Use toilet	0 (0.0)	54 (100)	0 (0.0)	0 (0.0)	29 (96.7)	1 (3.3)

The fact that tetrabenazine looked better on the FIS could be due to a floor effect. tetrabenazine was worse at baseline (significant) and placebo was close to the lower limit (better function) and had less room for improvement. Tetrabenazine had a very small improvement. In fact, the average week 12 score for placebo was still less than tetrabenazine (placebo: 0.55 vs TBZ: 1.15) even though the average changes from baseline numerically favored tetrabenazine (placebo +0.14 vs TBA -0.21). At baseline 58% of patients had the best possible score (=0) on the FIS. This would suggest that either the FIS is not capturing the functional impairment of these patients or they are not functionally impaired, which is unlikely. In addition, if the treatment effect varies with the baseline score in reality then comparison of the two groups that were different at baseline would not be fair. Also, the validity of the statistical tests based on ANCOVA that the sponsor presented for the FIS are questionable because the change in FIS fails a test for normality which is an underlying assumption. Therefore, the usefulness of the FIS seems questionable in this study. The FIS was one of the exploratory endpoints in the NDA submission since it had not been previously used. By contrast there is a long history of the use of the UHDRS, so the items regarding ADLs were singled out and analyzed separately on our initial review.

Known Adverse Events Attributable to Tetrabenazine as a Possible Explanation of Between-Group Differences in Endpoints

(see Safety Review by Dr. Lourdes Villalba)

The sponsor addressed the question “Are there alternative explanations for the differential decline in FA in Study 004, such as adverse effects from tetrabenazine?”

Sponsor’s Supporting Analysis:

- Correlation between changes in functional parameters with changes in the scales used to assess safety in the trial: HAM-D, Barnes Akathisia Rating Scale (BARNES), BA and the Epworth Sleepiness Scale (ESS)
- Any correlations found were further evaluated by examining the change in function by the degree of change (i.e., tertile) in the safety scale.

The sponsor states that with increasing impairment on Behavioral Assessment (BA) there is greater decline in the Functional Assessment Checklist.

Complementary analyses of the change in the IND, TFC and FIS by change in BA, HAM-D and ESS were conducted but were unrevealing. In the analyses, only the Functional Assessment (FA) Checklist appeared to be associated with changes in BA, HAM-D and ESS; the reason that an association is found only with the FA scale is unknown but one possible explanation is that FA is more sensitive in detecting subtle functional changes due to changes in cognitive and behavioral domains.

Sponsor's Interpretation:

“The association between the magnitude of FA decline in tetrabenazine-treated patients and the degree of change in BA, HAM-D and ESS raises the possibility of an association between the observed decline in FA and adverse effects of tetrabenazine. These observations are consistent with the side effect profile of tetrabenazine, which includes insomnia, sedation, fatigue and anxiety. However, while these analyses raise an alternative explanation for the small differential decline in FA between tetrabenazine and placebo in Study 004, they do not establish a cause and effect relationship.”

The sponsor feels that the association between the magnitude of FA decline in tetrabenazine-treated patients and the degree of change in BA, HAM-D and ESS raises the possibility of an association between the observed decline in FA and adverse effects of tetrabenazine, does not establish a cause and effect relationship.

This section is reviewed in the Safety Review, by Dr. Lourdes Villalba. The possibility of a cause and effect relationship is evaluated with a re-review of all reported AEs. The Safety Review will be submitted separately.

The sponsor feels that if the acute effects of tetrabenazine are causing small declines on the FA scale, the adverse effects can be described in product labeling, appropriately monitored and detected by physicians, and show reversibility upon dose reduction or discontinuation from therapy.

The effect of this argument must be addressed in the efficacy review. It is evident from the safety review that the AEs of tetrabenazine can adversely affect functional, cognitive and behavioral measurements. The sponsor's argument that these are known AEs and can be monitored poses a unique set of challenges with HD. One of the problems with that approach is the difficulty for the physician, or the caregiver, picking up on cognitive or behavioral changes that might be due to the drug treatment rather than to the progression of the disease. No new information has been presented in the CR that would make these changes easier to recognize or modify. Particularly problematic in the review is the inconsistency who was the responder on questions. For example, if a subject became more sedated, they might be easier for a caregiver to manage, thus rated improved rather than experiencing AEs.

7. Cognition changes associated with tetrabenazine vs placebo

Part II of the UHDRS contains five items which measure cognitive abilities (specifically evaluating attention and concentration). Each part of the Cognitive Assessment (UHDRS Part II) was analyzed individually by the sponsor as an exploratory endpoint assessing change from baseline to Week 12. These included Verbal Fluency, Symbol Digit Modalities, and the 3 Stroop Interference Tests (Color Naming, Word Reading, and Interference). The total score of the Cognitive Assessment showed the placebo group improved by 5.1 (± 4.5) points from an average baseline score of 172 (± 55), whereas the TBZ-treated group worsened by 7.7 (± 3.3) points from its mean baseline of 156 (± 56) points. The estimated difference of 12.8 (± 5.6) points was statistically significant (at ANCOVA p -value = 0.025) favoring the placebo group. All of the items at least nominally favored placebo. The Stroop Interference – Word Reading reached statistical significance (p -value = 0.0123).

In the CR, Prestwick addressed the FDA's concern that treatment with tetrabenazine may be associated with a decline in cognitive measures. Specifically, they looked at the observed difference in Stroop Word Reading between the tetrabenazine and placebo groups in Study 004.

Sponsor's Supporting Analysis:

- Mean and mean change in cognitive parameters at Week 12
- Correlation between change in cognitive parameters and changes in BA, HAM-D, ESS and BARNES at Week 12
- Analysis of change in cognitive parameters by:
 - Degree of change in BA, HAM-D, ESS
 - Presence or absence of anxiety and depression
- Comparison of the change in cognitive parameters (vs. Stroop Word/Symbol Digit) between Study 004 and CARE-HD

Possible alternative explanations include:

- baseline imbalances in cognitive impairment within the tetrabenazine group;
- a degree of decline in the tetrabenazine group, but not the placebo group, that is consistent with the natural history of cognitive decline in HD over 12 weeks;
- the acute and predictable pharmacologic effects of tetrabenazine.

Effect of Baseline Differences

At baseline, the tetrabenazine group was measured as slightly more cognitively impaired on four of the five cognitive tests. However, there is no significant difference in the sum of all the Stroop item's scores at baseline. The between-group difference on individual items reached statistical significance only for the Symbol Digit test ($p=0.0176$). At Week 12, tetrabenazine-treated patients had small declines in all three components of the Stroop test while the placebo-treated group showed small increases. The between-group difference achieved statistical significance for the total Cognitive Assessment score (total of the five cognitive tests) and on one of the individual components, the Stroop Word Reading test. Analyses of the Symbol Digit showed small numerical improvements in the tetrabenazine group over the placebo group at Week 12. The Symbol Digit test was the only cognitive component which had been measured as statistically significant in the

evaluation of baseline differences between the treatment and placebo groups. Again, as in the functional FIS analysis, the fact that the tetrabenazine-treated group looked better on the Symbol Digit test endpoint could be due to a floor effect, especially since this is an item for which there is no post-treatment difference.

The CR re-analysis showed that there was no clear evidence of confounding of the treatment effect by baseline levels on the cognitive scores. The baseline imbalance where it exists doesn't necessarily explain the unexpected observed differences in cognitive and functional endpoints

Possibility of a Chance Finding

The sponsor states that the lack of decline in the cognitive measures in the small placebo group in Study 004 was atypical for HD, and may have contributed to the observed differential decline in Stroop Word Reading between the tetrabenazine and placebo groups of Study 004. The comparison of the Study 004 endpoints to the CARE-HD Study is provided in the CR, and is contained in the following section (Section 8).

Known Adverse Events Attributable to Tetrabenazine

The sponsor's re-analysis deals primarily with the possibility that the known side-effects of tetrazenazine are responsible for the endpoint changes observed between groups in Study 004. The review of the possibility is addressed in the Safety Review by Dr. Lourdes Villalba.

The tetrabenazine treatment group was re-analyzed by the sponsor looking specifically at the subjects with reported AEs such as anxiety or depression at any time during the trial, or that required adjustment in medication dosage due to AEs. Patients who experienced an AE of depression during the trial, and to a lesser extent anxiety, had greater declines in Stroop Word Reading, and experienced a decline in Stroop test parameters that is consistent with the natural history of HD. Several of the subjects with the largest declines in Stroop Word Reading scores also had evidence of sleepiness or drowsiness. Among the tetrabenazine-treated subjects greater impairment on the BA, HAM-D and ESS was associated with greater decline in Stroop Word Reading.

During the study, 12 tetrabenazine-treated subjects and one placebo-treated subject had a decline in Stroop Word Reading scores of ≥ 14 words (range: -35 to -14 words). Of the 12 tetrabenazine-treated subjects 4 had increased ESS scores, 3 had reports of drowsiness or fatigue, 3 had changes in depression or anxiety at Week 12. The placebo-treated subject with a large decline on the Stroop Word Reading (-29 words) did not have a reported CNS-related AE.

The sponsor's conclusion of the cognitive endpoint differences is:

"Taken together, these data raise the question of a possible association between the observed decline in Stroop Word Reading and acute pharmacologic effects of tetrabenazine, such as anxiety and depression. However, these analyses do not establish a cause and effect relationship but suggest an alternative possible explanation for the differential decline in Stroop Word Reading between

treatment groups. Importantly, if acute AEs are causing small declines on Stroop Word Reading, it should be remembered that these AEs can be described in product labeling, recognized and properly managed by treating physicians, and show reversibility with dose reduction or discontinuation of therapy.”

The conclusions continue to pose the same dilemma for the efficacy review that was addressed in the initial NDA review. There were slight differences in cognitive measurements at baseline between the two groups and it is not possible to determine the exact significance of the role these might have had in the study outcome. There was statistical significant difference only for one of the five cognitive tests. The total cognitive score (the five assessments combined) showed a statistically significant difference between the tetrabenazine-treated and the placebo-treated groups and re-evaluation in the CR has not changed the finding. The relationship of changes in cognitive assessments and AEs of tetrabenazine (see Safety Review) provides some input on the causal effect of the AEs on the drug efficacy, and in subjects not experiencing AEs, the differences are minimized. However, without effective monitoring and dosage adjustments, efficacy is affected.

8. Comparison of the databases of the Study 004 to the CARE-HD Study

Natural History of Functional and Cognitive Decline in HD

The HSG clinical study, the CARE-HD Study (HSG, 2001) was analyzed as a “pseudo-cohort” to provide comparative information on the natural history and progression of HD. The CARE-HD Study was a 30-month trial of coenzyme Q10 (600 mg/d), remacemide (600 mg/d) and placebo in HD subjects. Although treatment interventions were used in the trial, the sponsor considers the trial population to be similar to a placebo comparison cohort since no short-term treatment effects on function or cognition were shown with any intervention. Three comparison populations were selected from the study:

- All patients regardless of treatment assignment (N=3447)
- Placebo-treated patients only (N=87)
- A sub-group of all patients similar to the “Tetra-HD” Study 004 patients with respect to chorea severity and Total Functional Capacity (TFC) at baseline. The group is termed the “THD” population (N=102). The THD population scored below the median CARE-HD TFC score (<10) and above the median chorea score (>9).

In Table 9, the data from the THD patients in the CARE-HD Study at Week 16 is compared to the Study 004 TBZ-treated subjects and placebo subjects at Week 12. The CR analyses were focused on comparison of the Study 004 subjects to the THD subgroup of subjects from the CARE-HD Study.

Table 9. Comparison of Functional and Cognitive Assessment in Study 004 and CARE-HD: Mean Change from Baseline in Observed Cases

Scale	CARE-HD (at Week 16)	Study 004 (at Week 12)	
	THD Patients (N=99*)	Tetrabenazine (N=48†)	Placebo (N=29)
Functional Assessment test	-0.82 ± 1.72	-0.40 ± 2.13	0.34 ± 1.11
Independence Scale Score	-2.47 ± 6.68	-1.17 ± 7.16	0.34 ± 8.12
Total Functional Capacity	-0.25 ± 1.10	-0.25 ± 1.44	-0.03 ± 1.27
Cognitive Assessment:			
Verbal Fluency	-4.59 ± 5.76	-2.69 ± 6.91	-1.07 ± 6.06
Symbol Digit	-0.57 ± 7.08	2.88 ± 6.27	2.52 ± 4.73
Stroop Interference Test:			
<i>Color Naming</i>	-1.88 ± 6.87	-1.17 ± 8.31	0.79 ± 12.46
<i>Word Reading</i>	-3.69 ± 9.57	-5.17 ± 12.81	0.97 ± 10.55
<i>Interference</i>	-0.62 ± 5.34	-1.92 ± 6.87	1.10 ± 6.04

Source: CR Tables 1.3.3, 1.3.4, 2.4, 3.4, 4.4, 6.1.4, 6.2.4 and 6.3 in Appendix 2

* N = 98 for Verbal Fluency and Color Naming and 97 for Word Reading and Symbol Digit

† N = 47 for FA and IND

Note: Higher scores on FA, TFC and IND are associated with better function. Higher scores on cognitive tests are associated with improvement.

The decline in the functional scales show somewhat similar changes when the Study 004 subjects are compared to the THD subjects (the sub-group of patients considered most similar at baseline to the Study 004 subjects) of the CARE-HD Study. The placebo-treated subjects of Study 004 showed an increase in FA (+0.34) and IND (+0.34), and a slight decrease in TFC (0.03) which was not consistent with the decline on functional measures in the CARE-HD Study THD subjects.

On two of the individual test of the cognitive assessment, the Study 004 subjects showed a greater decline than the CARE-HD THD patients, but in the other three tests, the Study 004 TBZ-treated subjects showed less cognitive decline.

Sponsor's Interpretation:

“The tetrabenazine treatment group in Study 004 experienced a decline in functional parameters that is consistent with the natural history of HD. The lack of decline in these measures in the small placebo group in Study 004 was atypical for HD and may have contributed to the observed differential decline in functional parameters between the tetrabenazine and placebo groups of Study 004”

Long-term Treatment with Tetrabenazine

The changes in functional and cognitive parameters over the course of Study 007 (the open-label follow-on of Study 004) are summarized in Table 10. These provide some information on the longer-term use of tetrabenazine for HD. Comparison data from the CARE-HD Study (the THD subgroup) are included in the table to offer a larger historical database.

Table 10. Mean Baseline and Mean Change from Baseline in Functional and Cognitive Measures: Study 007 vs. THD Subset of CARE-HD

	Study 007		CARE-HD (THD Group)	
	N	Mean (SD)	N	Mean (SD)
Functional Assessment				
Baseline	47†	17.79 (4.62)	102	20.46 (2.43)
Change From Baseline				
4-6 Months*	45	-0.47 (2.81)	99	-0.82 (1.72)
12 Months	38	-1.39 (2.25)	97	-2.67 (2.70)
20 Months	30	-3.40 (3.33)	90	-4.04 (3.31)
Total Functional Capacity				
Baseline	47†	7.62 (2.39)	102	8.73 (1.05)
Change From Baseline				
4-6 Months*	45	-0.49 (1.52)	99	-0.25 (1.10)
12 Months	38	-1.05 (1.39)	97	-1.30 (1.54)
20 Months	30	-2.03 (2.27)	90	-2.13 (1.70)
Independence Scale				
Baseline	47†	74.15 (12.26)	102	81.27 (8.43)
Change From Baseline				
4-6 Months*	45	-1.44 (6.54)	99	-2.47 (6.68)
12 Months	38	-3.55 (6.36)	97	-5.57 (7.21)
20 Months	30	-7.00 (9.15)	90	-10.50 (8.25)
Word Reading				
Baseline	47†	49.83 (20.57)	101	57.46 (17.88)
Change From Baseline				
4-6 Months*	44	-1.16 (9.35)	97	-3.69 (9.57)
12 Months	33	-5.58 (12.49)	95	-5.23 (10.00)
20 Months	28	-8.61 (17.62)	89	-10.44 (10.25)
Symbol Digit				
Baseline	44†	20.57 (10.29)	101	22.26 (8.53)
Change From Baseline				
4-6 Months*	41	-0.63 (5.30)	97	-0.57 (7.08)
12 Months	30	-1.47 (4.48)	93	-3.05 (4.42)
20 Months	21	-4.24 (10.98)	85	-3.34 (5.32)

Source: CR Tables 1.3.3, 1.3.4 and 9.1 in Appendix 2

* 4 months in CARE-HD and 6 months in Study 007

† Data provided for 47 (44 for Symbol Digit) of the 75 patients who had a delayed rollover from Study 004 into Study 007 and full UHDRS at baseline. Baseline for the 28 patients who rolled over directly from Study 004 into Study 007 came from the Week 13 UHDRS assessment, which was conducted after a one-week washout of tetrabenazine.

The CARE-HD TDR scores on the functional scales FA, TFC and IND and the cognitive scales are compared at 6, 12, and 20 months of therapy to the scores of the tetrabenazine-treated subjects on the extension Study 007 that followed-on from the Study 004. The sponsor presented the data for Stroop Word Reading and Symbol Digit. Their rationale is that these tests are deemed to be most sensitive to change among HD cognition experts.

Among tetrabenazine-treated patients, the decrease in FA at 12 and 20 months was -1.39 and -3.40, respectively, which is similar in magnitude to the decline observed in CARE-HD THD group. Mean decline in TFC at 12 and 20 months among tetrabenazine patients (-1.05 and -2.03, respectively) is similar to that observed in the CARE-HD THD population.

Decline on the two cognitive scores showed a similar trend for the Study 007 and the CARE-HD THD group. It should be noted, however, that the significantly higher score of the tetrabenazine-treated subjects in the Symbol Digit test has been discussed earlier in this review as possibly due to an outlier effect at the baseline scores and subject to a floor effect. By the 20-month comparison, the score on the test had significantly decreased (-4.24, compared to -3.34 for the CARE-HD THD group).

The comparison of either Study 004 or Study 007 subjects to the CARE-HD THD subgroup is difficult to assess. It can only be suggestive, but it is a reminder of why placebo groups are important to clinical trials since the stimulation of study inclusion cannot otherwise be assessed. Similarly, the measurements of long-term trials for efficacy and safety are difficult to adequately interpret without the inclusion of placebo groups within the clinical trials.

Prestwick's CR Conclusions from Additional Analysis of Function and Tetrabenazine

Prestwick conducted extensive descriptive analyses to investigate the difference in FA that emerged in Study 004. These analyses support the following conclusions.

- There was a small decline in the FA part of the UHDRS in patients assigned to tetrabenazine in Study 004 that achieved modest statistical significance.
- The overall FA effect size (change with tetrabenazine minus change with placebo) was small, measuring less than 1 unit on a 25-point scale. On analysis of individual items of the FA and TFC, those that assess complex tasks and, therefore, are susceptible to decreased attention, appear to decline more than ADLs. The FIS, which is a measure of ADLs, trended in favor of tetrabenazine.
- Baseline imbalances in disease severity were found between treatment groups, however a clear relationship between these baseline differences and on-treatment differences in secondary endpoints could not be established.
- The between-group difference in the FA was larger in patients having larger increases in BA, HAM-D, and ESS. Subsequent review of the individual items of the BA and HAM-D revealed that these changes were related primarily to increased anxiety and anxiety-related effects.
- Individual review of patients with declines in FA in Study 004 further supports the link between FA decline and acute changes due to tetrabenazine.
- Prestwick cannot exclude the possibility that the observed differential

decline in FA is associated with the established side effect profile of tetrabenazine, e.g., anxiety, sedation, and depressive symptoms.

- Many of these patients with FA decline in Study 004 were also treated with tetrabenazine in Study 007. In many cases, the FA returned toward the patient's baseline level or maintained the gradual decline expected in HD. These findings indicate that the small decline from baseline in FA after 12 weeks of tetrabenazine are acute, not chronic, effects.
- Individual review of patients in Study 004 who also were treated in the long-term Study 007 also confirmed the correlation between changes in FA and changes in BA, HAM-D and ESS. In many cases, the change in FA occurred without any change in TFC or FIS.
- The gradual decline in FA, IND and TFC observed among the tetrabenazine patients in Study 004 is consistent with the natural history of HD progression observed in CARE-HD. The lack of decline in these measures in the small placebo group was atypical for HD and may have contributed to the observed differential decline in functional parameters between the tetrabenazine and placebo groups in Study 004.

The review responses to the issues raised with Prestwick's conclusions have been included in the relevant sections. Prestwick undertook the re-analyses of the Agency's areas of concern and presented these in the CR. The material does not provide new insights. The arguments presented by the company are plausible as explanations of why the secondary and exploratory endpoints trended toward the placebo group. However, they still fail to provide reliable internal verification for the studies on which the NDA application depends. Particularly problematic is the lack of measures that could be used for looking at benefit, which makes any benefit: risk assessment purely speculative.

10. Phase 4/Post-marketing Recommendations

Approval for the drug would be as an orphan drug for the chorea of Huntington's disease. The potential for off-label use of tetrabenazine for other hyperkinetic movement disorders poses a concern. There are no trial data on the safety or efficacy of the drug in children, but it's known that it has been used for children with Tourette's syndrome. Huntington's disease has a well-defined and monitored population of patients. In the annual reports, Prestwick could provide the FDA with the percentage of the drug's sales that are not for HD patients (i.e., off-label). If their total sales far exceed the intended use, additional studies should be required addressing it the use of the drug for other disorders.

CLINICAL REVIEW

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Reviewer Name	Lourdes Villalba, M.D.
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Through	Alice Hughes, MD Team Leader, DNP Safety Team
Established Name	Tetrabenazine
Trade Name	Xenazine®
Therapeutic Class	VMAT-2 antagonist
Applicant	Prestwick Pharmaceuticals
Priority Designation	P
Formulation	Oral
Dosing Regimen	25 to 100 mg daily
Indication	Chorea of Huntington's Disease

Xenazine® (Tetrabenazine tablets)

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Recommendations

Tetrabenazine (TBZ) should be Approved for the treatment of chorea of Huntington's disease.

A Risk Minimization Action Plan that at a minimum includes an educational program for physicians, patients and families addressing adequate dosing and the risk of depression & suicidality should be in place before TBZ starts to be distributed.

Executive summary

1. Efficacy

Tetrabenazine (TBZ) has a beneficial effect on the chorea component of HD. In study 004, the primary efficacy analysis showed a mean change in Total Chorea Score (TCS) of -5.04 ± 0.49 among subjects receiving TBZ and -1.52 ± 0.67 among subjects receiving placebo ($p < 0.0001$). In a responder analysis at 12 weeks, 38% of subjects in the TBZ treatment group had a drop of $\geq 50\%$ in TCS as compared to no subjects on placebo and 69% had a drop of ≥ 3 points in the TBZ treatment group (which is considered to be clinically meaningful by HD experts), as compared to 23% on placebo. TCS reverted to baseline within one week after TBZ discontinuation.

TBZ had no beneficial effects on other components of the disease (behavioral, cognitive and functional components) and was associated with a small worsening in three out of four functional outcome scores, as well as some cognitive scores (See review by Dr. Carole Davis).

Post-hoc analyses suggest that there is a dose response relationship in terms of efficacy. Patients who had the highest TCS at baseline showed the greatest improvements in TCS (See review by Atul Bhattaram, Ph.D.). Patients with the least functional impairment at baseline had the smallest decrease in their functional outcome scores.

2. Safety

Evaluation of safety in this application is limited by the small database, the use of a flexible dose design and the fact that some of the adverse reactions associated with TBZ are also symptoms of or difficult to distinguish from the underlying disease (e.g. depression, dysphagia and bradykinesia in late HD).

The application includes a 12-week placebo controlled study (Study 004, 54 subjects on TBZ and 30 on placebo) with an open label extension up to 80 weeks (study 007 that included 75 subjects), and a five-day placebo-controlled withdrawal study (Study 005, 30 subjects) with an open label extension up to 48 weeks (study 006). Altogether these studies involved 111 unique subjects exposed to TBZ. Additional information comes

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NDA (Complete response to March 24, 2006 AE letter)
TBZ for the Treatment of Chorea of Huntington's Disease

from chart review of patients under a compassionate use IND, of whom approximately 10% had been lost to follow up.

By design, the dose of TBZ was to be titrated up over a seven week period to "desired effect", to a maximum of 100 mg/day (in study 004), 150 mg/day (in study 006) or 200 mg/day (in study 007) or "intolerable" toxicity. The flexible study design makes it difficult to assess a dose-response relationship in terms of toxicity. The decision to continue titration or decrease the dose in the presence of adverse events (AEs) was based on clinical judgment; therefore, the approach to managing treatment-emergent events was different from one investigator to another. Additionally, safety analyses are confounded by time.

The sponsor did not capture all adverse events in their analyses of incidence rates. In study 004 the FDA reviewer found 3 additional cases of parkinsonism, 2 additional cases of akathisia, 3 cases of restlessness that could have been cases of akathisia, 2 additional cases of depression, and one additional case of dysphagia, all in the active treatment group. This discrepancy between the FDA and the sponsor's analyses underscores the difficulty in distinguishing some of these adverse events from the underlying disease, as well as difficulties in coding of some events related to abnormal movements.

Common AEs observed in study 004, the 12-week study were as follows (FDA analysis, percentage rounded):

AE	TBZ (N=54)	Placebo (N=30)
Sedation	32 %	3 %
Fatigue	22 %	13%
Insomnia	22 %	0%
Akathisia	19 %	0 %
Depression	19 %	0 %
Falls/traumatic injury	19 %	13%
Anxiety	15 %	3 %
Parkinsonism	15 %	0 %

My review focused on whether four events of major concern mentioned in the Approvable letter of March, 2006 (referred to in this review as "AE of interest": akathisia, depression, dysphagia and parkinsonism) were recognized as drug-related AEs by the investigator, were reversible upon dose reduction or discontinuation, and on whether total chorea scores were adversely affected by the AE and/or dose reduction. I also attempted to evaluate risk and benefits associated with the use of TBZ.

- Adverse events of interest

Parkinsonism, akathisia and depression were not always recognized as probably or possibly related to study drug in this clinical program. Investigators may have preferred to tolerate mild adverse effects to decreasing the dose of TBZ and losing therapeutic benefit; however, in some cases is unclear whether the investigator thought of these

events as potentially related to TBZ. The sponsor states that the three additional AE of parkinsonism identified by FDA were cases in which the investigator thought that there was worsening of the underlying disease; however, it is impossible to know for sure what the investigator was thinking at the time that he/she recorded the event. Additionally, some investigators and/or coding personnel had difficulties in identifying or coding akathisia. The sponsor identified five cases of akathisia from the listings in study 004. The FDA identified two additional cases that had been recorded as akathisia in an ancillary file ("UH file") but not in the AE listings. We also called the sponsor's attention to the fact that several cases coded as restlessness could have been cases of akathisia. Upon review of these cases, based on the BARNES akathisia scores in these patients, the sponsor agreed that all cases coded as restlessness were in fact cases of akathisia. Therefore, in study 004 there were at least 10 cases of akathisia (18.5%) versus none on placebo.

Less than half of patients with depression/worsening depression underwent dose reduction. In four out of 51 cases of depression, investigators recorded a change in antidepressant regimen without recording depression or worsening depression as an adverse event. Four out of the 10 cases of depression/worsening depression in 006 received neither dose reduction nor antidepressant regimen change.

In the case of dysphagia, it appears that most investigators did not consider dysphagia as an adverse event potentially related to TBZ treatment. Only 4 out of 11 cases of dysphagia/choking in the Prestwick studies underwent dose reduction. In study 011 (Baylor Chorea report) there were 21 cases of dysphagia/choking. Of these, only two were thought to be possibly or probably related to study drug, and only three underwent dose reduction or discontinuation. Additionally, there were four cases of aspiration pneumonia in 011 with no reported AE of dysphagia.

In general, the AE of interest responded to dose reduction or discontinuation. If they did not respond to dose reduction, they did respond to discontinuation after study withdrawal or completion. However, as mentioned above, not all events underwent dose reduction. Moreover, some cases took several months to resolve (particularly depression and dysphagia), and recovery data after drug discontinuation were missing for most patients.

In general, total chorea scores (TCS) increased after dose reduction, however, most patients who had achieved a "responder" status (drop in TCS from baseline ≥ 3 points) maintained a responder status (if they did not require withdrawal). By week 12, only 2 out of 7 patients with akathisia, 6 out of 8 with parkinsonism, 5 out of 10 with depression and 1 out of two with dysphagia, achieved a TCS ≥ 3 points, suggesting that dose titration until reaching an "intolerable" toxicity—as used in the development program—may not be a good idea.

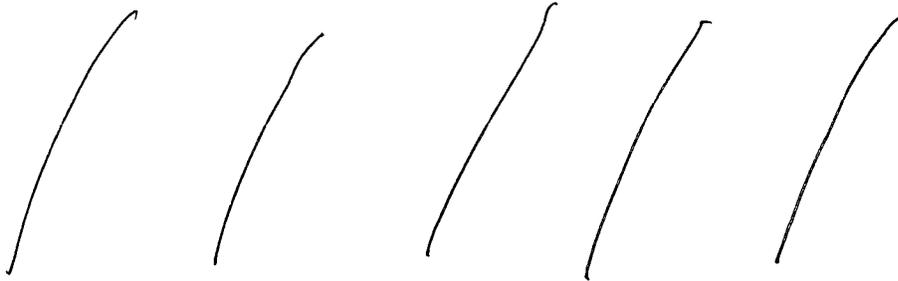
In my opinion the optimal dose or the optimal HD population that would achieve the best benefit to risk ratio may have not been adequately identified for TBZ. In study 004 the median dose at onset of the first event of akathisia, depression and parkinsonism was

> 50 mg/day (75 mg/day for akathisia and 62.5 mg/day for parkinsonism and depression [although some cases of depression occurred at doses <50 mg/day]). Notwithstanding the limitations of the database, based on post hoc analyses of the number of patients who at the end of the 12-week study achieved a drop in TCS from baseline ≥ 3 points (19 of 29 patients at doses 62.5 to 100 mg/day dose [66%] and 15 out of 19 patients at doses up to 50 mg/day dose [79%]), in the context of most concerning events occurring at doses above 50 mg/day, it appears that the 50 mg/day dose has a more favorable safety profile than the 100 mg/day dose.

Of all adverse events observed in this clinical program, the most concerning is the risk of depression/worsening depression and suicidality.

- RiskMAP

The sponsor proposed a Risk Minimization Action Plan (RiskMAP)



- Other safety issues

Other adverse events associated with TBZ (sedation, hyperprolactinemia, neuroleptic malignant syndrome, hypotension/orthostatic hypotension) have been observed either in clinical studies or in non-US postmarketing experience. These AEs are not unexpected based on the pharmacologic properties of TBZ (dopamine, serotonin and norepinephrine depletion) and should be labeled under the WARNINGS & PRECAUTIONS section of labeling. A mild prolongation of the QTc was observed in a Thorough QTc study, suggesting that TBZ has a possible arrhythmogenic effect. The size of the safety database is inadequate to assess the potential clinical implications of this positive study. Strong labeling for this safety concern is warranted.

- FDA Central and Peripheral Nervous System Advisory Committee

The FDA Central and Peripheral Nervous System Advisory Committee met on December 6, 2007 to discuss this application. The panel unanimously (12-0) voted to approve this application for the treatment of chorea of Huntington's disease.