VANDERBILT UNIVERSITY MEDICAL CENTER

# Post-Marketing Adverse Events Associated with Tetrabenazine: Findings Using the FDA Adverse Event Reporting System

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This study was funded by Teva Pharmaceutical Industries Ltd, Petach Tikva, Israel

*Presented at*
***9th European Huntington's Disease Network Plenary Meeting***
The Hague, The Netherlands
September 16–18, 2016

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## SUMMARY

- The incidence of adverse event (AE) case reports with tetrabenazine documented as the primary suspect has increased over time (2009–2015) and showed consistency between AEs reported in the real-world practice and clinical trial settings
  - Depression/agitated depression appeared to be reported into the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) more than would be expected from the evaluation of clinical trial results
- Disproportionality analyses identified a higher-than-expected safety concern for several individual neuropsychiatric AEs, including depression, agitation, agitated depression, insomnia, and somnolence, as well as for several relevant AE groups
  - These AEs warrant careful monitoring and highlight important unmet needs in the safe treatment of chorea in Huntington disease (HD)
- Although post-marketing AE reporting is a potentially more conservative estimate of safety signals compared with clinical trials, there was consistency between tetrabenazine-associated AEs reported in the clinical trial setting and those in spontaneous post-marketing AE reporting
  - The real-world spontaneous AE reporting could be a useful data source to guide patient care decisions

## BACKGROUND

- Tetrabenazine is the only therapy approved by the FDA (approval in 2008) for treating chorea associated with HD[1,2]; however, some peak concentration–related neuropsychiatric symptoms associated with tetrabenazine were observed in the pivotal clinical study[1–3]
  - Tetrabenazine carries a boxed warning in the US about increased risk of depression and suicidality[2]
- The FAERS database contains information on AEs and medication errors associated with approved and marketed products[4]
  - Although there are limitations with FAERS data,[4] these data may identify important safety concerns and unmet treatment needs, and may help guide treatment decisions in a real-world setting
- Evaluation of FAERS data for specific AEs that were observed with tetrabenazine in the pivotal clinical trial that supported the drug's approval will assist in identifying the most relevant safety concerns with the medication

## OBJECTIVE

- To summarize post-marketing reports of AEs associated with tetrabenazine by analyzing case reports from the FAERS database

## METHODS

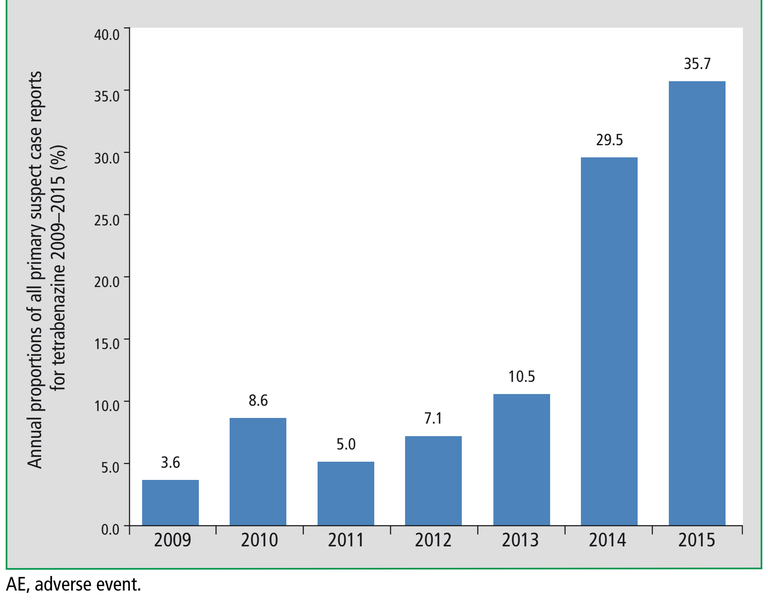
- FAERS data for branded tetrabenazine (Xenazine®) included case reports meeting minimal key identification field criteria
- RxFilter®, a tool using a combination of computer algorithms and in-house data analyses, was used for standardization of post-marketing case report data and was applied to tetrabenazine data to analyze AEs
  - Case reports that were missing or contained malformed key identification fields were discarded
  - Cases were also discarded if the drug name was unable to be determined
  - When there was more than one Individual Case Safety Report for the same ID number in the same calendar year, the earliest reported case was selected
- AE information was coded according to terms in the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1
- Primary suspect counts of AEs in which tetrabenazine was suspected as the causative agent and calculation of disproportional reporting rates were performed to identify potential safety signals
  - The primary suspect, chosen by the person submitting the case report, was the reporter's estimate of which drug was likely to be responsible for the observed AE; in conjunction with patient utilization data, primary suspect case reports were used to calculate incidence rates for key patient outcomes
  - ROR is a disproportionality analysis that was performed for these data; a score >1 indicates a higher-than-expected reporting rate for a given AE/drug combination, and a score >2 suggests a potential safety signal that warrants attention
- Incidence of AEs observed in clinical trials and in the FAERS post-marketing database are summarized in this report

## RESULTS

### FAERS Data and Analyses on Primary Suspect AE Case Reports for Tetrabenazine

- From approval of tetrabenazine on September 9, 2008 to FAERS data cutoff on December 31, 2015, there were 5198 cumulative primary suspect case reports for tetrabenazine across all AEs (**Figure 1**)

**Figure 1. Annual Proportions of All Primary Suspect Case Reports for Tetrabenazine Across All AEs (2009–2015)**




AE, adverse event.

- Because of the potential underreporting of real-world AEs to the FAERS database, it is important to review the relative reporting rates via rankings of AEs

### AE Incidence and Ranking

- Comparison of MedDRA AEs from FAERS safety data sets for tetrabenazine and the AEs reported in the FDA-approved prescribing information showed overlap of the most frequently reported AEs, including depression, somnolence, fatigue, fall, and insomnia (**Table 1**)
  - Evaluation of cumulative incidence (2009–2015) in the post-marketing data showed that depression was the most frequently reported AE (1.14%; 352/30,877)
  - In clinical trials, depression was the fourth most commonly reported AE (19%;10/54), with sedation/somnolence (31%; 17/54), insomnia (22%; 12/54), and fatigue (22%; 12/54) occurring more frequently

**Table 1. Incidence of 15 Most Common MedDRA AEs**

| | Post-Marketing AEs | | FDA-Approved Prescribing Information AEs[2] | |
|---|---|---|---|---|
| | n (%) | Rank | n (%) | Rank |
| Depression | 352 (1.14) | 1 | 10 (19) | 4 |
| Sedation/somnolence | 345 (1.06) | 2 | 17 (31) | 1 |
| Fatigue | 259 (0.86) | 3 | 12 (22) | 3 |
| Fall | 225 (0.73) | 4 | 8 (15) | 7 |
| Insomnia | 218 (0.66) | 5 | 12 (22) | 2 |
| Anxiety/anxiety, aggravated | 159 (0.49) | 6 | 8 (15) | 6 |
| Nausea | 120 (0.39) | 7 | 7 (13) | 8 |
| Balance difficulty | 92 (0.30) | 8 | 5 (9) | 11 |
| Vomiting | 91 (0.29) | 9 | 3 (6) | 13 |
| Irritability | 53 (0.17) | 10 | 5 (9) | 10 |
| Parkinsonism/ bradykinesia | 54 (0.17) | 11 | 5 (9) | 12 |
| Akathisia | 19 (0.06) | 12 | 10 (19) | 5 |
| Ecchymosis | 2 (0.04) | 13 | 3 (6) | 15 |
| Laceration | 12 (0.04) | 14 | 3 (6) | 14 |
| Upper respiratory tract infection | 4 (0.03) | 15 | 6 (11) | 9 |

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

### Disproportionality Analysis

- Disproportionality analysis identified a high ROR (>2) for some neuropsychiatric AEs, indicating that there is a higher-than-expected reporting rate for these AEs
  - These associations were observed when grouped by preferred terms (**Table 2**) or high-level group terms (**Table 3**)

**Table 2. Disproportionality Analysis of AEs (Preferred Term) with Tetrabenazine for 10 Clinical AEs with Highest ROR**

| Preferred Term | Primary Suspect Case Reports | ROR (95% CI) |
|---|---|---|
| Agitated depression | 2 | 29.16 (7.18–118.37) |
| Parkinsonism | 46 | 15.81 (11.81–21.17) |
| Somnolence | 318 | 6.14 (5.48–6.88) |
| Depression | 352 | 4.71 (4.22–5.24) |
| Akathisia | 19 | 4.18 (2.66–6.57) |
| Dysphagia | 130 | 4.07 (3.42–4.84) |
| Agitation | 121 | 4.06 (3.39–4.86) |
| Insomnia | 218 | 2.63 (2.30–3.02) |
| Fall | 225 | 2.53 (2.21–2.89) |
| Anxiety | 159 | 1.75 (1.49–2.05) |

AE, adverse event; CI, confidence interval; ROR, reporting odds ratio.

**Table 3. Disproportionality Analysis of AE groups (High-Level Group Terms) with Tetrabenazine for Three Clinical AE Groupings with Highest RORs**

| High-Level Group Term | Primary Suspect Case Reports | ROR (95% CI) |
|---|---|---|
| Movement disorders (including parkinsonism) | 649 | 4.90 (4.51–5.32) |
| Sleep disorders and disturbances | 623 | 3.47 (3.19–3.77) |
| Depressed mood disorders and disturbances | 401 | 4.07 (3.68–4.51) |

AE, adverse event; CI, confidence interval; ROR, reporting odds ratio.

### Acknowledgments

This study was funded by Teva Pharmaceutical Industries, Petach Tikva, Israel. We thank Rhonda Charles, PhD (Chameleon Communications International with funding from Teva Pharmaceutical Industries) for editorial assistance in the preparation of this report.

### Disclosures

**Daniel O. Claassen**: Grant support: NIH/NINDS, Michael J. Fox Foundation, Huntington Disease Society of America, Vaccinex, AbbVie, Auspex Pharmaceuticals. Consulting fees: Teva Neuroscience, Lundbeck, Acadia, AbbVie. **Ravi Iyer**: Employee of Teva Pharmaceutical Industries. **Mo Dimbil**: Financial support through research project sponsored by Teva Pharmaceutical Industries. **Abril Giron**: Financial support through research project sponsored by Teva Pharmaceutical Industries. **Lisa M. De Boer**: Employee of Teva Pharmaceutical Industries. **Sanjay Gandhi**: Employee of Teva Pharmaceutical Industries. **Keith B. Hoffman**: Financial support through research project sponsored by Teva Pharmaceutical Industries.

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