New Drug Overview
Gralise® (gabapentin)

Medication

- **Class:** anticonvulsant, miscellaneous
- **Food and Drug Administration Approved Indication**: management of postherpetic neuralgia (01/28/2011)[1]
- **Mechanism of Action:** Modulation of the α2Δ subunit of voltage-gated calcium channels.[1]
- **Availability:**[1,2]

Generic (Trade Name)	Dosage Form/Strength	Generic Availability
Gabapentin (Gralise®)	**Tablet: 300, 600 mg**	**-**
Gabapentin (Neurontin®*)	Capsule:* 100, 300, 400 mg Solution: 250 mg/5 mL Tablet:* 600, 800 mg	✔
Gabapentin enacarbil (Horizant®)	Extended-release tablet: 300, 600 mg	-

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Different formulation of a well established agent in the management of postherpetic neuralgia (PHN).
- Clinical trial information demonstrating the safety and efficacy of Gralise® is not published.
    - Because gabapentin immediate-release had prior Food and Drug Administration (FDA)-approval for PHN, the FDA required a single trial to establish the efficacy of the new formulation for this indication.[3]
- In an 11 week, placebo-controlled trial of patients with PHN persisting for at least six months following healing of herpes zoster rash (N=452), treatment with Gralise® significantly improved pain scores compared to placebo (*P* value not reported).[1]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[4-6]
    - Tricyclic antidepressants, gabapentin and pregabalin are recommended first-line for the treatment of post herpetic neuralgia (PHN).
    - Topical lidocaine is recommended second-line, but may be considered first-line in elderly patients.
    - Capsaicin cream and opioids are also recommended as second-line treatment options.
- Other Key Facts:
    - Gralise® is not interchangeable with other gabapentin preparations because of differing pharmacokinetic profiles that affect the frequency of administration.[1]
        - Gralise® should be titrated to 1,800 mg administered once daily with an evening meal.
    - For other gabapentin preparations, up to 3,600 mg/day of gabapentin has been evaluated in clinical trials for the treatment of PHN; however, doses >1,800 mg/day do not generally show greater benefit.[7]
        - Treatment is to be administered in divided doses, typically three times daily.
    - Gralise® has not been evaluated in patients with epilepsy.[1]
    - A 30 day starter pack of Gralise® is available.[1]
    - Gabapentin immediate-release and other recommended treatment options for PHN are available generically.

References

1. Gralise® [package insert]. Menlo Park (CA): Depomed, Inc.; 2011 Nov.
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3. No authors listed. Once-daily gabapentin (Gralise) for postherpetic neuralgia. Med Lett Drugs Ther. 2011 Nov;53(1378):94.
4. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010 Sep;17)9):1113-e88.

5. Dubinsky RM, Kabbani H, El-Chami, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2004;63:959.
6. American Academy of Family Physicians. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management [guideline on the Internet]. Charlottesville, Virginia: The American Academy of Family Physicians; 2005 [cited 2012 Feb]. Available from: http://www.aafp.org/afp/2005/0915/p1075.pdf.
7. Gabapentin capsule, tablet, and suspension [package insert]. Peapack (NJ): Greenstone LLC; 2011 Sep.

New Drug Review

Generic Name: (gabapentin)
Trade Name: (Gralise®)
Manufacturer: Depomed Inc.
Food and Drug Administration Approval Date: January 28, 2011
Product Launch Date: October 10, 2011

Overview/Summary

Gralise® (gabapentin) is a new once-daily formulation of the antiepileptic drug gabapentin that is Food and Drug Administration (FDA)-approved for the management of postherpetic neuralgia (PHN).[1] Gabapentin immediate-release (IR) is also indicated for the management of PHN; however, it is dosed three times a day.[2] Gabapentin is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid, and it is believe that its mechanism of action in relieving pain is due to modulation of the α2Δ subunit of voltage-gated calcium channels.[1,3] Specifically, this new formulation of gabapentin (Gralise®) is a gastroretentive tablet; therefore, it swells in gastric fluid and remains in the upper gastrointestinal tract, gradually releasing gabapentin over approximately 10 hours.[3] Due to differing pharmacokinetic profiles, Gralise® (gabapentin) is not interchangeable with other gabapentin products.[1]

Similar to gabapentin IR, the recommended total daily dose of Gralise® (gabapentin) is 1,800 mg. Both formulations require a titration schedule to achieve the effective maintenance dosage; however, with Gralise® (gabapentin) the period of titration should occur over 14 days compared to three days with gabapentin IR. The safety profiles of both formulations appear similar, with dizziness and somnolence being the most frequently reported adverse events with both.[1,2]

Because gabapentin IR had prior FDA-approval for the management of PHN, the FDA required a single trial to establish the efficacy of the new formulation for this indication. FDA-approval was based on an 11 week, placebo-controlled trial evaluating gabapentin 1,800 mg once-daily in 452 patients with PHN for at least six months. Results demonstrated that patients receiving gabapentin had significantly greater improvements in pain scores compared to placebo.[1,3] No head-to-head trials with other formulation of gabapentin have been conducted.[1]

Current clinical guidelines recommend tricyclic antidepressants, gabapentin, and pregabalin first-line for the management of PHN. Other recommended second-line therapies include topical lidocaine, particularly in elderly patients, opioids, and capsaicin cream. Guidelines do not distinguish or give preference to one specific formulation of gabapentin.[4-6]

Pharmacokinetics

Gralise® (gabapentin) is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.[1]

Table 1. Pharmacokinetics[7]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Gabapentin	Not reported	Not reported	None	5 to 7

Clinical Trials

Food and Drug Administration-approval of gabapentin (Gralise®) for the management of postherpetic neuralgia (PHN) was based on the evidence of safety and efficacy derived from one, 11 week, unpublished, placebo-controlled trial.[1,3] According to the approved package labeling, adult patients (21 to 89 years of age) with at least a six month history of PHN following healing of herpes zoster and a minimum baseline pain intensity score of at least four on an 11-point numerical pain rating scale (ranging from 0 [no pain] to 10 [worst pain]) were randomized to gabapentin 1,800 mg or placebo once-daily.

Treatment with gabapentin significantly improved the endpoint of mean pain score from baseline compared to placebo.[1]

Special Populations

Table 2. Special Populations[1]

Population	Precaution
Elderly	Use with caution as elderly patients are more likely to have decreased renal function.
Renal Dysfunction	Renal dosage adjustment required with renal dysfunction (specifics not reported). Contraindicated with creatinine clearances 15 to 30 mL/minute or in patients undergoing hemodialysis.
Hepatic Dysfunction	Not studied in hepatic dysfunction.
Pregnancy/ Nursing	Pregnancy category: C. Excretion through breast milk: Unknown; use with caution.
Children	Safety and efficacy in children have not been established.

Adverse Drug Events

Table 3. Adverse Events (%)[1]

Adverse Event	Gabapentin
Cardiac	
Blood pressure increase	✔
Hypertension	✔
Central Nervous System	
Confusional state	✔
Dizziness	10.9
Headache	4.2
Lethargy	1.1
Memory impairment	✔
Somnolence	4.5
Ear and Labyrinth Disorders	
Vertigo	1.4
Gastrointestinal	
Constipation	1.4
Diarrhea	3.3
Dry mouth	2.8
Dyspepsia	1.4
Nausea	✔
General Disorders	
Pain	1.1
Peripheral edema	3.9
Infections and Infestations	
Herpes zoster	✔
Nasopharyngitis	2.5
Pneumonia	✔
Upper respiratory infection	✔
Urinary tract infection	1.7
Viral gastrointestinal	✔
Investigations	
Weight increased	1.9

Adverse Event	Gabapentin
Musculoskeletal and Connective Tissue Disorders	
Back pain	1.7
Joint swelling	✔
Pain in extremity	1.9
Other	
Pyrexia	✔
Rash	✔
Seasonal allergy	✔

✔ Percent not specified.

Contraindications/Precautions

Gabapentin is contraindicated with demonstrated hypersensitivity to the drug or any component of the formulation.[1]

Gralise® (gabapentin) is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.[1]

The safety and efficacy of Gralise® (gabapentin) in patients with epilepsy has not been evaluated.[1]

Antiepileptic drugs, including gabapentin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Because of this, patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.[1]

Gabapentin should be withdrawn gradually; treatment discontinuation should occur gradually over a minimum of one week or longer.[1]

In standard pre-clinical *in vitro* lifetime carcinogenicity trials with gabapentin, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. The clinical significance of this finding is unknown. Furthermore, the effect of gabapentin on the incidence of new tumors in humans or on the worsening or recurrence of previously diagnosed tumors is unknown.[1]

Drug Reaction with Eosinophilia and Systemic Symptoms, also known as Multiorgan Hypersensitivity, has been reported with the use of antiepileptic drugs, including gabapentin. Some of these events have been fatal or life-threatening. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.[1]

Clinical trial data do not indicate that routine monitoring of clinical laboratory procedures is necessary for the safe use of gabapentin. The value of monitoring gabapentin blood concentrations has not been established.[1]

Drug Interactions

There are no clinically significant drug interactions associated with gabapentin.[8]

Dosage and Administration

Gralise® (gabapentin) cannot be used interchangeably with other gabapentin products.[1]

Table 4. Dosing and Administration[1]

Adult Dose	Pediatric Dose	Availability
Management of postherpetic neuralgia: Tablet: initial, 300 mg QD for one day, followed by 600 mg QD for one day, followed by 900 mg QD for four days, followed by 1,200 mg	Safety and efficacy in children have	Tablet: 300 mg 600 mg

Adult Dose	Pediatric Dose	Availability
QD for four days, followed by 1,500 mg QD for four days, followed by 1,800 mg QD; maintenance, 1,800 mg QD	not been established.	

QD=once-daily

Potential Advantages

- Gralise® (gabapentin) provides another treatment option for the management of postherpetic neuralgia (PHN).
- Gralise® (gabapentin) is a new formulation of a well established agent in the management of PHN.
- Gralise® (gabapentin) is available for once-daily dosing.

Potential Disadvantages/Unanswered Questions

- There are a lack of head-to-head trials with other gabapentin preparations.
- Gabapentin immediate-release is available generically.

Clinical Guidelines

Table 5. Clinical Guidelines

Clinical Guideline	Recommendations
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[4]	Postherpetic neuralgia (PHN) • Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin. • Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. • Strong opioids and capsaicin cream are recommended as second-line therapies.
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[5]*	• Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN. • There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. • Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. • Aspirin cream is possibly effective in the relief of pain in patients with PHN, but the magnitude of benefit is low, as seen with capsaicin. • In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. • The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN. • There is insufficient evidence to make any recommendations on the long-term effects of these treatments.
American Academy of Family Physicians: **Herpes Zoster and Postherpetic**	Prevention of PHN • Administration of antiviral agents within 72 hours of onset of acute herpes zoster can increase healing rates and decrease the incidence and duration of PHN. • Amitriptyline can be used to decrease the risk of PHN in older patients.

Clinical Guideline	Recommendations
Neuralgia: Prevention and Management (2005)[6]	Management of PHN • Tricyclic antidepressants and gabapentin should be used to decrease the pain associated with PHN. • Lidocaine patch, topical capsaicin and opioids can be used to decrease PHN pain.

*Information is current as of February 2012.

Conclusions

Gralise® (gabapentin) is a new once-daily formulation of the antiepileptic drug gabapentin that is Food and Drug Administration (FDA)-approved for the management of postherpetic neuralgia (PHN).[1] Gabapentin immediate-release (IR) is also indicated for the management of PHN; however, it is dosed three times a day.[2] This new formulation of gabapentin (Gralise®) is a gastroretentive tablet; therefore, it swells in gastric fluid and remains in the upper gastrointestinal tract, gradually releasing gabapentin over approximately 10 hours.[3] Due to differing pharmacokinetic profiles, Gralise® (gabapentin) is not interchangeable with other gabapentin products.[1]

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Current clinical guidelines recommend tricyclic antidepressants, gabapentin, and pregabalin first-line for the management of PHN. Other recommended second-line therapies include topical lidocaine, particularly in elderly patients, opioids, and capsaicin cream. Guidelines do not distinguish or give preference to one specific formulation of gabapentin.[4-6]

References

1. Gralise® [package insert]. Menlo Park (CA): Depomed, Inc.; 2011 Nov.
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