A Novel Gastroretentive Formulation of Gabapentin for the Treatment of Postherpetic Neuralgia

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Despite its efficacy for the treatment of postherpetic neuralgia (PHN), the potential benefits from treatment with gabapentin may be somewhat limited by its intrinsic properties. With a short elimination half-life of only 5 to 7 hours,[1] immediate-release (IR) formulations of gabapentin (gabapentin TID) must be taken at least 3 times per day to maintain efficacious levels.[2] Especially in older patients who are likely taking several medications multiple times per day,[3,4] frequent dosing may adversely affect patient adherence to treatment.[5-7]

Gabapentin is absorbed in a dose-dependent manner mainly in the upper small intestine. Following oral administration of gabapentin TID, exposure to gabapentin, as measured by maximal plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC), does not increase proportionally as single doses increase[8,9] or as daily dosages (given as divided doses) increase from 300 mg to 4800 mg gabapentin. Because gabapentin is eliminated from the plasma solely by renal excretion of the unchanged drug, the lack of proportionality between plasma concentrations and dosage of gabapentin TID likely results from saturation of intestinal absorption.[10-12] Gabapentin is absorbed primarily in the upper small intestine via an active uptake transporter that is saturable at clinically relevant dosages of gabapentin. Gabapentin TID tablets release the drug within 30 minutes, which leads to saturation of the transporter, especially at higher, therapeutic doses. Consequently, gabapentin TID requires dosing 3 or more times per day at lower unit doses.

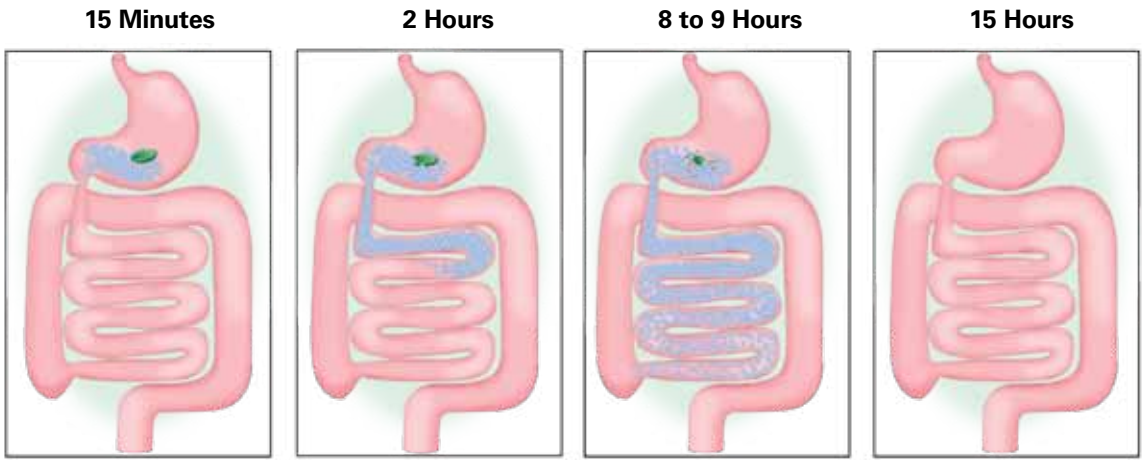
A retrospective analysis of an administrative claims database revealed that most patients treated with gabapentin for PHN never reached the target dosage of 1800 mg/day. This was demonstrated clearly in a retrospective study of medical claims from inpatients and outpatients taking gabapentin TID in which 86% of patients never achieved the effective dosage of 1800 mg/day.[9] Furthermore, titration of gabapentin TID to the efficacious dosage is done slowly and often requires up to 2 months or more.[13] Moreover, many patients never reach the efficacious dosage, resulting in addition of other therapies or switching to other therapies, including opioids.[9]

Gastroretentive Formulation of Gabapentin

Gabapentin's absorption characteristics—its active and saturable uptake within a narrow absorption window in the upper small intestine—pointed to the utility of a gastroretentive (GR) dosage form to improve the absorption of gabapentin at clinically relevant doses.

GRALISE® (gabapentin) tablets are indicated for the management of postherpetic neuralgia, and employ a unique polymer-based technology that has been successfully used in 2 previously US Food and Drug Administration–approved drug products, metformin (Glumetza®) and ciprofloxacin (Proquin® XR). The technology was designed to optimize drug delivery to gabapentin's primary site of absorption in the upper small intestine. The GRALISE tablets typically measure at least 10 mm in 2 dimensions and are shaped as a modified oval to ease swallowing and to prevent release of the tablet from the stomach via gastric emptying immediately after ingestion with a meal. Within 20 minutes of contact with gastric juices, GRALISE tablets swell to a size that exceeds the open pyloric diameter

Figure 1. Release and Absorption of Gabapentin From GRALISE Tablets Administered Once Daily With the Evening Meal[15]



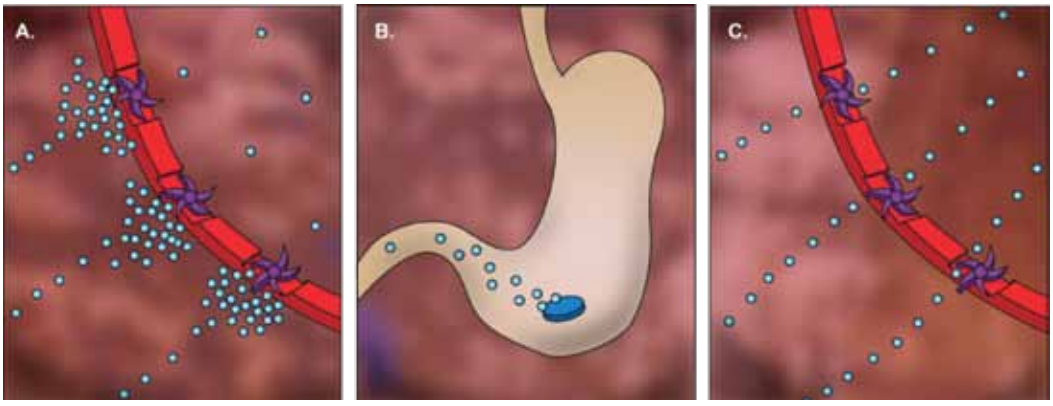
15 Minutes: Tablet absorbs water from gastric juices and begins to expand to 3 times its original size.
2 Hours: Enlarged tablet is retained in the stomach, and gradually releases drug.
8 to 9 Hours: All gabapentin has been released from GRALISE tablets; upper small intestine (the site of optimal absorption) is bathed in gabapentin.
15 Hours: GRALISE tablets completely dissolved; all gabapentin in circulation.
Source: Mathis JT, Cowles V, Sweeney M. Once-daily gabapentin for the treatment of postherpetic neuralgia [abstract]. *J Am Pharm Assoc.* 2012;52:271.

of 12 mm in the fed state,[14] and the tablets continue to swell over the next 2 hours to 3 to 4 times their original size (**Figure 1**).[15] At that size, GRALISE tablets are consistently retained in the stomach for approximately 8 to 9 hours when taken with a meal. In contrast, gabapentin TID tablets release over 90% of the drug in 30 minutes, with C_{max} occurring in 2 to 3 hours after oral administration. Thus, GRALISE tablets take significantly longer to release the same proportion (ie, 90%) of gabapentin from the tablet than do gabapentin TID tablets (~8 hours vs <0.5 hour) (Figure 1).[15-17] The combination of a prolonged release of gabapentin from the tablet and a prolonged retention of the tablet in the fed state are critical to the ability of GRALISE tablets to provide a gradual and prolonged presentation of gabapentin to the primary absorption site in the upper small intestine (**Figure 2**).[15] Based on the mechanism of absorption of gabapentin, it is expected that such delivery would minimize the saturation of the transporter, especially at higher doses, resulting in better absorption, higher plasma concentrations, and enhanced bioavailability (Figure 2).[8,15] In addition, GRALISE can be administered at the recommended 1800 mg per day of gabapentin as a once-daily dose taken with the evening meal. Once-daily administration of GRALISE may allow faster titration to a therapeutic dosage. Also, less frequent dosing may help improve adherence.[6]

Comparison of Pharmacokinetic Properties of Gabapentin TID and GRALISE Formulations

Studies conducted to compare the pharmacokinetic (PK) properties of gabapentin TID with once-daily GRALISE in healthy volunteers revealed distinct oral absorption properties of GRALISE.[8,18] Plasma concentration-time profiles showed that GRALISE has a prolonged time and slower rise to peak plasma concentration with an extended plateau. Increases in calorie and fat content of the meal resulted in a higher C_{max}, a longer time to reach C_{max}, and higher AUC compared with the same dosage taken without a meal or with a meal with fewer calories and/or lower fat content.[8,18] In addition, compared with gabapentin TID, the GRALISE formulation exhibits better dosage proportionality. Studies on effects of dosage on PK profiles and bioavailability in humans demonstrated that when gabapentin TID is given as a single dose of 1800 mg, the AUC is approximately 60% when compared with the same dosage of gabapentin TID given as 3 divided doses (600 mg TID).[2,8] In contrast, a dose-

Figure 2. Comparison of Absorption for Gabapentin TID and GRALISE[15]



TID indicates three times daily.
The saturable transporters located primarily in the upper small intestine are represented by purple pinwheels.
A. Gabapentin released from gabapentin TID reaches the transporters in bolus, saturating the transporters and limiting absorption.
B. As a result of their gastroretentive formulation, GRALISE tablets are held in the stomach for several hours where they gradually release gabapentin.
C. Gabapentin released from GRALISE reaches the transporters at a more steady rate over a longer period of time, allowing more linear absorption.
Source: Mathis JT, Cowles V, Sweeney M. Once-daily gabapentin for the treatment of postherpetic neuralgia [abstract]. *J Am Pharm Assoc.* 2012;52:271.

proportionality PK study of once-daily GRALISE (600- to 2400-mg single doses) demonstrated better proportionality between increasing dosage and plasma exposure as measured by AUC. This is illustrated in **Figure 3**, where the plasma concentrations of a single 600-mg dose (set at 100%) of GRALISE and gabapentin TID formulations are plotted as a function of dose.[2,8,18] For GRALISE, the reduction in AUC, and hence, relative bioavailability, with increasing dosage is less prominent than for the gabapentin TID formulation. Studies comparing the PK properties between GRALISE 1800 mg once daily with a high calorie evening meal (50% from fat) and gabapentin TID (600 mg TID) demonstrated an equivalent AUC between the 2 formulations,[18] confirming that the GR technology allows administration of the entire 1800-mg daily dosage of gabapentin as 1 dose without reducing bioavailability.

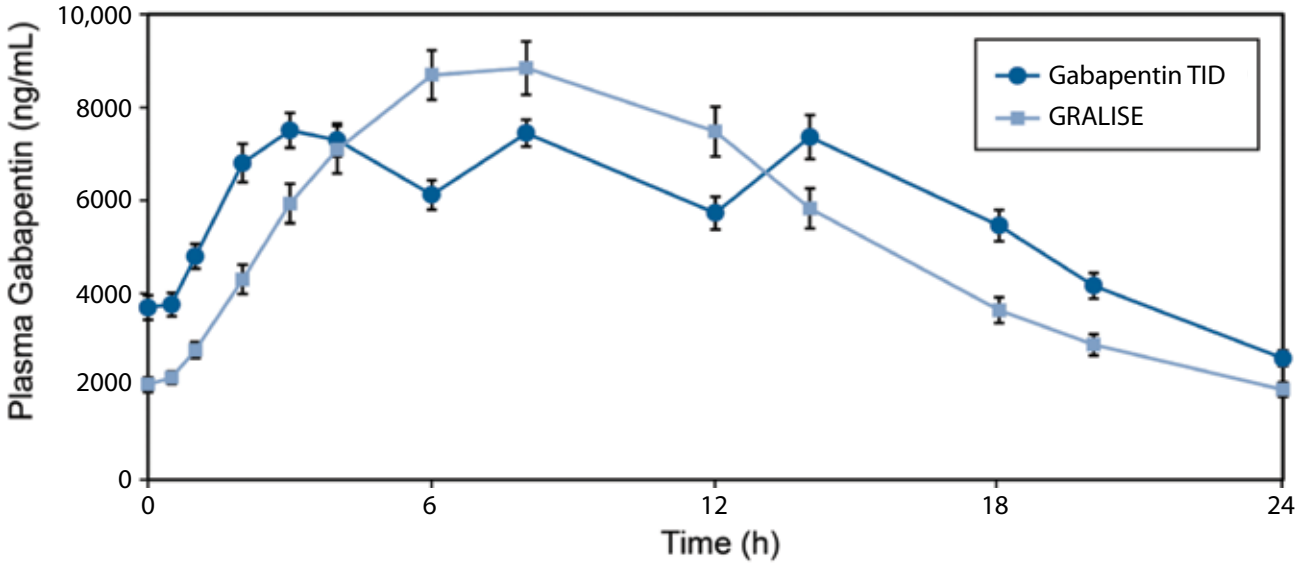
Efficacy and Safety of GRALISE

The efficacy of GRALISE 1800 mg administered once daily with the evening meal was demonstrated in placebo-controlled clinical studies. Patients with PHN underwent 2 weeks of dosage titration to 1800 mg/day (day 1: 300 mg; day 2: 600 mg; days 3-6: 900 mg; days 7-10: 1200 mg; days 11-14: 1500 mg; and day 15: 1800 mg), followed by 8 weeks of stable dosing. Using this dosing regimen, only 9.7% of patients treated with GRALISE and 6.9% of patients treated with placebo discontinued from the study due to adverse events.[19] Discontinuations from the study during the 2-week titration period were also low: 3.6% of patients treated with GRALISE and 3.0% of patients treated with placebo,[20] indicating that the 2-week titration schedule was well tolerated.

The types of adverse events reported in these clinical studies were generally similar to those observed for gabapentin TID, the most commonly reported events being dizziness and somnolence. The incidence of these adverse events was low: 10.9% for dizziness and 4.5% for somnolence.[19] Furthermore, once-daily dosing of GRALISE with the evening meal yielded peak concentration of gabapentin while the patient was asleep, a time when side effects of dizziness and somnolence are less likely to bother patients.

Peripheral edema was also reported as a common adverse event, and a subgroup analysis revealed a slightly higher incidence of peripheral edema in patients 65 years and older compared with patients younger than 65 years.[21] However, integrated analyses in patients 75 years and older did not show a similar increase in the incidence of peripheral edema in older patients.[22] Across all GRALISE

Figure 3. Comparison of Plasma Concentrations of Gabapentin Following Administration of GRALISE and Gabapentin TID[18]



TID indicates three times daily.
GRALISE is given once daily with the evening meal; gabapentin TID is given 3 times daily.
Reprinted with permission from Gordi T, Hou E, Kasichayanula S, Berner B. *Clin Ther*. 2008;30:909-916.

clinical trials, the other most common adverse reactions (≥2% vs placebo) were headache, diarrhea, dry mouth, and nasopharyngitis. Please see the full prescribing information including Medication Guide for additional safety information.

Dosage and Administration of GRALISE

GRALISE is available in 300-mg and 600-mg tablets. In clinical studies, GRALISE was well tolerated when titrated up to a daily dosage of 1800 mg over a period of 15 days.[2] To simplify dosage titration, a 30-day starter pack that includes the 2-week titration is available. The starter pack includes dosage steps at 300 mg/day (day 1), 600 mg/day (day 2), 900 mg/day (days 3-6), 1200 mg/day (days 7-10), and 1500 mg/day (days 11-14). The 1800-mg/day dosage is administered (as three 600-mg tablets) once daily with the evening meal. Because the tablets must remain whole to be retained in the stomach, they must not be split, crushed, or chewed prior to swallowing. If the GRALISE dosage is to be reduced, or if GRALISE is to be discontinued or substituted with an alternative treatment, it is recommended in the GRALISE prescribing information that dosage reduction be done gradually over a minimum of 1 week or longer (at the discretion of the prescriber).[19] GRALISE is contraindicated in patients with demonstrated hypersensitivity to the drug or its ingredients. GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

Economic Impact of Adding GRALISE to Treatment Options for PHN

A retrospective database analysis of 1645 patients taking gabapentin or pregabalin for treatment of PHN demonstrated that the economic burden of PHN in terms of total annualized direct costs ranged from $10,054 for commercially insured patients to $17,972 for Medicaid patients (2001-2003 US costs). Part of these costs were derived from the additional office visits and added medications required when therapy with gabapentin TID or pregabalin did not effectively control pain due to PHN.[23] The ability to titrate to an effective dose of GRALISE within 2 weeks may also help to reduce the use of add-on therapies including opioids, which bear additional costs due to office visits and potential side effects of their own that may also require treatment.

Conclusions

Patients taking immediate-release formulations of gabapentin for the treatment of PHN reach therapeutically effec-

tive dosages at a relatively low rate. This often results in switching of therapy, or addition of therapy, which in turn leads to greater costs. By releasing gabapentin gradually over a longer period of time, GRALISE reduces saturation of the uptake transporter, increasing absorption and making it easier for patients to reach an efficacious dosage. Thus, GRALISE may help to reduce therapy switching or the use of add-on therapies such as opioids, which bear additional costs, not only in terms of medication costs, but also office visits, potential side effects, and potential drug-drug interactions. The low incidence of side effects associated with GRALISE may decrease the need for side effect management with associated costs (eg, office visits) and increases the likelihood of achieving an effective dose to manage pain in PHN. Our analyses found that the economic impact of these benefits from GRALISE may lead to non-pharmacy cost savings and a cost-neutral total budget impact from GRALISE.

Acknowledgments

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