

Dalfampridine Extended Release Tablets: One Year of Post-Marketing Safety Experience in the United States

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Background

- Dalfampridine extended release tablets, 10 mg taken 12 hours apart, were approved by the US Food and Drug Administration (FDA) to improve walking in patients with multiple sclerosis (MS).¹ This was demonstrated by an increase in walking speed
 - Dalfampridine extended release has been available in the US market since March 2010
- Dalfampridine, known as fampridine outside the US, was approved in Australia² (where it is known as modified-release fampridine) and received conditional marketing authorization in the European Union³ (where it is known as prolonged-release fampridine)
- Improvement in walking was demonstrated in a Phase 2 and two Phase 3 trials by a consistently faster walking speed on the Timed 25-Foot Walk among dalfampridine responders relative to placebo⁴⁻⁶
- In clinical trials, dalfampridine was observed to have a generally favorable safety and tolerability profile at the recommended therapeutic dose and regimen
 - Drug safety information from clinical trials may not be representative of general clinical use of a product
 - Seizures are recognised to be a dose-dependent risk for the product and a Risk Evaluation and Mitigation Strategy (REMS) was instituted to inform healthcare providers and patients about seizure risk⁷
- Assessment of post-approval adverse events (AEs) is also part of the pharmacovigilance program initiated upon FDA approval of dalfampridine extended release, including enhanced pharmacovigilance for reported cases of seizure and events indicative of a possible seizure
- Dalfampridine is dispensed via a closed distribution system of 16 specialty pharmacies, making information available on the number of patients exposed and enabling estimates of patient-years of exposure
- Safety experience is now available from clinical trials and from the exposure of approximately 46,200 patients in the US, or 14,500 patient-years, from product launch through March 2011

Objective

- To provide a descriptive analysis of the post-marketing safety of dalfampridine in the US based on spontaneously reported adverse events from product approval through the first year of marketing

Methods

- A descriptive analysis was performed of all post-marketing dalfampridine AEs that were spontaneously reported since product approval
- AE data were extracted from the safety database from product launch through March 31, 2011
- All events in the database were classified using the internationally recognised Medical Dictionary for Regulatory Activities (MedDRA)

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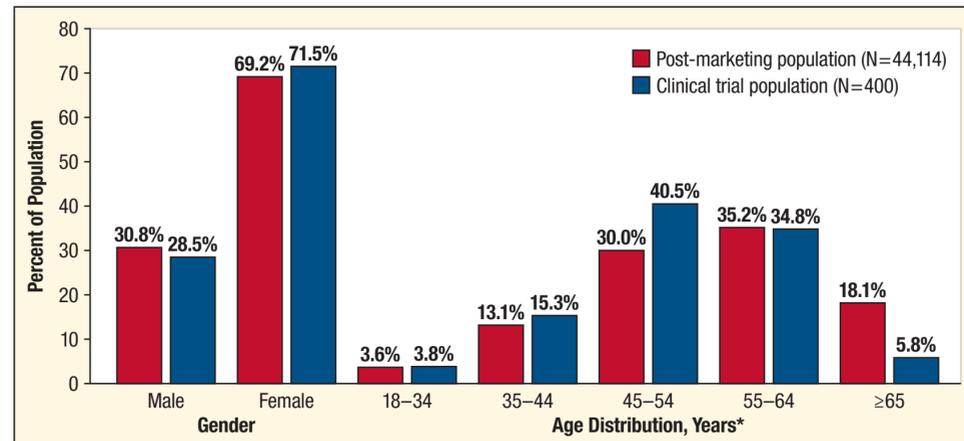
- A separate query of all database terms that could identify potential or confirmed seizures was conducted and each case was reviewed to ascertain patient demographics, time to event from treatment onset, and potential risk factors
 - All confirmed and potential seizure reports were subject to detailed, active follow-up using a structured seizure questionnaire designed to collect information on
 - Dose
 - Regimen
 - Proper usage
 - Seizure history
 - Prior use of a pharmacy-compounded formulations
- AEs for pharmacy-compounded 4-aminopyridine (4-AP) reported through the Acorda Medical Information Call Center were also recoded and reported
 - 4-aminopyridine is the chemical name for dalfampridine
 - The safety database was queried to determine the number of seizure reports out of the total number of adverse event reports for compounded 4-AP
- The proportion of adverse event reports was estimated by event, as classified at the MedDRA preferred term level
 - Commonly reported events were defined as those with a prevalence of ≥2% of all reported AEs
 - Incidence rates were calculated using the estimate of person-time of exposure of 14,500 person-years based on data from the closed distribution system
 - The incidence rate of seizure was also calculated
 - The post-marketing incidence rate estimates were used to make informal comparisons with the incidence rates from placebo-controlled clinical trials of dalfampridine

Results

Population Characteristics

- Data on the post-marketing safety experience were available from the exposure of approximately 46,200 patients from product approval through March 2011
 - This patient exposure represents approximately 14,500 patient-years
 - Demographic data were available for 44,114 patients (95.5%)
- Gender distribution was similar between clinical trial and postmarketing populations (Figure 1)
- Overall, the age distribution of the post-marketing population was generally similar to that in the clinical trials (Figure 1), although the post-marketing population had a wider age range, 14–101 years vs 25–73 years, and a higher proportion of patients ≥65 years of age
 - The mean age of the post-marketing population, 54.8 years, was older than that of the clinical trial population, 51.7 years

Figure 1. Demographic Characteristics of the Post-Marketing Surveillance Population Relative to the Clinical Trial Population



*8 patients in the post-marketing population were ≤17 years of age

Common Adverse Events

- As of March 31, 2011 11,549 adverse events were reported
- During the first year of marketing, the majority of the most frequently reported adverse events, including dizziness, insomnia, balance disorder, headache, nausea, urinary tract infection, asthenia, and back pain, were previously detailed in product labeling (Table 1)

Table 1. Adverse Events by MedDRA Preferred Term with a Prevalence of ≥2% of All Reported Cases in the Post-marketing Population Through 31 March 2011

Preferred Term	n (% of events)	Event Status
Dizziness	658 (5.7)	Labeled
Insomnia	524 (4.5)	Labeled
Balance disorder	450 (3.9)	Labeled
Headache	375 (3.2)	Labeled
Nausea	323 (2.8)	Labeled
Urinary tract infection	276 (2.4)	Labeled
Asthenia	235 (2.0)	Labeled
Back pain	232 (2.0)	Labeled
Condition aggravated	347 (3.0)	Not listed
Gait disturbance	239 (2.1)	Not listed
Drug ineffective	517 (4.5)	Expected
Inappropriate schedule of drug administration	573 (5.0)	Not listed

- New findings of clinical significance reported from the post-marketing data are related to inappropriate dosing and lack of efficacy under the following circumstances:
 - If an adverse event was reported and dosing was less than the approved daily dose, an additional event code of ‘inappropriate schedule of dose administration’ was assigned (n=573)

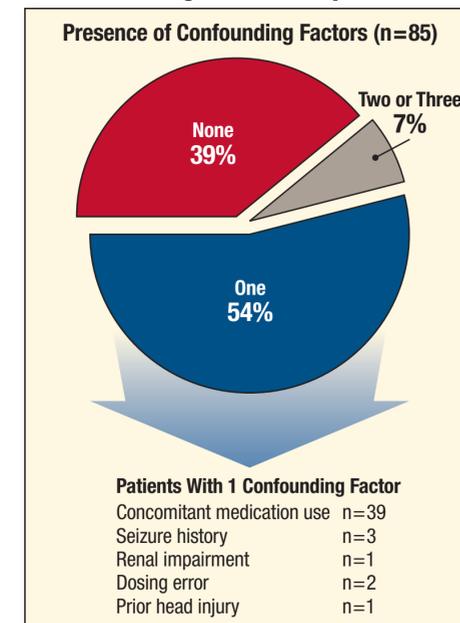
- For adverse events where a double dose of drug was ingested or the dosing interval was reported as less than 8 hours, an additional event was assigned to either accidental overdose (n=36), intentional overdose (n=1) or overdose (n=5) depending on individual case information
- The observed incidence rates for commonly reported AEs in the post-marketing population were substantially lower than those observed among 10 mg dalfampridine treated patients in controlled clinical trials
 - For previously labelled events, incidence rates in the clinical trial population were on average 15 times higher than the rates estimated in the post-marketing population based on spontaneously reported AEs

Seizures

- As of March 31, 2011, of the 46,200 patients exposed, 82 seizures had been either reported or confirmed by a healthcare practitioner, representing a seizure rate of approximately 5.7/1000 patient-years
 - An additional three cases of seizure were reported directly by patients and were not confirmed by a healthcare practitioner, increasing the combined estimated incidence rate to ~5.9/1000 patient-years of use
- The demographics of patients reporting seizures were reflective of the overall post-marketing population
 - 78% of the reported cases were in women (66 women, 19 men)
 - The mean age of the patients was 53 years (range, 15–76) with 3 cases missing age information
- Duration of treatment prior to the event ranged from 1 dose to 365 days
 - 23 of the 82 (28%) patients suffered a seizure within a week of starting treatment
- Of 106 unsolicited adverse events received by Acorda for compounded formulations of 4-aminopyridine during the same time period, 7.5% (8) were seizures, compared with 0.7% for dalfampridine (82 seizures of 11,549 adverse events) reported in the same time period

- In addition to the risk of seizures already inherent in the MS population,^{8,9} 61% of the reported seizure cases had an additional confounding factor for seizure, with a small proportion of patients having multiple confounding factors (Figure 2)

Figure 2. Presence of Potential Confounding Factors Increasing Seizure Risk Among Patients Experiencing Seizures in the Post-Marketing Surveillance Program of Dalfampridine



- Confounding factors included:
 - A previous history of convulsion
 - Renal impairment
 - Dosing error (double dose or dosing interval less than 12 hours)
 - Use of concurrent medications with a labelled seizure risk
 - Head injury with a subdural haematoma prior to the event
- Of patients experiencing a seizure on dalfampridine, 53% had concomitant use of one or more medications with a labeled seizure risk, 6% had a history of seizure (n=5), 4% had some level of renal impairment (n=3) and 6% had an associated dosing error (n=5)
- One case met three criteria for confounding factors: epileptogenic concomitant medication use, seizure history, and renal impairment

Discussion

- The most commonly reported post-marketing events with dalfampridine were those that were also identified in the clinical trials, although the post-marketing incidence was lower
 - Under-reporting of AEs is recognized in the uncontrolled post-market setting, particularly when events are not considered serious or severe

- Regarding the most common AEs:
 - Dizziness, insomnia, balance disorder, headache, nausea, urinary tract infection, asthenia, and back pain are already detailed in the US product labeling¹
 - While ‘condition aggravated’ and ‘gait disturbance’ were reported frequently post-marketing, neither of these events was reported more frequently in dalfampridine patients relative to placebo in clinical trials
 - Although lack of efficacy was reported as an adverse event, dalfampridine has been demonstrated to be effective in approximately 37% of users in clinical trial data; therefore a lack of product effectiveness is expected
 - Given that there is only one approved dose, reports of inappropriate dosing were higher than expected (5%). All reports of inappropriate dosing were of under-dosing
 - Dosing at intervals shorter than recommended was a risk factor in several of the reported seizures, making it especially important to adhere to the approved dosing schedule for extended release dalfampridine
 - The overall incidence rate of seizure in the first year of marketing was 5.7/1000 patient-years of use; less than one third of the cases occurred within the first week of exposure
 - This rate is comparable to the incidence rate from the long-term open-label trials, at 4.1/1000 patient-years of use (95% CI=1.3–9.6/1000 patient-years)
 - In the US, cases of seizure and convulsion are expected events and we actively seek additional information on seizures as part of the REMS commitment, making significant under-reporting for this event unlikely
- Literature suggests that MS itself is a risk factor for development of seizures, with a general consensus that the risk is approximately three-fold higher than that of the general population,^{10,11} but estimates of incidence vary
 - The most relevant estimate is likely to be from Eriksson et al.,¹² who estimated a first seizure incidence of 3.49/1000 patient-years (95% CI=1.96–5.02/1000 patient-years) in a Swedish MS population

Conclusions

- Spontaneous safety data emerging from the US post-marketing experience of dalfampridine are consistent in terms of types of events with the safety profile seen during clinical development
- New events were related to lack of efficacy and inappropriate dosing
- These data suggest that the generally favorable safety and tolerability profile observed in clinical trials extends to the clinical setting
- First year seizure incidence was not substantially different than the incidence observed in clinical trials

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