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Improved Lidocaine Patch Adhesion Expands Treatment Options

Faculty

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Introduction

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster (shingles),[1] which develops following reactivation of the varicella-zoster virus (VZV).[2] PHN describes a syndrome of persistent neuropathic pain (duration >3 months) following resolution of the herpes zoster rash[2]; the reactivation of latent VZV also may produce chronic neuropathic pain similar to PHN pain without the presence of a rash.[3] PHN-associated herpes zoster pain may be perceived as constant or intermittent burning, aching, or throbbing that occurs with or without stimulus[4]; a majority of patients with PHN (~70%) develop allodynia.[4] PHN pain is similar to other pain conditions, as its initial clinical presentation is acute before developing into chronic, intermittent, or stimulus-evoked forms.[4,5]

With no disease-modifying therapy currently available for PHN,[6] treatment has been based on symptom management, using both systemic and topical approaches.[7] Over the past 20 years, the 5% lidocaine topical patch has emerged as a widely used treatment modality[6]; however, difficulties with patch adhesion and a resultant reduction in patient treatment compliance have been reported.[6] A recent poll of patients and caregivers by market research company Harris Insights & Analytics revealed that 85% of patients with PHN using 5% lidocaine patches had experienced patch detachment or had moved at least once during prescribed 12-hour treatment.[8]

To address these issues, ZTlido, a novel 1.8% lidocaine topical system, has been developed by Scilex Pharmaceuticals.[6] ZTlido uses a proprietary, single-layered polymer matrix system that is bioequivalent to the 5% lidocaine patch to provide equivalent drug delivery in the treatment of PHN pain.[9] This article summarizes existing data on ZTlido and offers guidance on its appropriate use in clinical practice.

Benefits of Topical Agents in PHN

Because PHN pain may persist for years, pharmacotherapy often is required for prolonged periods— a significant concern, given many of those with PHN are elderly and may have experienced declines in cognitive and physical function and/or developed age-related comorbidities that include the use of multiple prescription medications.[5,10] Elderly patients may have altered pharmacokinetics or altered clearance of drugs compared with younger, healthier patients, potentially placing them at risk for clinically relevant drug-to-drug interactions (DDIs).[10] Oral systemic agents used to treat PHN may cause adverse events (AEs) that are amplified and/or deleterious in older adults[10]; as a result, systemic medications must be prescribed with caution and careful titration.

Given these considerations, topical agents have emerged as an attractive option.[11] Applied directly to the affected skin, topical analgesics act locally as opposed to transdermal analgesics, which are absorbed systemically and act at remote sites within the central nervous system (eg, buprenorphine, fentanyl).[10] With the lower systemic levels, the risk for DDIs and systemic AEs generally is lower for topical modalities than for oral agents; in addition, topical analgesics do not require dose titration and may be more convenient for some patients, particularly those who have difficulty with oral medications (eg, difficulty swallowing).[12-14]

Please see Important Safety Information on page 4 and full Prescribing Information attached.

5% Lidocaine Patch

One of the most commonly prescribed topical analgesics to date, the 5% lidocaine patch (Lidoderm®), was first approved by the FDA for the relief of pain associated with PHN in 1999.[15] Extensive postmarketing surveillance has confirmed the favorable safety profile of the 5% lidocaine patch, now available in generic form, with multiple studies confirming that the product is easy to use and is well tolerated, with the most frequently reported AEs occurring at the application site (ie, erythema, pruritus, rash, edema).[9,16]

Poor Adhesion

Despite positive findings, research suggests use of the 5% lidocaine patch remains relatively low in PHN patients. A recent analysis found that the patch was used as first-line treatment in 8% of patients (22% by contrast received opioid analgesics).[17] It has been suggested that this low utilization may be due to poor adhesion seen in conventional lidocaine patches.[6] Since its initial approval of the product, the FDA has received numerous reports of inadequate adhesion for branded and generic topical lidocaine patches.[18] In fact, of the 1,936 total cases reported to the FDA's Adverse Event Reporting System as of March 2018, 1,347 (69.6%) were related to poor adhesion.[6] The adhesive performance of topical patches is a critical factor that may determine drug delivery and patient compliance.[6,19]

In the aforementioned Harris poll of 153 US patients with PHN who used the 5% lidocaine patch, 49% of respondents said the patches "sometimes," "rarely," or "never" stayed in place, and 85% reported some detachment issues at least once during the 12-hour treatment period.[8] Forty-six percent of respondents said they used tape to help keep the patches in place over the area of pain or attached to the skin.[8] In addition, 51% said their patch became detached or moved off the application area at least 3 times during the treatment period.[8] Because of these issues, 49% switched patch brands at least once and 16% stopped using the patch altogether.[8]

Improved Adhesion With ZTlido

Like the 5% lidocaine patch, ZTlido is indicated for the relief of pain associated with PHN.[9] It is applied to the skin once for up to 12 hours within a 24-hour period (12 hours on and 12 hours off).[9] Because of differences in bioavailability of ZTlido (~45%) compared with Lidoderm (3±2%), only 36 mg of lidocaine are needed in ZTlido (vs 700 mg in Lidoderm) to deliver the same dose of lidocaine (~15 mg). Additionally, 1.8% (ZTlido) and 5% (Lidoderm) represent the percent ratio of lidocaine to adhesive, not dose strength.[9] Regardless of the difference in dose, ZTlido has been shown to be bioequivalent to the 5% lidocaine patch.[9] In clinical studies, mean plasma lidocaine concentrations with both products increased during the application period, reaching mean peak concentrations at 12.8 hours for ZTlido 1.8% and 11 hours for the 5% lidocaine patch.[9,20]

Table. ZTlido® Demonstrated Superior Adhesion to a Generic 5% Lidocaine Patch In a Head-to-Head Study

	ZTlido (n=24)	Generic 5% Lidocaine Patch (n=24)
Total Number of Patches Detached After 12-h Administration Period, (n) %	0 (0)	7 (29)
After 3 h		1
After 9 h		2
After 12 h		4
Mean Adhesion at 12-h Administration Period, %	93.4 (P<0.0001)	26.8 (P<0.0001)

Based on reference 24.

Please see Important Safety Information on page 4 and full Prescribing Information attached.

ZTlido has been developed with proprietary adhesion patch technology, and is 7 times lighter and 50% thinner than Lidoderm.[9,21,22] It is the first and only lidocaine patch proven to maintain greater than 90% adhesion in more than 90% of patients at the end of the prescribed 12-hour administration period.[23] In addition, ZTlido demonstrated superior adhesion to a generic 5% lidocaine patch (Mylan) in a head-to-head study, with mean adhesion at 12 hours of 93.4% for ZTlido versus 26.8% for the generic lidocaine patch ($P<0.0001$). Twenty-nine percent of the generic patches completely detached versus 0% for ZTlido (Table).[24] There were 2 AEs (pruritus) with ZTlido and none for the generic, but they did not rise to the level of clinical significance.[25]

ZTlido in Clinical Practice

With its improved adhesion, ZTlido is an important addition to the PHN pain management armamentarium and can be utilized in a variety of patient types. For active patients, ZTlido is the only lidocaine patch proven to maintain adhesion during moderate exercise (tested after biking for 30 minutes).[9] Like other topical analgesics, ZTlido carries a low risk for systemic AEs and DDIs.[6,9] Improved adhesion means the patch is more likely to provide an adequate dose and that patients, particularly elderly patients, may be more likely to comply with the prescribed treatment.[6,19] Lidocaine patches have been shown to be effective in patients on multimodal systemic therapies (eg, gabapentin/pregabalin) for whom dose titration is needed but also complicated by comorbidities and potential DDIs.[26] Lastly, in patients using over-the-counter patches that have proved to be suboptimal at managing pain symptoms in these patients, ZTlido offers an effective alternative.

Conclusion

ZTlido has been shown to be an effective and well-tolerated treatment option for the management of PHN.[6] As it is a topical lidocaine system, ZTlido mitigates the systemic AEs associated with oral therapies.[12-14] AEs associated with use of lidocaine patches tend to be mild, self-terminating, and relate mainly to application site reactions.[27] The development of ZTlido allows clinicians to provide pain control for patients with PHN while mitigating the adhesion problems found in older, conventional lidocaine patches.[6]

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Please see Important Safety Information on page 4 and full Prescribing Information attached.

Indication and Important Safety Information

Indication

ZTLIDO is indicated for relief of pain associated with post-herpetic neuralgia (PHN).

Important Safety Information

Contraindications

ZTLIDO is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

Warnings and Precautions

Accidental exposure can occur even after a ZTLIDO patch has been used. Small children or pets could suffer serious adverse effects from chewing or ingesting a new or used ZTLIDO patch. Store and dispose of patches properly and keep out of reach of children and pets.

Excessive dosing or overexposure to lidocaine can occur. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increased blood concentration levels of lidocaine. If lidocaine overdose is suspected, check drug blood concentration. Management of overdose includes close monitoring, supportive care, and symptomatic treatment.

Cases of methemoglobinemia have been reported with local anesthetic use, although patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, or concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. Signs and symptoms include cyanotic skin discoloration and/or abnormal coloration of the blood and may occur immediately or may be delayed after exposure. Methemoglobin levels may continue to rise leading to more serious central nervous system and cardiovascular adverse effects. Discontinue ZTLIDO and any other oxidizing agents. Depending on severity of the symptoms, patients may respond to supportive care or may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Application site reactions can occur during or immediately after treatment with ZTLIDO. This may include development of blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours. Inform patients of these potential reactions and that severe skin irritation may occur with ZTLIDO if applied for a longer period than instructed.

Hypersensitivity cross-reactions may be possible for patients allergic to PABA derivatives. Manage hypersensitivity reactions by conventional means.

Eye exposure with ZTLIDO should be avoided. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye (eg, eye glasses/eye wear) until sensation returns.

Adverse Reactions

Side effects of ZTLIDO include application site reactions such as, irritation, erythema, and pruritus. These are not all of the adverse reactions that may occur. Please see full Prescribing Information for more information.

Use in Specific Populations

Use of ZTLIDO during lactation should be used with caution as lidocaine is excreted into breast milk. The limited human data with lidocaine in pregnant women are not sufficient to inform drug-associated risk for major birth defects and miscarriage.

To report SUSPECTED ADVERSE REACTIONS, contact SCILEX Pharmaceuticals Inc. at 1-866-SCILEX3 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Disclosure
Dr Pergolizzi reported that he is a consultant to BioDelivery Sciences International, Neumentum, Salix Pharmaceuticals, and US WorldMeds; has received honoraria from Salix Pharmaceuticals and US WorldMeds; has received grant/research support from EMF Medical and Salix Pharmaceuticals; has received speaking fees from BioDelivery Sciences International, Salix Pharmaceuticals, and US WorldMeds; and has stock ownership in Enalare Therapeutics and Neumentum.

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