The same independent cardiologist reviewed the QT interval findings from TBZ 104,012 (a 2-period crossover bioavailability study of 25 mg in healthy volunteers) and TBZ 203,008 (a 4-day, randomized double-blind, placebo-controlled 2-period crossover study to evaluate the effect of treatment on pituitary hormones in males). He felt that there was no significant prolongation of the corrected QT interval seen in these studies.

- TBZ 104,012: There was a mean decrease in QTc from baseline seen. No subject had a post-dose QTc(B) >450 ms; one subject (1247-130) had a pre-dose QTc (B) >450 ms. No subject had a change from baseline in QTc which exceeded 60 ms.

Table 20: QTc (Bassett) data

	N	Mean	Std Dev	Minimum	Maximum
Pre-Dose	52	400.67	22.18	359.21	450.33
Post-Dose Period 1	28	394.66	20.31	340.5	430.68
Change from baseline		-5.95	15.84	-34.38	22.94
Post-Dose Period 2	23	392.95	25.09	318.89	438.87
Change from baseline		-6.35	22.66	-55.99	41.08

(table 12-4 from the ISS)

Table 21: QTc (Fridericia) data

	N	Mean	Std Dev	Minimum	Maximum
Pre-Dose	52	400.57	16.58	372.32	446.03
Post-Dose Period 1	28	400.25	15.62	359.28	425.85
Change from baseline		-0.78	12.93	-22.74	20.45
Post-Dose Period 2	23	397.54	20.38	338.08	435.89
Change from baseline		-1.15	17.65	-43.37	27.81

(table 12-5 from the ISS)

- TBZ203,008: Small increases in QTc from baseline were seen during the tetrabenazine period, as shown in the table below.

Table 22: Changes in QTc

	Placebo Period			Tetrabenazine Period		
Correction	Baseline (N=26)[a]	Post-dose (N=132)	Change from Baseline	Baseline (N=28)	Post-dose (N=147)	Change from Baseline
QTc (B)	400.4 (359.0-431.3)[a]	396.8 (355.9-440.3)	-3.1 (-15.0 to 5.2)	397.3 (360.7-428.7)	398.3 (356.0-465.0)	1.2 (-11.9 to 23.7)
	Placebo subtracted Treatment Effect[c]					4.3
QTc (F)	405.3 (369.1-435.9)	397.3 (363.8-433.4)	-6.7 (-14.7 to 3.2)	399.9 (370.0-437.5)	398.2 (360.6-459.5)	- 1.2 (-13.0 to 21.6)
	Placebo subtracted Treatment Effect[c]					5.5

(Table 12-6 from ISS)

Two subjects had a post-dose QTc>450 ms. Subject 847-036, who had a baseline QTc(F) of 412, had a QTc(F) of 459.5 on day 2 after the afternoon dose. The sponsor asserts that since the baseline value was based upon 2 ECGs and the on treatment value was based upon a single ECG, the increase of 47.5 ms is below the threshold for inferring drug effect, citing

Pratt (1996) in support of their assertion. At the Day 4 pre-AM dose ECG, Subject 847-039 had a 66.6 ms increase in QTc(B) and a 30.4 ms increase in QTc(F) in association with a heart rate increase of 32 beats/minute over baseline.

Phase III placebo-controlled studies: TBZ 103,004 and TBZ 103,005

103,004

While there were no "abnormal, clinically significant" ECGs in the normal volunteers, there were treatment emergent abnormalities seen in three patients who participated in this 12 week phase III study: non-specific lateral T-wave abnormalities; sinus bradycardia; borderline right atrial enlargement.

ECGs were performed at baseline and at study termination: 96 records from 48 patients were available for review from study TBZ 103,004. While three patients had QTc values which exceeded 450 ms at baseline (QTc(B) which ranged from 454 to 461 ms), none of the patients had on-treatment QTc which exceeded 450 ms.

Table 23: QTc (Bassett) data from study 103,004	N	Mean	Std Dev	Minimum	Maximum
Baseline	48	410.92	26.40	327.04	460.82
On-Treatment	48	414.16	24.60	338.53	447.36
Change from baseline		3.24	19.30	-38.45	43.05

(table 12-10 from ISS)

Table 24: QTc (Fridericia) data from study 103,004

	N	Mean	Std Dev	Minimum	Maximum
Baseline	48	403.94	20.54	340.77	452.40
On-Treatment	48	406.32	20.28	351.83	446.97
Change from baseline		2.38	20.74	-50.75	62.35

(table 12-11 from ISS)

Four patients were noted to have QTc changes from baseline which were >30 ms, as displayed below.

Table 25: QTc changes form baseline

Patient ID	Change in QTc (B)	Change in QTc (F)
447-225	**32.8**	**31.9**
447-267	**34.6**	25.6
447-274	**40.2**	**33.9**
447-275	**35.1**	29.7
447-316	**43.0**	**62.4**

(Table 12-12 in ISS)

The tracings were sent for review by the independent cardiologist. While he concluded that there was no evidence that the QTc interval was prolonged by tetrabenazine, he noted that "the results of his interpretations should be interpreted with caution for reasons including but not limited to

the retrospective analysis, the small number of ECG samples available for evaluation, the inherent limitations of paper ECG tracings, the failure to correlate ECG sampling times with peak drug concentrations and the absence of a positive control study drug for assay sensitivity (ISS p.813-814)."

103,005

No abnormal clinically significant ECGs were seen in patients who participated in this 5-day phase III study.

ECGs were performed at baseline and at study termination: 58 records from 29 patients were available for review from study TBZ 103,005. Thirteen of those patients were considered drug free at the time of Day 5 ECG recording so it is their information which was analyzed to determine mean change values. While three of these patients had QTc values which exceeded 450 ms at baseline (QTc(B)) which ranged from 450 to 460 ms), none of the patients had on-treatment QTc which exceeded 450 ms. No patient had a change in QTc of greater than 60 ms; one patient (547-425) had a change in QTc(F) of 30.9 ms.

The independent consultant concluded that there was no evidence that the QTc interval was prolonged by tetrabenazine in the pooled data from the 13 patients whose data was provided for primary analysis. He was given data from the 16 patients who had persistent blood levels on Day 5 but he was not able to make any "meaningful statements" about possible drug effect since he did not have baseline ECG data available.

Table 26: QTc (Bassett) data from study 103,005

	N	Mean	Std Dev	Minimum	Maximum
Off-Treatment (Day 5)	13	421.03	23.22	383.86	457.47
On-Treatment (Day 1)	13	412.66	22.93	367.01	444.5
Change from baseline		-8.38	20.05	-46.76	26.64

(Modification of table 12-13 from the ISS)

Table 27: QTc (Fridericia) data table 12-14 from the ISS study 103,005 (modified)

	N	Mean	Std Dev	Minimum	Maximum
Off-Treatment (Day 5)	13	406.21	16.00	382.57	431.18
On-Treatment (Day 1)	13	402.30	14.73	371.50	437.80
Change from baseline		-3.91	16.95	-30.18	30.93

(Modification of table 12-14 from the ISS)

A review of the 16 patients with persistent blood levels was done: the mean change and the range of QTc(F) values on-treatment and on Day 5 were all <450 ms; the mean change in QTc(B) values on-treatment and on Day 5 were both <450 ms but the range on treatment was 398.0-457.5 and the Day 5 range was 390.0 to 466.2. Two patients had values QTc(B) >450 ms:

- Patient 547-409, a 57 year old female who was receiving concomitant doses of amitriptyline and tolteridine, had an on-treatment QTc(B) value of 457.5 and day 5 value of 466.2 ms. Her QTc(F) were 430.0 and 431.6 respectively.
- Patient 547-412, a 60 year old female with a history of hypertension and hyperthyroidism, had an on-treatment QTc(B) value of 452.9 and day 5 value of 466.1 ms. Her QTc(F) were 441.7 and 439.2 respectively. Her ECGs were significant for left axis deviation, right bundle branch block and possible left anterior fascicular block.

7.1.9.4 Additional analyses and explorations

Pharmacovigilence
The sponsor reviewed the available periodic safety update reports (PSURs) through 2004. Nine adverse events categorized as heart rate and rhythm disorders were recorded: cardiac arrest (n=3); ventricular extrasystole (n=1); atrial fibrillation (n=1); abnormal ECG (n=1); Tachycardia (n=1); bundle branch block (n=1); bradycardia (n=1). While detailed information was not available for most of the adverse events, the sponsor reports that the 3 patients who had cardiac arrests "had confounding factors and none [of the events] were suspected to be due to tetrabenazine (ISS p.816, section 12.3)."

7.1.9.5 Reviewer's summary

While there were no abnormal clinically significant ECGs in the normal volunteers, there were three treatment emergent abnormalities seen during the 12 week phase III study: non-specific lateral T-wave abnormalities; sinus bradycardia; borderline right atrial enlargement. We are not provided with any further information upon these abnormalities since no follow-up ECGs appear to have been done.

The mean change from baseline in corrected QTc was minimal in the clinical pharmacology studies. The placebo-controlled studies revealed negative changes from baseline in the 5 day staggered withdrawal study; a change of 2.38 ms for QTc(F) and a change of 3.24 ms for QTc(B) was seen in the patients treated with tetrabenazine in the 12 week study.

While we have data from the clinical pharmacology studies which would seem to indicate that QTc prolongation is not to be expected, I would note that those subjects received doses of 25-50 mg/day; forty percent of the patients in the efficacy studies were treated with higher doses. We cannot, from the data provided, determine that tetrabenazine when used at doses higher than 50 mg has no effect on QT prolongation.

7.1.10 Immunogenicity

There was no data provided to assess the impact of immunogenicity on safety, efficacy, clinical pharmacokinetics or pharmacology. While any drug product may elicit an idiosyncratic hypersensitivity response, there is no evidence that this product has any increased potential for producing such reactions.

7.1.11 Human Carcinogenicity

Three women, who have been discussed in detail in earlier sections of this review, were found to have had breast cancer. While two of the women were known to have had prolactin-negative tumors, it is not clear whether the tumor growth in the third patient may have been affected by the use of tetrabenazine.

One man, who was been discussed earlier, had prostate cancer: 747-264.

7.1.12 Special Safety Studies

The sponsor performed a study to evaluate the effect of a single 25mg or 50 mg dose of tetrabenazine on QTc using moxifloxacin as a positive control. Tetrabenazine caused an apparent 7-10 millisecond increase in QT interval, corrected. No subject had a QTc of more than 500 msec. In light of the available pharmacokinetic data, the QT data was evaluated to determine whether poor metabolizers of CYP2D6 had QTc values which could be considered outliers; they did not.

[*Reviewer's note: The recommended dose of 100mg/day taken as divided doses was not evaluated in this study, so no comment can be made regarding the effect of that dose on QT interval.*]

7.1.13 Withdrawal Phenomena and/or Abuse Potential

7.1.13.1 Abuse potential

The sponsor reports that there have been no reports of illicit use from the countries in which tetrabenazine is currently marketed. There was no evidence of recreational use of tetrabenazine among the participants in the Prestwick sponsored trials. However, the potential for tetrabenazine abuse, tolerance and/or physical dependence has not been evaluated in a systematic manner.

7.1.13.2 Withdrawal phenomena

The discontinuation of tetrabenazine is associated with the return of choreic movements. The reduction of monoamine levels in the striatum by tetrabenazine causes a reduction in chorea. When the medication is stopped, the monoamine levels return to baseline and the chorea returns. This association between discontinuation of tetrabenazine and the return of choreic movements is supported by the results from the two placebo-controlled trials, one of which was a staggered withdrawal study (TBZ 103,005), as well as by cases in the literature and anecdotal reports.

Additionally, in the staggered withdrawal study, the following adverse events were seen in association with abrupt drug discontinuation: anxiety (7%); decreased appetite (7%); insomnia/decreased sleep (7%); dysphagia (7%); aggravated restlessness (3%); diarrhea (3%); hallucinations (3%); mood swings (3%); obsessive reaction (3%); inflicted injury (3%).

7.1.14 Human Reproduction and Pregnancy Data

There were no reports of pregnancy during the clinical trials.

There are two postmarketing reports of women who were using tetrabenazine who became pregnant. By the sponsor's report, abnormalities in pregnancy, labor or delivery were not noted nor were abnormalities seen in the children of these women.

Since the data from studies done in males indicates that an increase in serum prolactin is seen after exposure to tetrabenazine, there is at least a theoretical possibility that use of tetrabenazine by females may affect lactation. A published report by Stockhausen (1960), reported 'frank lactation" in 5 of the 70 (5%) female schizophrenics treated with tetrabenazine and metrorrhagias in "more than 20%" of those same patients.

It is not known whether tetrabenazine is excreted in the breast milk.

7.1.15 Assessment of Effect on Growth

The majority of the studies submitted in support of this application did not enroll patients under 18 years old. However at Baylor, pediatric patients were enrolled as per the inclusion criteria of open-label compassionate use study H-721. There were 52 of these patients: 41 of whom were males. Twelve of the 52 pediatric patients had hyperkinetic conditions other than Tourette's syndrome.

The provided data (tabulated below) is not adequate for conclusions about the potential effect of tetrabenazine on growth. The sponsor did not provide the children's height and weight converted to z-scores. However even if such information had been provided, it would be difficult to interpret because these children were participants in an open label study.

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Table 28 : Data from pediatric patients enrolled in Baylor compassionate-use protocol

Study ID #	Sex	Diagnosis	Age (yrs)	TBZ duration (months)	Initial/final dose (milligrams)	Initial/final weight (lbs)
309	Male	Tourette's	13	33	37.5/37.5	106/147
508	Male	Tourette's	14	43	37.5/25	193/248
513	Male	Tourette's	10	15	25/50	80/104
2238	Male	Tourette's	11	38	12.5/25	82/142
2490	Female	Prev Dystonia musculorum	15	7	25/37.5	172/196
2531	Male	Tourette's	11	3	25/37.5	100/not given
2726	Female	Hallervorden-Spatz	16	22	25/50	Not given/85
2839	Female	Prev Dystonia musculorum	13	169	100/125	75/82
3909	Female	Tourette's	12	36	37.5/6.25	76/118
4162	Male	Tourette's	11	8	37.5/37.5	91/110
4585	Female	Tourette's	11	Not provided	75/not provided	94/not given
4796	Male	Tourette's	13	5	37.5/37.5	150/not given
5472	Male	Prev Dystonia musculorum	12	0	25/25	Not given/73
5550	Male	Tourette's	15	6	75/50	124/122
5554	Male	Tourette's	16	20	50/not provided	148/173
5890	Female	Tourette's	16	96	100/25	151/145
6111	Male	Tourette's	17	0	25/25	154/not given
6217	Male	Tourette's	17	40	75/75	142/165
6737	Male	Tourette's	13	Not given	25/not given	114/not given
7228	Female	Paroxysmal dyskinesia	9	6	37.5/50	65/not given
7329	Male	Tourette's	12	14	50/75	115/142
7407	Male	Tourette's	13	1	25/25	160/not given
7507	Male	Tourette's	9	6	37.5/37.5	87/not given
7521	Male	Tourette's	17	81	75/25	254/302
8008	Male	Tourette's	17	17	12.5/75	133/122
8055	Male	Ataxia	4	6	12.5/12.5	33/38
8087	Male	Tourette's	11	4	25/37.5	127/not given

Table 28 (continued): Data from pediatric patients enrolled in Baylor compassionate-use protocol

Study ID #	Sex	Diagnosis	Age (yrs)	TBZ duration (months)	Initial/final dose (milligrams)	Initial/final weight (lbs)
8439	Male	Tourette's	15	1	12.5/25	178/147
8688	Male	Tourette's	11	41	25/37.5	72/103
8703	Male	Tourette's	15	245	25/25	119/214
9186	Male	Tourette's	17	4	25/25	161/not given
9853	Female	Essential tremor	13	5	37.5/75	99/122
10017	Male	Tourette's	16	16	25/75	133/164
13085	Male	Tourette's	14	6	37.5/50	163/168
19016	Male	Tourette's	9	2	25/62.5	69/81
11421	Male	Tourette's	16	1	75/50	218/220
11665	Male	Tourette's	15	Not given	25/not given	219/not given
12005	Male	Tourette's	14	22	50/12.5	127/140
12026	Female	Not given	12	1	75/50	128/132
12088	Male	Hemidystonia	12	Not given	12.5/not given	99/not given
12993	Male	Tourette's	16	11	25/62.5	131/130
13133	Male	Tourette's	12	2	75/75	76/76
13391	Male	Tourette's	10	4	75/50	81/84
13579	Female	Focal	15	5	75/75	96/94
13664	Male	Tourette's	11	6	25/50	121/124
13761	Male	Not given	10	10	37.5/37.5	50/50
13923	Male	Tourette's	10	5	12.5/75	Not given/82
14061	Male	Tourette's	14	4	75/50	207/214
14078	Male	Tourette's	16	3	75/75	242/not given
14296	Female	Hallervordern-spatz	6	5	37.5/6.25	Not given/not given
14319	Male	Tourette's	12	7	37.5/100	68/70
14512	Male	Tourette's	12	Not given	25/not given	122/not given

7.1.16 Overdose Experience

7.1.16.1 Prestwick-Phase I: clinical pharmacology studies

There were no reported cases of overdose in these 7 studies.

7.1.16.2 Prestwick: Placebo-controlled double-blind studies: TBZ 103,004 and TBZ 103,005

There were no reported cases of overdose in these studies.

7.1.16.3 Prestwick: Open-label long-term studies

7.1.16.3.1 TBZ 103,006: A 48 week extension of protocol TBZ 103,005

A 45-year-old woman (647-402), who had been previously maintained on 50 mg/day during study TBZ 103,005, enrolled in this extension study. She was started at 100 mg/day, twice her previous dose on November 21 2003. Two weeks later, she experienced insomnia, nausea, diarrhea, fever and severe depression which led to hospitalization. She was discharged after 24 hours. Her dose of tetrabenazine was reduced on January 21 2004.

7.1.16.3.2 TBZ 103,007: An up to 80 week extension of protocol TBZ 103,004

There were no reported cases of overdose in this study.

7.1.16.4 CSR TBZ 103,011: an analysis of all chorea patients treated at Baylor College of Medicine since 1979

A 71 year old woman (00258) who was being maintained on 25 mg/day, was accidentally given 100 mg in a single dose by the staff at her nursing home. She was hospitalized due to her decreased consciousness, bradycardia and catatonia. Her symptoms are noted to have resolved though the time course is not given.

7.1.16.5 H-721: an analysis of all patients treated at Baylor College of Medicine since 1979 with hyperkinetic disorders other than chorea

An overdose was reported for a 40 year old man with Tourette's syndrome (patient 212). He had first received tetrabenazine in 1993 and received it intermittently for 2.5 years.

He took thirty-six 25mg tablets, for a total dose of 900 mg, in ——— While fatigue, nausea and vomiting lasting approximately one week were reported at the time of the overdose, no persistent AE were reported. His tetrabenazine was stopped temporarily then restarted along with additional unspecified psychiatric treatment.

Ultimately, he committed suicide by hanging. By report this occurred approximately one month after cessation of tetrabenazine therapy. It is not clear why the tetrabenazine therapy was stopped. The possibility that it was due to ongoing depression cannot be ruled out.

7.1.16.6 Nitoman 003 study

A 23 year old man, who was being treated for post-traumatic chorea, entered the study on March 30 1990. He stopped taking his tetrabenazine in June 1990 due to a complaint of depression. On ——— he was hospitalized after taking an overdose of 100 tetrabenazine tablets. During that hospitalization he attempted to slash his wrists. The patient was withdrawn from the study.

7.1.16.7 Literature reports

7.1.16.7.1 Kidd and McLellan (1972)

A 27 year old female was being treated for post-traumatic chorea. She had been given a supply of 25 mg tablets with instructions to titrate up from a dose of 12.5 mg. After her second dose, she ingested 40 tablets at once. She became somnolent and diaphoretic. She recovered after 24 hours. Prior to this ingestion, she had a history of depression in association with premenstrual stress.

7.1.16.7.2 Mateo et al. (1992)

A 53 year old female developed neuroleptic malignant syndrome (NMS) after beginning treatment for Huntington's chorea. She was supposed to have had a gradual discontinuation of her on-going haloperidol treatment while titrating her tetrabenazine up to 100 mg/day. Instead of the planned gradual change, her medications were abruptly switched. While there was no immediate effect, three weeks after the switch, she had symptoms of NMS.

7.1.16.7.3 Dietrichs et al (1996)

A 21 year, who was being treated for Tourette's syndrome took 750 mg of tetrabenazine in a suicide attempt. She presented to the hospital with rubor, tremor, nausea and vomiting. Within 24 hours of the overdose, she developed torticollis and oculogyric crisis. Her symptoms abated with treatment.

7.1.16.7.4 Magnusson et al (1996)

A patient ingested 750 mg in a suicide attempt and developed dystonia over the following 24 hours.

7.1.16.7.5 Osseman et al (1996)

A 52 year old man was being treated for Huntington's chorea with 82.5 mg/day tetrabenazine and 2.5 mg/day clonazepam. Subsequent to ingesting 500 mg tetrabenazine, he began complaining of falls, hypotension, nausea, vomiting, diarrhea, hallucinations and worsening of confusion. He recovered without sequelae 3 days after discontinuing tetrabenazine. At hospital discharge, he was started on 100 mg/day tetrabenazine and 4.5 mg/day clonazepam. Two months later, after an increase in tetrabenazine up to 131 mg/day, he had neuroleptic malignant syndrome.

7.1.16.8 Reviewer's summary

Neuroleptic malignant syndrome (NMS) is a potentially life-threatening complication of overdose. Depression, another adverse event described in association with overdose, is also significant and potentially life-threatening if it leads to suicidal ideation/gestures. Other adverse events seen in the setting of overdose include dystonia, gastrointestinal complaints, insomnia, and altered levels of consciousness.

7.1.17 Postmarketing Experience

No postmarketing safety assessments have been conducted by the office of Drug Safety (ODS) at the FDA.

The postmarketing data in this review was provided by the sponsor based upon three reports, as tabulated below. The information from the UK was not included in the ISS because that material is believed, by the sponsor, to be duplicates of what is in the Roche 1994 PSUR. The sponsor acknowledges that this belief cannot be confirmed since there are no numeric identifiers for each reported event in the ./database. The list of patients reported from Roche France does include 9 subjects who are captured in the 1998 Roche database as confirmed by cross referencing of the unique identifiers. The sponsor also accessed the ADR online tracking system maintained by the United Kingdom Medicines control Agency on 11 August 2005. [*Reviewer's note: I accessed the same database on 24 January 2006 and found a few additional reports filed subsequently.*]

Table 29: summary of postmarketing data provided

Source of Safety Update	Reporting Period	Patients with Reports	Total No. Events	Included in the ISS Analysis
Roche	8/1/71 – 11/30/94	132	221	Yes
Roche	12/1/94 – 11/30/98	35	75	Yes
Cambridge				
United Kingdom	8/20/71 – 11/30/04	[redacted]	[redacted]	[redacted]
France (Roche)	10/4/99 – 4/3/03	19	31	Yes
	TOTALS†	186	327	

(Table 1-33 in the ISS)

The available data on postmarketing experience with this product in other countries has been placed in the appropriate sections of this review. A table listing deaths reported in the literature may be found in appendix 10.5. The reported deaths were predominantly, as in the studies conducted in the development plan, related to aspiration pneumonia, cardiovascular disease and suicide.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

As may be seen in the table below, the majority of the unique patient exposures occurred in patients *without* Huntington's disease associated chorea (n=464, 71%) [emphasis added].

Table 30: Studies performed and submitted for review

Protocol Number	Title of Protocol	Persons Exposed to TBZ	Unique Exposures to TBZ
Clinical Pharmacology Studies in Healthy Volunteers and Liver-Impaired Patients			
TBZ 202,001	Effect of a Single Administration of Tetrabenazine on Prolactin Blood Levels. A Randomized, Double-Blind, Placebo Controlled, Cross-Over Study in Healthy Volunteers	6	6
TBZ 103,003	An Open-Label, Randomized Two-Treatment, Two-Sequence, Two-Period Study of the Effect of Food on the Absorption of Tetrabenazine in Healthy Adult Volunteers	28	28
TBZ 104,012	An Open-Label, Randomized, Two-Treatment, Two-Sequence, Two Period Study of the Bioequivalence of 12.5 and 25 MG Tetrabenazine Tablets in Healthy Adult Volunteers Under Fasted Conditions	28	28
CL 1700114 (A)	An Open Label Study to Establish the Bioavailability of Tetrabenazine and Dihydrotetrabenazine Comprising A Single Dose Two-Way Cross Over Study Comparing 12.5 and 50 mg Doses in Healthy Male and Female Subjects	12	12
TBZ 203,008	Effect of a Single and Repeated Doses of Tetrabenazine on Serum and Plasma Concentrations of Various Hormones, a Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study in Healthy Male Volunteers	13	13
CL 1700114 (B)	An Open Label Study to Establish the Bioavailability of Tetrabenazine and Dihydrotetrabenazine Comprising A Repeat Dose Study (25 mg) in Healthy Male and Female Subjects	25	25
TBZ 203,009	Study of the Interaction of Tetrabenazine with P-Glycoprotein Based on Digoxin Bioavailability in Healthy Subjects	13	13
TBZ 203,009	Study of the Interaction of Tetrabenazine with P-Glycoprotein Based on Digoxin Bioavailability in Healthy Subjects	13	13
TBZ 203,010	A Comparison of the Pharmacokinetic Characteristics of a Single Dose of Tetrabenazine in Liver Impaired and in Healthy Subjects	12	12

Table 30 (continued): Studies performed and submitted for review

Protocol Number	Title of Protocol	Exposed to TBZ	Unique Exposures to TBZ
Tetrabenazine-Naive Patients with Chorea Associated with HD			
TBZ 103,004	A Randomized, Double-Blind, Placebo-Controlled, Study of Tetrabenazine for the Treatment of Huntington's Chorea	54	54
TBZ 103,007[c]	An Open-Label, 24-Week Extension Study of Tetrabenazine for the Treatment of Huntington's Chorea	75	27[c]
TBZ 103,011[d]	An Analysis of a Prospective, Open-Label, Dose-Titration Study of Tetrabenazine in the Treatment of Patients with Chorea	98	76[d]
Tetrabenazine-Experienced Patients with Chorea Associated with HD			
TBZ 103,005	A Randomized, Double-Blind, Placebo-Controlled, Staggered Withdrawal Study in Patients with Huntington's Disease Treated with Tetrabenazine	30	30
TBZ 103,006[e]	An Open-Label, 24-Week Treatment Study of Tetrabenazine in Patients with Huntington's Disease	29	0[e]
Tetrabenazine-Naive Patients with Chorea Not Associated with HD			
TBZ 103,011	An Analysis of a Prospective, Open-Label, Dose-Titration Study of Tetrabenazine in the Treatment of Patients with Chorea	47	47
Tetrabenazine-Naive and Tetrabenazine-Experienced Patients with Hyperkinetic Disorders Other than Chorea			
Baylor Non-Chorea Review	Compassionate use of Tetrabenazine in the Treatment of Hyperkinesias	280	280
	Total	**750**	**651**

(table 1-1 from the ISS)

[Reviewer' note: Protocol H-721 comprises the Baylor non-chorea review as well as TBZ,011. The patients who entered 103, 005 were former patients on study 103, 011.]

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7.2.1.2 Demographics

Table 31: Demographics

Demographic and Illness Characteristics	Clinical Pharmacology Studies N=140	Study TBZ 103,004 N=84	Study TBZ 103,005 N=30	CSR TBZ 103,011[a] N=145	Baylor Non-Chorea Report N=280
Gender					
Male	78 (56%)	32 (38%)	12 (40%)	58 (40%)	121 (43%)
Female	62 (44%)	52 (62%)	18 (60%)	87 (60%)	159 (57%)
Age (years)					
Mean ± SD	-	49.2 ± 11.7	56.8 ± 10.0	51.3 ± 19.4	49.1 ± 23.2
Median	-	49.5	59.5	55	-
Range	18 – 66	25 – 77	39 – 75	3 - 80	4.3 – 87.6
Race					
White	103 (73%)	79 (94%)	28 (93%)	112 (77%)	-
Black	33	0	0	10	-
Hispanic	19	0	0	12	-
Asian	1	0	0	6	-
Other	2	5	2	4	-
Unspecified	0	0	0	1	-
Disease Duration (years)					
Mean ± SD	NA	8.2 ± 4.6	10.0 ± 5.1	7.9 ± 7.7	7.2 ± 8.3
Range	NA	1.6 – 25.6	0.5 – 22.2	0 - 55	0.03 – 5.32

(modification of table 3-1 in the ISS)

7.2.1.3 Extent of exposure (dose/duration)

The sponsor exposed a total of 606 unique patients and healthy volunteers to tetrabenazine at doses ranging from 12.5 to 300 mg/day over periods ranging from 1 day to 21 years.

Table 32: extent of exposure

Study/Project [Source]	Number of Subjects (n)	Mean Dose (mg) Range (mg/day)	Duration of Exposure	Subject Characteristics
Phase 1 Studies (7 total)	137	28.53 12.5 - 50	1-5 days (Mean: 2 days)	Healthy Volunteers
Tetra HD TBZ 103,004	54	72.4 ± 29.54 (SD) 12.5-100	12 weeks	HD patients
Tetra Withdrawal TBZ 103,005	29	52.92 ± 27.40 (SD) 12.5 - 150	5 days	HD patients previously on chronic TBZ treatment

Table 32 (continued): extent of exposure

Study/Project [Source]	Number of Subjects (n)	Mean Dose (mg) Range (mg/day)	Duration of Exposure	Subject Characteristics
Open-label Extension TBZ 103,007	27	73.19 ± 41.62 (SD) 12.5 - 200	Up to 48 + weeks	HD patients previously on placebo in Tetra HD and not counted above
Baylor Chorea Database TBZ 103,011	145	65.3 ± 35.4 (SD)[2] 12.5-300	5 days - 13 years [3] (Mean: 2.6 ± 2.5 yrs.)	HD and non-HD chorea patients
H-721 1997-2002	234	67.5 12.5-300	1 week-21 years (Mean: 33 mo.)	Hyperkinetic patients (all etiologies)
Total Unique Patients/Subjects	**606**			

[1]Numbers are based on Week 9 and 12 only (maintenance phase of study) [2] Two patients have unknown doses [3] One patient has an unknown duration of treatment n = number of patients; mg/day = milligrams perday; HD = Huntington's Disease; TBZ = Tetrabenazine

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

7.2.2.1.1 Nitoman 003

This open-label compassionate use clinical evaluation of tetrabenazine (Nitoman®) in the management of hyperkinetic movement disorders was conducted by Roche Canada from July 1989 through 1995. The reason for study termination is not known.

The inclusion criteria allowed enrollment of patients with chorea and dyskinesias. The exclusion criteria included the following: use of levodopa containing drugs, reserpine, barbiturates, MAO inhibitors; current or past history of Parkinson's disease, drug-induced parkinsonism, depression or hypotension; lactation.

Patients were to initiate therapy on a dose of 12.5 mg three times daily. The dose was to be increased until either a dose of 200 mg/day (divided doses) was reached or limiting side effects were present.

Of the 541 patients for whom records are available, 66 had Huntington's disease and 475 had other hyperkinetic disorders. There were 45 deaths in the group; 10 of whom had Huntington's chorea.

7.2.2.1.2 Open label prospective study

The sponsor provided safety information from an open label, dose-titration study of tetrabenazine in the treatment of patients with hyperkinetic movement disorders other than chorea [*emphasis added*].

This study (protocol H-721) was performed at the Parkinson's Disease Center and Movement Disorders Clinic at Baylor college of Medicine under individual investigator IND 16,161 (Joseph Jankovic MD, principal investigator). Patients who were found eligible for study were enrolled and instructed to find a dose which was efficacious and tolerable by titrating by 12.5 mg increments every 3-7 days as needed. The maximum suggested dose was 200mg/day given in divided doses. The patients were first evaluated 3-6 months after treatment initiation. Most patients were reassessed at Baylor 2 to 4 times a year subsequently. The patients were responsible for the cost of travel to the facility as well as the cost of their medications.

The provided analyses included 280 patients treated between 01 January 1997 and 31 March 2002. The patients seen had dyskinesiae (32%), tics (24%), dystoniae (38%), or a non-chorea movement disorder (6%).

The mean duration of therapy was 33.4 months (range <1 month to 21 years). Under half (n=128, 47.1%) of the patients discontinued treatment. Of the 128 who discontinued, the most common reasons for discontinuations were adverse events (n=49, 38%), lack of efficacy (n=29, 23%), travel difficulties or financial reasons (n=23, 18%).

7.2.2.2 Postmarketing experience

7.2.2.2.1 Roche summary

This Roche internal report summarizes the efficacy and safety of tetrabenazine in 1200 patients with schizophrenia at doses up to 600 mg/day.

7.2.2.2.2 Published reports of efficacy and safety of tetrabenazine in chorea and involuntary movement disorders

These publications report on findings from over 2000 patients.

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7.2.2.2.3 Post-marketing pharmacovigilence reports from Roche Pharmaceutical and Cambridge laboratories from 1963 to 2004

The first of these reports encompassed the period between 1974 through November 1994. At that time ——— defined daily doses were sold. Twelve deaths were reported and 221 spontaneous reports of adverse events were recorded (see table below).

Table 33: Roche Pharmacovigilance report 1974-1994

System Organ Class (SOC)	No	%
Central and Peripheral Nervous System Disorders	63	28.5
Psychiatric Disorders	29	13.1
Body as a Whole – General Disorders	29	13.1
Gastro-Intestinal System Disorders	25	11.3
Respiratory System Disorders	15	6.8
Cardiovascular Disorders, General	9	4.1
Musculo-Skeletal System Disorders	6	2.7
Heart Rate and Rhythm Disorders	5	2.3
Skin and Appendages Disorders	5	2.3
Urinary System Disorders	5	2.3
Myo-, Endo-, Pericardial and Valve Disorders	5	2.3
White Cell and RES Disorders	4	1.8
Metabolic and Nutritional Disorders	4	1.8
Platelet, Bleeding and Clotting Disorders	4	1.8
Vascular (Extracardiac) Disorders	3	1.4
Liver and Biliary System Disorders	2	0.9
Vision Disorders	2	0.9
Autonomic Nervous System Disorders	2	0.9
Neoplasm	2	0.9
Foetal Disorders	1	0.5
Special Senses Other, Disorders	1	0.5
Total	221	100.0

(Table 2.7.4-33 Roche Pharmacovigilance report 1974-1994)

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The second of these reports encompassed the period between December 1994 through November 1998. At that time ——→ defined daily doses were sold. Seven deaths were reported during this time period. Seventy-five spontaneous reports of adverse events were recorded, most of which were coded as Central Nervous System symptoms (see table below).

Table 34: Roche Pharmacovigilance report 1994-1984

System Organ Class	N Pts with at least 1 AE/SOC	N Pts Who Died	N Serious Adverse Events	Serious Adverse Events %	N Total Adverse Events	Total Adverse Events %
Skin and Appendage Disorders	5	0	1	2.0%	5	6.7%
Musculo-Skeletal System Disorders	3	0	2	4.0%	3	4.0%
Central and Peripheral Nervous System Disorders	15	2	13	26.0%	19	25.3%
Psychiatric Disorders	5	0	8	16.0%	11	14.7%
Gastro-Intestinal System Disorders	4	0	2	4.0%	5	6.7%
Liver and Biliary System Disorders	2	0	2	4.0%	2	2.7%
Endocrine Disorders	2	0	1	2.0%	2	2.7%
Cardiovascular Disorders, General	1	0	2	4.0%	2	2.7%
Myo-, Endo-, Pericardial and Valve Disorders	1	1	1	2.0%	1	1.3%
Heart Rate and Rhythm Disorders	1	0	1	2.0%	1	1.3%
Vascular (Extracardiac) Disorders	1	0	1	2.0%	1	1.3%
Respiratory System Disorders	6	1	6	12.0%	6	8.0%
White Cell and RES Disorders	1	0	0	0.0%	1	1.3%
Platelet, Bleeding, & Clotting Disorders	1	0	0	0.0%	1	1.3%
Urinary System Disorders	2	0	1	2.0%	3	4.0%
Body as a Whole – General Disorders	9	2	7	14.0%	10	13.3%
Resistance Mechanism Disorders	2	1	2	4.0%	2	2.7%
Total	5	7	50	100.0%	75	100.0%

(Table 2.7.4-34 Roche Pharmacovigilance report 1994-1984)

7.2.2.3 Literature

No studies from the literature, other than those provided by the sponsor, were used in the evaluation of safety for this NDA.

Multiple scientific literature references were provided (section 5.4.2). While not an exhaustive review of the literature, the provided articles addressed behavioral changes in Huntingdon disease including depression and psychosis, racial variation in Huntingdon disease, and symptoms associated with disease progression.

A Medline search using the key words (jankovic and tetrabenazine) performed on December 19, 2005 revealed 21 articles reported varying degrees of success with use of tetrabenazine in treatment of hyperkinetic movement disorders.

7.2.3 Adequacy of Overall Clinical Experience

This application reported tetrabenazine exposures to 606 unique persons in the ISS. Post marketing data from other countries was available as well as the results from other open label studies using tetrabenazine.

The majority of the studies were open-label: only 84 patients received tetrabenazine as part of a placebo-controlled study; that represents 14% of the unique exposures. The absence of a long-term placebo group makes it difficult to determine what the potential drug effect is in most cases. The exclusion criteria, though not consistent across studies, would not limit the relevance of the safety assessments for patients with Huntington's disease. The doses and durations studied were adequate to assess safety for the intended use. The gender ratio was appropriate.

While achieving greater ethnic diversity is a problem endemic to clinical trials and not specific to this development program, it is striking that the controlled studies and uncontrolled studies did such a poor job of enrolling minority patients. Since tertiary referral centers were used in an effort to augment the numbers of the safety database, one would have expected that there would be some minority patients enrolled and studied. Even if one is convinced that Huntington's chorea is rare in minorities, which I am not, and has a presentation with less marked chorea in those affected minorities, it is still notable that even the non-chorea population has a paucity of blacks and Asians. The sponsor-provided references (Folstein SE et al. 1987; Marshall FJ, Shoulson I, 1997; Fahn 2000) did not support the notion that Huntingdon disease would be less commonly seen in Blacks, though they did support the notion that the disease is uncommon in persons of Japanese and Finnish ancestry. The article by Folstein et al. did note that Blacks had, in a Maryland survey, an earlier age of onset, more severe bradykinesia and eye movement abnormalities with less frequent report of depression. The latter article does note that in their analysis Blacks were twice as likely to be misdiagnosed and therefore go unreported; they projected a prevalence of 3.34/100,000 in Blacks.

The sponsor did, at our prompting, do a through search for adverse effects of special interest in this population, e.g. depression, suicidality. The results of this search have been described earlier in this review.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The pre-clinical testing was adequate to explore general toxicity as well as reproductive toxicity. During the preclinical studies, female rats were noted to have "vaginal mucification, increased incidence of proestrus and mammary gland hyperplasia" which was thought to be secondary to increased serum prolactin concentrations. Since prolactin levels were not measured in that study, it was not possible to make a more definitive comment regarding possible causality. The sponsor performed a subsequent PK study in rats which included measurement of prolactin: [redacted] study 7425-114. The interested reader is referred to the review by the pharmacotoxicologist, Dr. Andrea Powell for additional information on that study.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing done was adequate and appropriate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Prestwick did not perform formal assessments of drug-drug interactions in support of this application.

It is noted that tetrabenazine and 2 of its metabolites are CYP2D6 substrates and so potential effects on their metabolism may be seen when tetrabenazine is used in conjunction with CYP2D6 inhibitors.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor performed studies to assess the effect of tetrabenazine on prolactin and other hormones in humans: TBZ 202,001 and 203,008. No female volunteers were enrolled in these studies. The administration of tetrabenazine resulted in increased prolactin levels in healthy male volunteers. The sponsor should have made a concentrated effort to assess the effect of tetrabenazine in females, especially in light of the sponsor-provided reference which noted evidence of hyperprolactinemia in female schizophrenics who were given tetrabenazine, albeit at higher doses and the preclinical data.

7.2.8 Assessment of Quality and Completeness of Data

7.2.8.1 Primary source data

Initially, each of the individual study reports which utilized prospectively collected data appeared to be complete. However, we were notified on March 2, 2006 that a DSI investigation revealed that Dr. Jankovic did not report increased dysphagia in a number of patients on study 103, 011 due to his belief that the dysphagia was related to the underlying disease. We may fairly assume that the incidence of dysphagia in the patients from Baylor has been underreported in the database. It is not known which other adverse events experienced were not incorporated into the database due to the PI's determination that these were disease related and not drug-related. The studies from Baylor comprise Study 103, 005 (the staggered withdrawal study which enrolled patients who were followed at Baylor), Study TBZ103, 011 (the study describing the Baylor patients with chorea) and Study H-721 (the study which followed patients with hyperkinetic disorders other than chorea).

The data from TBZ 103, 004 appears to be complete. Dr. Jankovic did not enroll any patients on that study.

7.2.8.2 Secondary source data

7.2.8.2.1 Nitoman protocol 003: Clinical evaluation of tetrabenazine (Nitoman®) in the management of hyperkinetic movement disorders

This open-label compassionate use protocol was conducted by Roche Canada from July 1989 through 1995. Prestwick (the current sponsor) was provided with paperwork and case report forms (CRFs) for 541 of the 757 patients who participated in the trial. Electronic files, datasets,

patient listings are not available for this trial. The whereabouts of the data on the 216 remaining patients is not known. There is no final study report for this protocol.

The sponsor notes the following deficiencies in the provided data (study report page 8 of 39):

- Missing data for 216 study participants
- Inclusion of patients with primary movement disorders that were not the target of the Nitoman Protocol 003 (e.g. dystonias or tics)
- Incomplete data for a substantial number of the study participants, e.g. :
    - Missing CRFs for entire study visits
    - Investigator failure to complete efficacy assessments at follow-up visits
    - Missing tetrabenazine dosage logs (the mechanism for study drug exposure tracking)
    - Missing AE case report forms
    - Missing laboratory data and/or data obtained in a time frame not permitted by the protocol
    - Incomplete data regarding the circumstances, cause and outcome of patient deaths during the study
- Missing, conflicting or ambiguous CRF data entries which may contribute to misclassification errors
- An inconsistent adverse event (AE) numbering system that impedes the ability to definitively match study participants who had SAEs (including deaths) with entries in the Roche Pharmacovigilance Reports.

7.2.8.2.2 H-721: A review of safety results of an open-label, dose titration study of tetrabenazine in the treatment of patients with hyperkinetic movement disorders other than chorea

This data was collected retrospectively from the records of a compassionate use protocol administered by an individual investigator, Dr. Joseph Jankovic at the Parkinson Disease Center and Movement Disorders Clinic at Baylor College of Medicine (IND 16,161). Two people, a study coordinator and a research fellow were responsible for review of the patient records and abstraction of the data onto the CRFs which were later entered into a database.

The analysis for this submission was limited to those patients without chorea who were treated with tetrabenazine between 01 January 1997 and 31 March 2002, inclusive. The available records included data from patients who initiated tetrabenazine prior to January 1997 and those who began therapy as late as March 2002.

Some patient information was missing from the records e.g. initial or final vital sign records, weights and/or medication dosages. No case report forms for deaths, other serious adverse events or withdrawals for adverse events were provided.

7.2.8.2.3 Roche summary

This Roche internal report summarizes the efficacy and safety of tetrabenazine in 1200 patients with schizophrenia at doses up to 600 mg/day.

7.2.8.2.4 Published reports of efficacy and safety of tetrabenazine in chorea and involuntary movement disorders

These publications report on findings from over 2000 patients.

7.2.8.2.5 Post-marketing pharmacovigilence reports from Roche Pharmaceutical and Cambridge laboratories from 1963 to 2004

The findings from these reports have been discussed above in Section 7.2.2.2.

7.2.9 Additional Submissions, Including Safety Update

The sponsor submitted an executive summary of the available QTc data, which was reviewed by Dr. Sally Yasuda of Biopharmaceutics. No other additional clinical data had been received as of the completion date of this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Tetrabenazine may be considered capable of producing the following adverse effects:

- Somnolence
- Parkinsonism
- Insomnia
- Hyperprolactinemia
- Depression
- Dysphagia

Tetrabenazine may be associated with the following adverse effects, though causality is less certain:

- Suicide/suicidal ideation
- Pneumonia
- Dystonia

There are other adverse events which have been reported in association with routine use but the causality is less clear in those cases.

In the setting of drug overdose, neuroleptic malignant syndrome (NMS) has been described.

The major limitation of the data provided is that we are given 84 patients with Huntington's disease and associated chorea who were exposed to tetrabenazine in placebo-controlled trials. This is a small number upon which to base major conclusions. Many of the assessment related to potential adverse events are based upon the entire database which included patients who were on placebo-controlled trials, patients who received open label therapy and were followed prospectively as well as retrospective data from patients who were participants in a long-term open label compassionate use trial.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The data for these studies was not pooled as the populations studied were not similar.

7.4.1.2 Combining data

The data for these studies was not combined as the populations studied were not similar.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Prior to study initiation, the sponsor had determined from a review of the literature that the common adverse events related to monoamine depletion were thought to be dose-related and could be remedied by judicious dose relation. The specific adverse events which were thought to fall into this category were sedation, depression, parkinsonism, akathisia, anxiety, nervousness, insomnia, irritability, confusion, increased salivation, nausea, vomiting, dizziness and diaphoresis.

Having reviewed two studies which suggested that the risk of dysphagia was increased with doses greater than 100 mg/day, the sponsor used 100 mg as the maximal dose in placebo-controlled study TBZ103, 004.

In all studies, patients were titrated to a dose which produced adverse events then reduced to a lower maintenance dose. In Study TBZ 103,044 the dose was capped at a maximum of 100 mg/day; the most common AEs leading to discontinuation of upward dose titration and/or to reduction in daily dose during this study were sedation (28% of active group, 0 in placebo group), akathisia (9% of active group, 0 in placebo group), parkinsonism (6% of active group, 0 in placebo group), depression (3% of active group, 0 in placebo group). In almost all cases, the adverse event resolved once the dose was reduced: sedation (93% of cases), akathisia (80%), parkinsonism (66%), depression (66%).

7.4.2.2 Explorations for time dependency for adverse findings

Upon the advice of a steering committee, the sponsor chose to perform up-titration of tetrabenazine every 4 days as opposed to the every 2-3 days which had been used in much of the literature. It was felt that since parkinsonism might take up to 4 days to become apparent, a more rapid titration schedule might risk "overshooting" the individual best dose for a given patient.

The sponsor provided summary data for the patients who participated in either Study TBZ 103, 004 and extension study TBZ103, 007 or Study TBZ 103, 005 and extension study TBZ103, 006, specifically reviewing the incidence of depression, insomnia and parkinsonism.

The sponsor also looked at the 54 patients who participated in the 12 week double blind study and the subsequent extension to determine whether their AE complaints persisted in to the maintenance phase. The majority of the adverse events experienced in this tetrabenazine naïve cohort occurred during the upward titration phase, as may be seen in the table below.

Table 35: Adverse event during TBZ 103, 004 divided by time of occurrence

AE Preferred Term	Titration Period Weeks 0-9 Total n (%)	Maintenance Period Weeks 9-12 Total n (%)
Psychiatric Disorders		
Insomnia	7 (13%)	5 (9%)
Depression	7 (13%)	1 (2%)
Sedation/somnolence/drowsiness/sleepiness	17 (31%)	-
Restlessness Aggravated	6 (11%)	1 (2%)
Irritability	4 (7%)	1 (2%)
Anxiety	3(6%)	5 (9%)
Obsessive Reaction	2 (4%)	-
Central & Peripheral Nervous System		
Akathisia	5 (9%)	-
Balance Difficulty	4 (7%)	1 (2%)
Bradykinesia	3 (6%)	-
Dizziness	2 (4%)	-
Dysarthria	2 (4%)	-
Gait Unsteady	2 (4%)	-
Headache	2 (4%)	-
Gastrointestinal Disorders		
Nausea	7 (13%)	-
Diarrhea	3 (6%)	-
Vomiting	2 (4%)	1 (2%)
Body/Whole		
Fatigue	11 (20%)	1 (2%)
Secondary Terms		
Fall	7 (13%)	3 (6%)
Inflicted Injury	2 (4%)	1 (2%)
Respiratory System Disorders		
Upper Respiratory Tract Infection	3 (6%)	4 (7%)
Coughing	2 (4%)	1 (2%)
Platelet, Bleeding, Clotting		
Bruise/ecchymosis	7(13%)	-

(Modification of ISS table 5-8)

7.4.2.3 Explorations for drug-demographic interactions

The majority of the participants in these trials were Caucasian; the small sample size for the other ethnicities makes it difficult to perform explorations for drug-demographic interactions.

There is no consistent evidence that age and/or gender have an effect on the safety or efficacy of this product.

7.4.2.4 Explorations for drug-disease interactions

Prestwick performed a hepatic impairment study. In an interim PK report, the sponsor noted that the first pass metabolism of tetrabenazine was reduced in patients with hepatic impairment leading to an increased exposure in these patients as compared to controls.

7.4.2.5 Explorations for drug-drug interactions

Prestwick did not perform formal assessments of drug-drug interactions in support of this application.

7.4.3 Causality Determination

Tetrabenazine may be considered capable of producing the following adverse effects:

- Somnolence
- Parkinsonism
- Insomnia
- Hyperprolactinemia
- Depression
- Dysphagia

Tetrabenazine may be associated with the following adverse effects, though causality is less certain:

- Suicide/suicidal ideation
- Pneumonia
- Dystonia

There are other adverse events which have been reported in association with routine use but the causality is less clear in those cases.

In the setting of drug overdose, neuroleptic malignant syndrome (NMS) has been described.

8 ADDITIONAL CLINICAL ISSUES

This information may be found in the efficacy review done by Dr. Carole Davis, DNP.

9 OVERALL SAFETY ASSESSMENT

The major limitation of the data provided is that it describes 84 patients with Huntington's disease-associated chorea who were exposed to tetrabenazine in a placebo-controlled trial; 54 of whom received study drug. This is a small number upon which to base major conclusions. Many of the assessments related to potential adverse events are based upon the entire database which included patients who were on placebo-controlled trials, prospective data from patients who received open label therapy as well as retrospective data from patients who were participants in a long-term open label compassionate use trial: a total database of 651 patients. Exposure data ranged from up to 12 weeks (n=651) to over 10 years (n=20) at doses which varied from 12.5 mg to 300 mg per day.

Tetrabenazine may be considered capable of producing the following adverse effects:

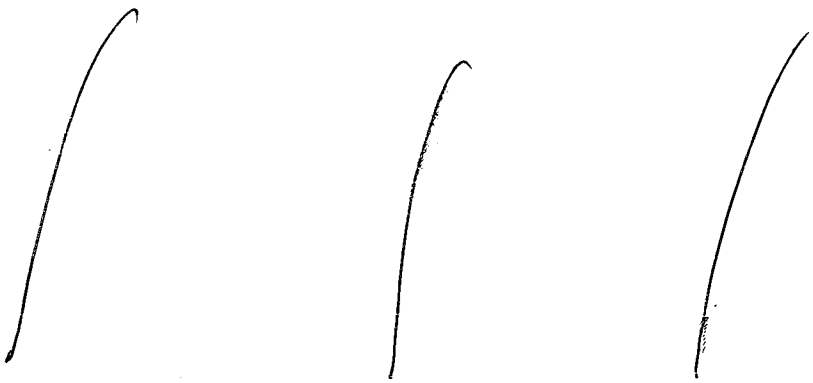
- Somnolence
- Parkinsonism
- Insomnia
- Depression
- Dysphagia
- Hyperprolactinemia

While causality is less certain, Tetrabenazine may be associated with the following adverse effects:

- Suicide/suicidal ideation
- Pneumonia
- Dystonia

There does not appear to be a risk of intentional misuse of tetrabenazine for recreational purposes, based upon the clinical trial data. In the setting of drug overdose, neuroleptic malignant syndrome (NMS) has been described.

The safety profile of this product is acceptable in light of the intended indication, the treatment of chorea in patients with Huntington's disease.



10 APPENDICES

10.1 Review of Individual Study Reports

These reviews may be found in the efficacy review done by Dr. Carole Davis, DNP.

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10.2 Deaths during open-label Canadian study Nitoman 003

[*Reviewer's note: When available, the cause of death is noted in bold font.*]

10.2.1.1.1 Subject-screening failure, no number assigned

A 13 year old male was screened and found to be already receiving tetrabenazine for Tourette's. He had known exposure from October 1993 to December 1993. He was noted to have died though the date and cause of his demise were not provided. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.2 Subject without ID number, [redacted]

This 77-year-old man with tardive dyskinesia entered the study on January 17, 1992. A treatment summary sheet dated [redacted] states that the patient died of a **pulmonary embolus.** The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.3 Subject 004, [redacted]

A 43 year old male was treated with tetrabenazine for Huntington's chorea. His initial study visit was in May 1989. His dose ranged from 87.5 mg to 112.5 mg. He sustained a skull fracture as a result of a fall in [redacted]. He had a seizure in [redacted] with subsequent clinical deterioration to coma. While his death was noted on a care record form, no date or cause of death are given. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.4 Subject 005, [redacted]

A 49 year old female was treated with tetrabenazine for Huntington's chorea. Her initial study visit was in August 1989. Her highest recorded dose was 150 mg. A letter from March 1994 notes her death though the date and cause of her death are not specified. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.5 Subject 009, [redacted]

A 78 year old female, who was being treated with tetrabenazine for tardive dyskinesia, entered the study in March 1984. She died of **pneumonia** on an unspecified date. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.6 Subject 012 [redacted]

A 74 year old female was being treated with tetrabenazine for idiopathic chorea. She began treatment in March 1984. On a dose of 25 mg/day, she was noted to have somnolence, impaired rapid alternating movements, micrographia and difficulty walking. Mouth cancer was diagnosed in [redacted]. She died from **pneumonia** in [redacted] The paucity of available information makes it impossible to completely rule out an association with study drug.
[*Reviewer's note: This patient had evidence of sedation, gait difficulties and possible parkinsonism.*]

10.2.1.1.7 Subject 021, —

A 73 year old female, who was being treated with tetrabenazine for orolingual dystonia, entered the study in June 1989. She apparently died in ——— from an **acute myocardial infarction**. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.8 Subject 053, —

A 79 year old woman was treated with tetrabenazine for tardive dyskinesia. She began treatment in November 1983. She died in ——— No further information is available. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.9 Subject 070, —

A 72 year old woman, who was being treated with tetrabenazine for dyskinesia, had a history of tetrabenazine-related parkinsonism. She entered the study in October 1989. A treatment summary sheet dated April 1992 reported her death but did not specify date or cause. Her last documented study visit was in November 1991. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.10 Subject 105, —

A 71 year old female, with past medical history notable for advanced coronary artery disease, was treated with tetrabenazine for chorea and dyskinesia. She began treatment in April 1988. Her daily dose ranged from 75 to 150 mg/day. She died in her sleep in ——— The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.11 Subject 108 —

A 40 year old male was treated with tetrabenazine for Huntington's chorea. He died from **pneumonia** in ——— having begun the study in December 1988. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.12 Subject 111 —

A 65 year old woman was treated with tetrabenazine for idiopathic dystonia and tardive dyskinesia. She began treatment in December 1988. In ——— , she developed neuroleptic malignant syndrome which was thought to be tetrabenazine related. In October 1989, after resuming tetrabenazine therapy, she complained of insomnia and other disturbances to her sleeping pattern as well as a confused delusional state. She died in ——— from a presumed **myocardial infarction**. The available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.13 Subject 114 —

A 76 year old female enrolled in the study in June 1989 for treatment of tardive dyskinesia. One month later, she was noted to have drug-induced parkinsonism which was partially ameliorated by dose reduction. In March 1990, she continued to have evidence of parkinsonism, weight loss and decreased appetite. Her dose was again reduced. She died of a presumed **pneumonia** in ——— At the time of her death her dose was 37.5 mg/day. While definite causality cannot

be determined, the use of study drug may have contributed to this patient's demise if the pneumonia in question were due to aspiration.

10.2.1.1.14 Subject 138, —

A 78 year old woman was treated for dyskinesia. She had already been receiving tetrabenazine when she entered the study in March 1990. She died in ——— with the following diagnoses noted of **pneumonia, tardive dyskinesia, chronic depression**. While definite causality cannot be determined, the use of study drug may have contributed to this patient's demise if the pneumonia in question were due to aspiration.

10.2.1.1.15 Subject 146, —

An 88 year old woman was treated for dyskinesia. She entered the study in March 1990. She died in —— of **bronchopneumonia, organic brain syndrome and adult-onset diabetes**. While definite causality cannot be determined, the use of study drug may have contributed to this patient's demise if the pneumonia in question were due to aspiration.

10.2.1.1.16 Subject 149, —

An 80-year old man, who was already receiving tetrabenazine for dyskinesia, enrolled in the study in June 1990. He died during a hospital evaluation for anorexia, malaise and anemia. During that hospitalization, he was found to have two pre-pyloric ulcers. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.17 Subject 152, —

An 80 year old male was treated with tetrabenazine for tardive dyskinesia. He began treatment in August 1990. He was withdrawn from the study in September 1991. He died in ——— rom complications of **diabetes and peripheral vascular disease**. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.18 Subject 157, —

A 77 year old diabetic woman was treated with tetrabenazine for hemiballismus. She began treatment in September 1989. Whilst being treated she developed parkinsonism, dry mouth, fatigue and drooling; all of which were thought to be related to tetrabenazine use. She died of unspecified causes at sometime prior to —— .. While definite causality cannot be determined, the use of study drug may have contributed to this patient's demise.

10.2.1.1.19 Subject 161, —

A 40 year old female was treated with tetrabenazine for Huntington's chorea. The investigator noted that the patient had what appeared to be worsening lymphopenia whilst on treatment. She started treatment in November 1989 and continued on tetrabenazine "with little clinical improvement" at a dose of 200 mg until her death of **aspiration pneumonia** in ———
While definite causality cannot be determined, the use of study drug may have contributed to this patient's demise since the pneumonia in question was due to aspiration.

10.2.1.1.20 Subject 171, —

A 97 year old woman was treated with tetrabenazine for dyskinesias. She began treatment in July 1988. She ran out of pills on 11/27/1989 and her tardive dyskinesia returned. She died on ——— No cause of death was given. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.21 Subject 235, —

A 48 year old female was treated with tetrabenazine for Huntington's chorea. She began treatment in April 1990. Her dose ranged from 75 mg to 225 mg. In July 1990, she was noted to have what was described as a good response to tetrabenazine. She died in ——— from **dehydration** due to an inability to consume food or drink. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.22 Subject 248, —

A 72 year old female was treated with tetrabenazine for Huntington's chorea. She began treatment in August 1989. Her dose ranged from 25 mg to 150 mg. In a note dated ——— the investigator reports that the patient died from a **ruptured berry aneurysm.** The narrative provided states the last study visit was in May 1995. The inconsistency in the chronology notwithstanding, the paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.23 Subject 254, —

A 58 year old female was treated with tetrabenazine for Huntington's chorea. She began treatment in September 1989. Her dose ranged from 50 mg to 75 mg. According to a treatment summary dated ; she died from probable **pneumonia.** The date of her death was not given. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.24 Subject 256, —

A 75-year-old female with dyskinesias was being treated with tetrabenazine at the time of study entry. She was exposed, on study, to tetrabenazine from June 26, 1990 through at least January 24 1995. She died of unspecified causes on ——— The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.25 Subject 279, —

No initial CRF was found. The only information known is that this patient died in ——— while a resident at a nursing home. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.26 Subject 316, —

A 58 year old female was treated with tetrabenazine for Huntington's chorea. She began treatment in November 1991. Her past medical history was also significant for Alzheimer's type dementia. Her tetrabenazine dose is not known. In ——— , she died from **aspiration pneumonia** after choking on food. While definite causality cannot be determined, the use of

study drug may have contributed to this patient's demise since the pneumonia in question was due to aspiration.

10.2.1.1.27 Subject 318, —

An 80 year old woman was treated for dyskinesia. She entered the study in December 1991. She died in —— from a **cardiopulmonary arrest** secondary to a cerebrovascular accident. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.28 Subject 322, —

A 78 year old female was treated with tetrabenazine for dyskinesias. She began therapy in June 1990. She died of **complications from "end-stage dementia"** in —— The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.29 Subject 340, —

A 74 year old man was treated for possible dystonia. At his last study visit in October 1995, he was noted to have parkinsonism at a dose of 12.5mg QID. He had several hospitalizations for pneumonia and recurrent pleural effusions. He died in —— 5 of presumed **staphylococcus sepsis and aspiration pneumonia**. While definite causality cannot be determined, the use of study drug may have contributed to this patient's demise.

10.2.1.1.30 Subject 347, —

A 64 year old woman was treated with tetrabenazine for chorea. She had a syncopal episode in —— She died in —— from "**choking.**" According to the investigator, she had a history of choking episodes which predated her use of tetrabenazine. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.31 Subject 363, —

Since no initial visit CRFs were provided, there is no information regarding demographics or diagnosis available. The patient received tetrabenazine from November 1990 through July 1991. Death occurred in —— The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.32 Subject 419

An 84-year-old woman was treated for dyskinesia. She entered the study in February 1992. She was on a steady dose of 75 mg beginning on February 19, 1992. She died of unspecified causes on —— The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.33 Subject 428, —

A 67 year old female was treated with tetrabenazine for tardive dystonia and mild chorea. She began treatment in March 1992. While in May 1992 she was noted to have fatigue and mild confusion. These AE resolved following a reduction in the tetrabenazine dose. Her dose ranged from 25 to 100 mg/day. She died of a **myocardial infarction**. The date of this occurrence is not

available, though the summary sheet is dated ——— The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.34 Subject 469, ———

An 84 year old woman was treated with tetrabenazine for dyskinesias and choreoathetoid movements. She was already taking tetrabenazine at the time of study entry in July 1992. Her dose ranged from 75 to 150 mg/day. She developed depression in January 1994. She had a **cerebrovascular accident** in ——— her second, and died. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.35 Subject 476, ———

A 86 year old woman with Alzheimer's disease was treated with tetrabenazine 50 mg/day for dyskinesia. She entered the study in December 1992. She died of **aspiration pneumonia** in ——— . The use of study drug may have contributed to this patient's death although causality is not definite.

10.2.1.1.36 Subject 477, ———

A 70 year old man was treated with tetrabenazine for chorea related to cerebrovascular disease. He began treatment in October 1992. He died in ——— due to **complications of cardiac and cerebrovascular disease**. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.37 Subject 565, ———

An 82-year-old female was being treated for tardive dyskinesia. Her initial dose of tetrabenazine was 25 mg/day beginning on September 15 1993. This was raised to 37.5 mg on September 20 1993. She was noted to have increasing somnolence between September 23 and 25. She **aspirated** on ———; tetrabenazine was stopped. Her level of consciousness continued to decline and she died on ——— . The use of study drug may have contributed to this patient's death although causality is not definite.

10.2.1.1.38 Subject 581, ———

A 78 year old male was treated with tetrabenazine for chorea. He began treatment in October 1993. His daily dose of medication ranged from 37.5 to 50 mg. He had a **cardiac arrest** at home In ——— No further information is available. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.39 Subject 589, ———

A 64 year old man was treated for tardive dyskinesia. He was exposed to tetrabenazine from October 22, 1993 through his last study visit on August 19, 1994. A treatment summary dated ——— states that the patient died from a large **stroke** on an unspecified date.

10.2.1.1.40 Subject 598, ———

Since no initial visit CRFs were provided, there is no information regarding demographics or diagnosis available. The patient died of **metastatic prostatic cancer** in ——— . The

paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.41 Subject 610, ——

A 66-year–old woman with dyskinesia and blepharospasm was exposed to tetrabenazine from August 1 1994 through September 30 1994. A treatment summary sheet dated ——— states that the patient died of cancer. The type of cancer and the date of death were not specified. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.42 Subject 716, ——

An 82 year old woman began treatment with tetrabenazine for dyskinesias. She began treatment in August 1994. She had parkinsonism noted in September 1994 which was managed by dose adjustment. A treatment summary from ——— reported that she had died from **aspiration pneumonia**. No further information is available. While definite causality cannot be determined, the use of study drug may have contributed to this patient's demise.

10.2.1.1.43 Subject 783, ——

A 73 year old female with Alzheimer's type dementia was treated with tetrabenazine for Huntington's chorea. She began treatment in March 1995. Her tetrabenazine dose ranged from 37.5 mg to 150 mg/day. Her lactate dehydrogenase was noted to rise from 437 U/L to 918 U/L. She had two AE during the study: foaming at the mouth in March 1995; epidermolytic lesions of the right hand in March 1995. In ——— she was admitted with pulmonary congestion and treated with antibiotic therapy. She continued to deteriorate and died in ——— The paucity of available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.44 Subject 815, ——

A 38 year old male began treatment with tetrabenazine for Huntington's chorea in June 1995. His tetrabenazine dose ranged from 37.5 mg to 150 mg/day. He complained of an AE in June 1995: vomiting. In April 1996, he was reported to have dehydration with possible aspiration. He began having violent outbursts and refusing to eat or drink. He died on ——— from dehydration after intravenous and tube feedings were withheld at his mother's request. The available information makes it impossible to completely rule out an association with study drug.

10.2.1.1.45 Subject 882, ——

A 51 year old female was treated with tetrabenazine for a combination of dystonia, dyskinesias, and chorea involving the head and neck. Her doses ranged from 75 mg to 200 mg. She died in ——— No further information is given. The paucity of available information makes it impossible to completely rule out an association with study drug.

10.3 Frequent Adverse Events reported in patients treated with tetrabenazine across all studies (Table 5-30 from ISS)

		Study								
		TBZ 103,004		TBZ 103,005	TBZ 103,006	TBZ 103,007	TBZ 103,011		Baylor Non-Chorea Report N=280 N (%)	Post-Marketing Surveillance Reports N
Body System	Preferred Term for WHO, COSTART, or Baylor Dictonaries	TBZ N=54 N (%)	Placebo N=30 N (%)	N=30 N (%)	N=29 N (%)	N=75 N (%)	HD N=98 N (%)	Non-HD N=47 N (%)		
PSYCHIATRIC DISORDERS	Insomnia	12 (22%)	0 (0%)	2 (7%)a	3 (10%)	18 (24%)	32 (33%)	9 (19%)	15 (5%)	1
	Depression	8 (15%)	0 (0%)	0 (0%)	7 (24%)	19 (25%)	34 (35%)	10 (21%)	26 (9%)	6
	Sedation	8 (15%)	0 (0%)	0 (0%)	3 (10%)	28 (37%)	0 (0%)	0 (0%)	0 (0%)	5
	Restlessness Aggravated	7 (13%)	0 (0%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
	Drowsiness/ Sleepiness	5 (9%)	1(3%)	0 (0%)	0 (0%)	13 (17%)	0 (0%)	0 (0%)	74 (26%)	9
	Irritability	5 (9%)	1(3%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1
	Anxiety	4 (7%)	1(3%)	1 (3%)	5 (17%)	15 (20%)	11 (11%)	4 (9%)	18 (6%)	0
	Anxiety Aggravated	4 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
	Somnolence	4 (7%)	0 (0%)	0 (0%)	2 (7%)	3 (4%)	38 (39%)	27 (57%)	0 (0%)	5
	Appetite Decreased	2 (4%)	0 (0%)	2 (7%)	2 (7%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0
	Obsessive Reaction	2 (4%)	0 (0%)	1 (3%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0
	Agitation	1 (2%)	0 (0%)	0 (0%)	1 (3%)	4 (5%)	8 (8%)	1 (2%)	0 (0%)	1
	Emotional Lability	1 (2%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
	Lethargy	1 (2%)	0 (0%)	0 (0%)	0 (0%)	4 (5%)	0 (0%)	0 (0%)	0 (0%)	0
	Hallucinations	0 (0%)	0 (0%)	1 (3%)	1 (3%)	0 (0%)	3 (3%)	1 (2%)	0 (0%)	2
	Nervousness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (11%)	5 (11%)	0 (0%)	0
CENTRAL & PERIPHERAL NERVOUS SYSTEM	Akathisia	5 (9%)	0 (0%)	0 (0%)	0 (0%)	13 (17%)	11 (11%)	5 (11%)	21 (8%)	1
	Balance Difficulty	5 (9%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	4 (1%)	0
	Bradykinesia	3 (6%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	2
	Parkinsonism	3 (6%)[b]	0 (0%)	0 (0%)	3 (10%)	2 (3%)	11 (11%)	9 (19%)	54 (19%)	12
	Abnormal gait	2 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)	0 (0%)	3 (6%)	0 (0%)	1
	Dizziness	2 (4%)	0 (0%)	0 (0%)	1 (3%)	5 (7%)	8 (8%)	2 (4%)	9 (3%)	2
	Dysarthria	2 (4%)	0 (0%)	0 (0%)	0 (0%)	3 (4%)	8 (8%)	0 (0%)	4 (1%)	0
	Chorea	1 (2%)	0 (0%)	0 (0%)	0 (0%)	5 (7%)	0 (0%)	0 (0%)	0 (0%)	0
	Dystonia	1 (2%)	1 (3%)	0 (0%)	0 (0%)	6 (8%)	0 (0%)	0 (0%)	0 (0%)	3

Body System	Preferred Term for WHO, COSTART, or Baylor Dictonaries	Study								
		TBZ 103,004		TBZ 103,005	TBZ 103,006	TBZ 103,007	TBZ 103,011		Baylor Non-Chorea Report N=280 N (%)	Post-Marketing Surveillance Reports N
		TBZ N=54 N (%)	Placebo N=30 N (%)	N=30 N (%)	N=29 N (%)	N=75 N (%)	HD N=98 N (%)	Non-HD N=47 N (%)		
CENTRAL & PERIPHERAL NERVOUS SYSTEM (continued)	Speech Disorder	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (5%)	3 (6%)	0 (0%)	2
	Amnesia/Memory Impairment/loss	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	5 (5%)	3 (6%)	8 (3%)	2
	Ataxia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (7%)	2 (4%)	0 (0%)	2
	Movement Disorder	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	0 (0%)	0
	Thinking Disorder	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	0 (0%)	0
GASTRO-INTESTINAL SYSTEM	Nausea	7 (13%)	2 (7%)	0 (0%)	2 (7%)	3 (4%)	10 (1%)	3 (6%)	21 (8%)	1
	Diarrhea	3 (6%)	3 (10%)	1 (3%)	1 (3%)	6 (8%)	12 (12%)	1 (2%)	0 (0%)	3
	Vomiting	3 (6%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	4 (4%)	2 (4%)	0 (0%)	2
	Constipation	1 (2%)	0 (0%)	0 (0%)	1 (3%)	2 (3%)	9 (9%)	2 (4%)	0 (0%)	0
	Dysphagia/Swallowing Difficulty	1 (2%)	1 (3%)	2 (7%)	2 (7%)	3 (4%)	19 (19%)	3 (6%)	0 (0%)	6
	Dry Mouth	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	5 (11%)	0 (0%)	0
	Saliva Increased	1 (2%)	0 (0%)	0 (0%)	2 (7%)	1 (1%)	12 (12%)	7 (15%)	8 (3%)	8
	Fecal Incontinence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (6%)	1 (2%)	0 (0%)	2
	GI Disorder	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (4%)	3 (6%)	0 (0%)	0
BODY AS A WHOLE-GENERAL	Fatigue	12 (22%)	4 (13%)	0 (0%)	0 (0%)	12 (16%)	0 (0%)	0 (0%)	0 (0%)	4
	Headache	2 (4%)	1 (3%)	0 (0%)	0 (0%)	1 (1%)	4 (4%)	5 (11%)	5 (2%)	3
	Back Pain	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	3 (6%)	0 (0%)	0
	Pain	1 (2%)	1 (3%)	0 (0%)	1 (3%)	2 (3%)	5 (5%)	7 (15%)	0 (0%)	0
	Accidental Injury	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	25 (26%)	5 (11%)	0 (0%)	0
	Asthenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (10%)	5 (11%)	0 (0%)	2
RESPIRATORY SYSTEM	Upper Respiratory Tract Infection	6 (11%)	2 (7%)	0 (0%)	0 (0%)	4 (5%)	0 (0%)	0 (0%)	0 (0%)	0
	Coughing	3 (6%)	3 (10%)	0 (0%)	0 (0%)	3 (4%)	4 (4%)	2 (4%)	0 (0%)	0
	Pneumonia	1 (2%)	0 (0%)	0 (0%)	1 (3%)	3 (4%)	0 (0%)	3 (6%)	0 (0%)	10
PLATELET, BLEEDING & CLOTTING	Bruise	4 (7%)	2 (7%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0
	Ecchymosis	3 (6%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	3 (3%)	2 (4%)	0 (0%)	0

Body System	Preferred Term for WHO, COSTART, or Baylor Dictonaries	Study								
		TBZ 103,004		TBZ 103,005	TBZ 103,006	TBZ 103,007	TBZ 103,011		Baylor Non-Chorea Report N=280 N (%)	Post-Marketing Surveillance Reports N
		TBZ N=54 N (%)	Placebo N=30 N (%)	N=30 N (%)	N=29 N (%)	N=75 N (%)	HD N=98 N (%)	Non-HD N=47 N (%)		
URINARY SYSTEM	Urinary Tract Infection	1 (2%)	0 (0%)	0 (0%)	3 (10%)	1 (1%)	3(3%)	3 (6%)	0 (0%)	3
	Urinary Incontinence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	9 (9%)	1 (2%)	0 (0%)	1
MUSCULO-SKELETAL SYSTEM DISORDERS	Hypertonia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	0 (0%)	1
METABOLIC & NUTRITIONAL	Weight Gain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (9%)	0 (0%)	1
	Weight Loss	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	17 (17%)	4 (9%)	0 (0%)	0
SECONDARY TERMS	Fall	8 (15%)	4 (13%)	0 (0%)	1 (3%)	19 (25%)	0 (0%)	0 (0%)	0 (0%)	1
	Inflicted injury	3 (6%)	0 (0%)	1 (3%)	0 (0%)	4 (5%)	0 (0%)	0 (0%)	0 (0%)	0

Source: Tables in this section of the ISS: Table 5-7 for TBZ 103,004; Table 5-12 for TBZ 103,005; Table 5-16 for TBZ 103,006; Table 5-18 for TBZ 103,007; Table 5-21 for TBZ 103,011;

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10.4 Patients who reported one or more SAE

Body system	AE Preferred Term (WHO and COSTART together when possible)	Study or Project Number					
		TBZ 103,004		TBZ 103,005	TBZ 103,006	TBZ 103,007	TBZ 103,011
		Tetrabenazine	Placebo	Tetrabenazine	Tetrabenazine	Tetrabenazine	Tetrabenazine
		4 of 54 (7%) with SAE	0 of 30 with SAE	0 of 30 with SAE	7 of 29 (24%) with SAE	8 of 75 (11%) with SAE	31 of 145 (21%) with SAE
PSYCHIATRIC DISORDERS	Depression	-	-	-	1 (3%)	1 (1%)	3 (2%)
	Insomnia	-	-	-	-	-	1 (1%)
	Restlessness aggravated	1 (2%)	-	-	-	-	-
	Anxiety / Anxiety attack	-	-	-	-	1 (1%)	-
	Agitation	-	-	-	-	1 (1%)	-
	Confusion	1 (2%)	-	-	-	-	-
	Hallucinations	-	-	-	-	-	1 (1%)
	Paranoia	1 (2%)		-	-	-	-
	Psychosis/Delusions	1 (2%)	-	-	1 (3%)	-	1 (1%)
	Delirium / Disorientation	-	-	-	-	-	1 (1%)
CENTRAL & PERIPHERAL NERVOUS SYSTEM	End-stage HD[c]	-	-	-	-	-	8 (6%)
	Akathisia	-	-	-	-	1 (1%)	-
	Choreoathetosis[b]	-	-	-	-	-	1 (1%)
	Coma	-	-	-	-	-	1 (1%)
	Creutzfeldt-Jakob disease	-	-	-	-	-	1 (1%)
	Neuritis	-	-	-	-	-	1 (1%)
BODY AS A WHOLE SYSTEM	Accidental injury/ Inflicted injury	-	-	-	-	-	2 (2%)
	Falls	1 (2%)	-	-	1 (3%)	2 (3%)	-
	Back pain	-	-	-	-	-	2 (2%)
	Chest pain	-	-	-	1 (3%)	-	-
	Infection	-	-	-	-	-	1 (1%)

(copy of table 8-5 in ISS)

Patients who reported one or more SAE (continued)

Body system	AE Preferred Term (WHO and COSTART together when possible)	Study or Project Number					
		TBZ 103,004		TBZ 103,005	TBZ 103,006	TBZ 103,007	TBZ 103,011
		Tetrabenazine 4 of 54 (7%) with SAE	Placebo 0 of 30 with SAE	Tetrabenazine 0 of 30 with SAE	Tetrabenazine 7 of 29 (24%) with SAE	Tetrabenazine 8 of 75 (11%) with SAE	Tetrabenazine 31 of 145 (21%) with SAE
BODY AS A WHOLE SYSTEM (con't)	Infection bacterial	-	-	-	-	-	4 (3%)
	Overdose	-	-	-	-	-	1 (1%)
	Sepsis	-	-	-	-	-	1 (1%)
	Suicide	1 (2%)	-	-	-	-	-
	Suicide attempt		-	-	-	-	1 (1%)
	Suicide ideation	1 (2%)	-	-	1 (3%)	-	-
GASTROINTESTINAL SYSTEM DISORDERS	Dysphagia / swallowing difficult	-	-	-	-	1 (1%)	2 (1%)
	Diarrhea	-	-	-	1 (3%)	-	1 (1%)
	Nausea	-	-	-	1 (3%)	-	-
	Vomiting	-	-	-	-	-	1 (1%)
	Colitis	-	-	-	-	-	1 (1%)
	Esophageal hemorrhage	-	-	-	-	-	1 (1%)
	Fecal impaction	-	-	-	-	-	1 (1%)
	Gastrointestinal disorder	-	-	-	-	-	1 (1%)
	Gastrointestinal hemorrhage	-	-	-	-	-	1 (1%)
	Peptic ulcer	-	-	-	-	-	1 (1%)
RESPIRATORY SYSTEM	Pneumonia	-	-	-	1 (3%)	2 (3%)	4 (3%)
	Aspiration pneumonia	-	-	-	-	-	5 (4%)
	Apnea	-	-	-	-	-	1 (1%)
	Carcinoma of lung	-	-	-	-	-	1 (1%)
	Lung disorder	-	-	-	-	-	1 (1%)

(copy of table 8-5 in ISS)

Patients who reported one or more SAE (continued)

Body system	AE Preferred Term (WHO and COSTART together when possible)	Study or Project Number					
		TBZ 103,004		TBZ 103,005	TBZ 103,006	TBZ 103,007	TBZ 103,011
		Tetrabenazine	Placebo	Tetrabenazine	Tetrabenazine	Tetrabenazine	Tetrabenazine
		4 of 54 (7%) with SAE	0 of 30 with SAE	0 of 30 with SAE	7 of 29 (24%) with SAE	8 of 75 (11%) with SAE	31 of 145 (21%) with SAE
METABOLIC & NUTRITIONAL DISORDERS	Dehydration	-	-	-	1 (3%)	-	5 (3%)
	Hyperkalemia	-	-	-	-	-	1 (1%)
	Hyponatremia	-	-	-	-	-	1 (1%)
	Lactic acidosis	-	-	-	-	-	1 (1%)
URINARY SYTEM DISORDERS	Urinary tract Infection	-	-	-	1 (3%)	-	-
	Hemorrhagic cystitis	-	-	-	-	-	1 (1%)
	Kidney calculus	-	-	-	-	-	1 (1%)
	Kidney failure	-	-	-	-	-	1 (1%)
SKIN & APPENDAGES DISORDERS	Skin ulcer	-	-	-	-	-	1 (1%)
CARDIOVASCULAR SYSTEM DISORDERS	Hypotension	-	-	-	-	-	1 (1%)
	Deep thrombophlebitis	-	-	-	-	-	1 (1%)
	Heart arrest	-	-	-	-	-	1 (1%)
	Myocardial infarction	-	-	-	-	-	2 (1%)
MUSCULOSKELETAL SYSTEM DISORDERS	Pathological fracture / Bone Fracture spontaneous	-	-	-	-	1 (1%)	2 (1%)
	Hip replacement	-	-	-	-	1 (1%)	-
	Bone disorder	-	-	-	-	-	1 (1%)
	Rhabdomyolysis	-	-	-	-	-	1 (1%)

(copy of table 8-5 in ISS)

Patients who reported one or more SAE (continued)

Body system	AE Preferred Term (WHO and COSTART together when possible)	Study or Project Number					
		TBZ 103,004		TBZ 103,005	TBZ 103,006	TBZ 103,007	TBZ 103,011
		Tetrabenazine 4 of 54 (7%) with SAE	Placebo 0 of 30 with SAE	Tetrabenazine 0 of 30 with SAE	Tetrabenazine 7 of 29 (24%) with SAE	Tetrabenazine 8 of 75 (11%) with SAE	Tetrabenazine 31 of 145 (21%) with SAE
VISION DISORDERS	Cataract	-	-	-	-	-	1 (1%)
	Eye disorder	-	-	-	-	-	1 (1%)
	Optic atrophy	-	-	-	-	-	1 (1%)
	Ptosis	-	-	-	-	-	1 (1%)
VASCULAR (EXTRA-CARDIAC) DISORDERS	Subarachnoid hemorrhage	1 (2%)	-	-	-	-	-
	Subdural hematoma	-	-	-	-	-	1 (1%)
REPRODUCTIVE DISORDERS, MALE	Prostate cancer	-	-	-	-	1 (1%)	-
NEOPLASM	Breast cancer	1 (2%)	-	-	-	2 (1%)	-
ENDOCRINE SYSTEM DISORDERS	Adrenal cortex insufficiency	-	-	-	-	-	1 (1%)

(copy of table 8-5 in ISS)

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10.5 Summary of patient deaths from secondary sources

Reference [source]	Number of Patients in Study	Number of Deaths	Diagnoses	Comments
Deaths Reported in the Cambridge-Baylor Review 1997-2002				
The Cambridge-Baylor Review (IND #16,161 1997-2002) [5.3.5.2.1]	309	5	Various abnormal involuntary movement disorders (AIMDs)	All deaths were considered unrelated to tetrabenazine exposure and included 3 patient deaths due to cardiovascular disease. One patient committed suicide more than 1 month after discontinuing treatment and 1 patient died with end-stage HD. These 5 may be double-counted in Jankovic and Beach below.
Deaths reported in the literature				
Jankovic and Beach (JankovicBeach, 1997)	526	20	Various abnormal involuntary movement disorders (AIMDs)	All deaths were judged unrelated to tetrabenazine exposure, although details regarding the causes of death or associated adverse events (AEs) were not reported. This report may include the 5 reported in the Baylor Study above.
Mikkelsen (Mikkelsen, 1983)	124	5	Various AIMDs	The deaths were classified as unrelated to tetrabenazine exposure, although neither cause of death nor the related AEs were specified.
Kingston (Kingston, 1979)	40	3	Huntington's chorea (24), tardive dyskinesia (6), various AIMDs (10)	The reasons for deaths were considered unrelated to tetrabenazine exposure, although neither the cause of death nor the associated AEs were reported.
McLellan, D.L. (McLellan, 1972)	30	1	Huntington's chorea	The patient was a 51-y-old male who died of bronchopneumonia while being treated with 200 mg/d tetrabenazine. No additional details were provided in the publication
Lingjærde (Lingjaerde, 1963)	25	2	Chronic schizophrenia (24), undescribed psychosis (1)	One patient (age 64) experienced extreme fatigue, weakness, and slight unilateral paralysis in the extremities shortly after study initiation, possibly exacerbated by her weakened health resulting from a case of diarrhea 6 mo before study initiation. Her death was considered a result of concurrent cerebral thrombosis possibly related to tetrabenazine exposure. One patient (age 85) died followed a similar course of progressive fatigue and weakness (without paralysis) but her course was not preceded by any significant clinical event such as diarrhea. Her death resulted from pneumonia, but there may have been "an indirect connection" between tetrabenazine treatment and the pneumonia.

(reproduction of table 2.7.4-27)

Summary of patient deaths from secondary sources (continued)

Reference [source]	Number of Patients in Study	Number of Deaths	Diagnoses	Comments
Brauchitsch (Brauchitsch, 1962)	134	2	Schizophrenia and other chronic psychiatric conditions	One patient was 80 y old with senile dementia and cardiac insufficiency; the other was of a younger, unspecified age and died with symptoms of acute, malignant catatonia, which began before tetrabenazine dosing. The authors concluded the deaths were not related to tetrabenazine exposure.
Snaith, RP and Warren H (Snaith et al., 1974)	N/A	3	Huntington's chorea (3)	The authors describe three (3) patients with Huntington's disease who developed swallowing difficulties and died from pneumonia while taking tetrabenazine
Manji et al. (Manji., 1998)	N/A	2	Status dystonicus (2)	The authors reviewed the available literature on status dystonicus and described the deaths of two (2) boys, ages 11 and 13, who were treated with tetrabenazine and various other agents for this condition.
Deaths Reported in Global Pharmacovigellance				
The Cambridge Laboratories Periodic Safety Report [Section 5.3.6.3]	N/A	7	Huntington's disease (1); Tardive Dyslinesia (1); Unknown diagnosis (2); Not available (2)	Two cases of pneumonia and 1 of hyperpyrexia had a fatal outcome among the 95 AEs reported to the United Kingdom Medicines Control Agency between July 1963 and March 2001
				A patient taking tetrabenazine 12.5 mg t.i.d. and Venlafaxine 75 mg/d with a diagnosis of non-specified cardiomegaly. The patient was reported to have died from an overdose although the specific drug taken is not known; the patient had cardiomegaly and at autopsy had detectable blood levels of alcohol, ecstasy and both prescribed medications; an open verdict was recorded at the coroner's inquest.
				A 56 year old female with Huntington's disease, was taking tetrabenazine and carbamezapine. She suffocated while eating and died. The post-mortem toxicological studies were non-conclusive. (Roche France).
				A 75 year old female, was taking tetrabenazine, clopidogrel, refocoxib, isosorbide mononitrate for unknown diagnoses. She was also taking digoxin for atrial fibrillation. It is unknown whether she was actually taking tetrabenazine at the time of her death.
				In 1983, an 81 year old European female taking fluphenazine, tetrabenazine, benztropine mesylate, orphenadrine citrate and nitrofurazone suffered dehydration, tardive dyskinesia, hypotension and coma. The patient subsequently died from an unknown cause. (New Zealand Centre for Adverse Reactions Monitoring)
Canada Phase 4 Reporting	N/A	3	Not available	Three AEs of 5 reported had a fatal outcome. Of these three, 1 patient experienced parkinsonism, pleural effusion, and septicemia; the second experienced myocardial infarction; the third experienced parkinsonism. A relationship to drug exposure was suspected for these AEs for all three patients.

(reproduction of table 2.7.4-27 from study report)

Summary of patient deaths from secondary sources (continued)

Reference [source]	Number of Patients in Study	Number of Deaths	Diagnoses	Comments
Roche Pharmaceuticals Safety Report (up to 1994) [Section 5.3.6.1]	N/A	4	Huntington's disease (2); unknown (2)	A total of four (4) deaths are reported; they are summarized as follows: • A 73 year old female with Huntington's disease, osteoarthritis, chronic obstructive pulmonary disease and respiratory infection died from respiratory causes • A 52 year old man with Huntington's disease died from neuroleptic malignant syndrome while taking tetrabenazine; his death is the subject of a literature report 3 • A female died from a mixed overdose of tetrabenazine and other agents; no other details available • A 53 year old male died an unexpected, sudden death; autopsy showed 75% stenosis of coronary arteries

(reproduction of table 2.7.4-27 from study report)

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Reference [source]	Number of Patients in Study	Number of Deaths	Diagnoses	Comments
Roche Pharmaceuticals Safety Report (1994-1998) [Section 5.3.6.2]	N/A	28	Huntington's disease (4); other chorea (5); other diagnoses (18); unknown diagnosis (1)	Twenty-three (23) of the reported deaths occurred in patients participating in an open-label safety study conducted in Canada (1989-1996). • An 80 year old female died of pneumonia. It is unclear whether aspiration was involved; • An adult female died from dysphagia and pneumonia aspiration; • A 64 year old female patient died from impaired swallowing; • An elderly male died from GI tract bleed; • A 49 year old female died from dehydration and inability to eat or drink; • An elderly female died of a myocardial infarction; • An elderly female died of a myocardial infarction; • A 78 year old male died of a myocardial infarction; • A 79 year old male died of cardiac arrest. The patient had with a history of rheumatic fever which led to valvular disease and angina; • An 82 year old female died of cardiopulmonary arrest and cerebrovascular accident (CVA). She had a history of CVA with left hemiparesis; • An 86 year old female died of a cerebrovascular accident. This event was judged to be related to underlying disease and not tetrabenazine use; • An 82 year old female died of aspiration. The patient aspirated because of drowsiness, but dysphagia was present prior to taking tetrabenazine. A small pulmonary embolus found at autopsy; • An elderly female died of pneumonia. She had a history of repeated pneumonia, that was not judged to be related to tetrabenazine; • An 81 year old female died of pneumonia; • An elderly female died of bronchopneumonia. She had a history of organic brain syndrome and diabetes. Her pneumonia was not judged to be drug related; • A 44 year old female died of pneumonia aspiration. She also suffered from lymphopenia and had a urinary tract infection She was taking unspecified tranquilizers; • An 86 year old female died of pneumonia aspiration. She had a history of Alzheimer's disease and severe dysphagia leading to aspiration pneumonia • An elderly female died a sudden death, cause of death unknown; • A patient died a sudden death, no details are available;

(reproduction of table 2.7.4-27 from study report)

Summary of patient deaths from secondary sources (continued)

Reference [source]	Number of Patients in Study	Number of Deaths	Diagnoses	Comments
Roche Pharmaceuticals Safety Report (1994-1998) (continued)				• 75 year old female died, the cause of death was not judged to be related to tetrabenazine; • An elderly male died suddenly of cardiac and cerebrovascular disease. His death was not judged to be related to tetrabenazine; • An 85 year old female died from progression of her neurological disease. The patient suffered from senile dementia, probably of the Alzheimer's type; • A 54 year old female died from progression of her neurological disease and complications of Huntington's chorea. Five (5) of the reported deaths occurred in patients receiving tetrabenazine who were not part of the open-label safety study are summarized as follows: • A 54 year old male taking 100mg/day of tetrabenazine committed suicide. The patient had discontinued tetrabenazine at least 1 month prior to first suicide attempt; • An 84 year old female died of congestive heart failure. She had congestive heart failure for at least 1 year prior to her death; a myocardial infarction was suspected, no autopsy was performed; • A 69 year old male died of a myocardial infarction (MI). He also had a history of chronic obstructive pulmonary disease; his MI was not judged to be related to tetrabenazine use; • A 48 year old male died of a cardiac arrest; a cardiac arrhythmia was suspected and may have been caused by loxapine; • An elderly female died of aspiration that was thought to be disease related.

(reproduction of table 2.7.4-27 from study report)

Summary of patient deaths from secondary sources (continued)

Reference [source]	Number of Patients in Study	Number of Deaths	Diagnoses	Comments
Roche Canada Open-Label Safety Study (1989-1995) [Section 2.7.4.6.4]	757 estimated	20	Huntington's disease (5); other chorea (3); other diagnoses (10); unknown diagnosis (2)	Twenty (20) additional patient deaths which occurred in an open-label safety study conducted in Canada (1989-1995) were not included in either of the two Roche Pharmaceuticals safety summaries. Brief summaries of these cases follow; more extensive narratives are appended to this report: • An 82 year old female with diabetes and a history of depression died as a result of an aspiration pneumonia; • A 74 year old female with idiopathic chorea died from pneumonia; she had been diagnosed with oral cancer 7 months earlier that was treated with radiation therapy • A 97 year old female with diabetes, anemia and compensated heart failure with severe tardive dyskinesia died of unknown causes six days after running out of her supply of tetrabenazine • A 78 year old female died of complications from a severe dementia • A 38 year old male with Huntington's disease who was unable to eat or drink died from dehydration following withdrawal of all supportive measures at the request of his family • A patient of unknown age died in a nursing home of unknown causes • A 79 year old female with tardive dyskinesia died of unknown causes • A 72 year old female with a history of schizophrenia and coronary artery disease died of unknown causes • An 80 year old male with tardive dyskinesia died from complications of diabetes and peripheral vascular disease • A 43 year old male with Huntington's disease died following a fall associated with skull fracture; he had pneumonia and was comatose, the exact cause of death is not available • A 40 year old male with Huntington's disease died from pneumonia; according to his doctor, he had a good response to tetrabenazine • A 13 year old male with Tourette's syndrome died under unknown circumstances • A 77 year old male with a history of recent cerebrovascular accident died from a pulmonary embolus • A 66 year old female with two months of documented exposure to tetrabenazine died of an unspecified carcinoma

(reproduction of table 2.7.4-27 from study report)

Summary of patient deaths from secondary sources (continued)

Reference [source]	Number of Patients in Study	Number of Deaths	Diagnoses	Comments
Roche Canada Open-Label Safety Study (1989-1995) [Section 2.7.4.6.4] (continued)				• A 58 year old female with a history of chorea died from suspected pneumonia A 64 year old male with a history of tardive dyskinesia died from a large cerebrovascular accident A 75 year old female with dyskinesia and dementia died from an unknown cause A 72 year old female with Huntington's chorea died from a ruptured berry aneurysm; the patient's death was felt to be unrelated to tetrabenazine use A 51 year old female with dystonia, dyskinesias and chorea died on an unknown cause; she had a prior history of pneumococcal sepsis and critical illness polyneuropathy A male patient of unspecified age died from pre-existing metastatic prostate cancer

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