Post-herpetic neuralgia (PHN), a neuropathic pain disorder resulting from nerve fiber damage following herpes zoster (HZ) infection, is caused by reactivation of the varicella zoster virus (VZV). VZV reactivation leads to the symptom complex commonly known as shingles. PHN is defined as VZV-associated pain persisting for more than 3 months after resolution of a VZV infection. PHN symptoms often include allodynia, whereby normally innocuous stimuli, such as the light brushing of the skin, can elicit pain, paresthesia, and dysesthesia. The incidence of PHN increases with age. In population-based data from 1996 to 2005, out of 1,669 adult residents (≥22 years) of Olmsted County, MN, US, the proportion of individuals who developed PHN increased from 5% in those aged <60 years to 10% in those aged between 60 and 69 years, 17% in those aged 70 to 79 years, and 20% in individuals aged ≥80 years. Apart from age, other risk factors for PHN include severe acute pain related to the VZV infection, rash severity (>50 lesions), and the presence of a prodrome.

Pharmacologic Treatments and Unmet Needs
Guidelines issued by the American Academy of Neurology, the International Association for the Study of Pain, and the European Federation of Neurological Societies categorize tricyclic antidepressants (TCAs), anticonvulsants such as gabapentin and pregabalin, and the lidocaine 5% topical patch as first-line treatments for PHN. TCAs, gabapentin, and topical lidocaine have demonstrated efficacy in reducing the pain of PHN and have mostly acceptable tolerability profiles. In a recent systematic review and meta-analysis of 229 studies, the use of TCAs, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin were strongly recommended. The use of TCAs in treating PHN, however, is hampered by a slow onset of action and systemic adverse events such as urinary retention, weight gain, constipation, and sedation. TCAs have also been associated with cardiotoxic events, including myocardial infarction and cardiac dysthymias. Elderly patients appear particularly susceptible to these
The Role of the Capsaicin 8 % Patch (Qutenza®) in the Treatment of Postherpetic Neuralgia

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components, including microtubules. Thus, multiple mechanisms are crucial for capsaicin’s mechanism of action. Intra-epidermal nerve fibers containing substance P are depleted by capsaicin; this depletes substance P from the CNS. Natural stimuli such as tissue burns, noxious heat, and spider toxins can activate TRPV1-expressing C-fibers, which may play an essential role in the chronic pain-induced plastic changes in the nociceptor nerve terminals.31–33

Unique Mechanism of Action
The transient receptor potential (TRP) family of ion channels are selective for calcium and magnesium over sodium ions. TRPV1 channels are expressed in the CNS in areas that process pain signals. TRPV1, a member of the TRP family of ion channels, is a calcium-permeable channel, which is modulated by a diverse range of exogenous noxious stimuli including pH changes, high temperatures, and irritant and pungent compounds. The capsaicin 8 % w/w; 640 µg/cm² patch (Qutenza®) is indicated in the US for the management of neuropathic pain associated with PHN. Capsaicin, 8-methyl-N-vanillyl-6-nonenamide (see Figure 1), is the active ingredient in chili peppers that evokes burning and “flare and weal” responses and is a highly selective agonist for the TRPV1 receptor. TRPV1 receptors are found on a portion of primary sensory neurons with cell bodies in the dorsal root ganglion and are selectively expressed in the epidermis cutaneous nociceptors making them accessible to local treatment. In general, the TRPV1-expressing neurons are peptidergic, small diameter, and give rise to thin, unmyelinated C fibers, which may play an essential role in the chronic pain-induced plastic changes in the CNS. Natural stimuli such as tissue burn, noxious heat, and spider toxins can activate TRPV1 expressing C-fibers.

Inactivation of voltage-gated sodium ion channels and direct pharmacologic desensitization of plasma membrane TRPV1 receptors may contribute to an immediate reduction in neural excitability and pain, while more persistent effects may be due to sustained increased levels of intracellular calcium. Such raised levels can activate calcium-dependent enzymes, such as proteases, which can induce depolymerisation of cytoskeletal components, including microtubules. Thus, multiple mechanisms are believed to be important for capsaicin-induced analgesia (see Figure 2). Capsaicin-induced local depletion of substance P is not thought to be crucial for capsaicin’s mechanism of action. Intra-epidermal nerve fibers degenerate following high-dose capsaicin application; these nerve fiber endings have been shown to recover after 24 weeks in healthy volunteers.

Pharmacokinetic Profile
The capsaicin 8 % dermal patch measures 280 cm² and contains 179 mg of capsaicin (640 µg/cm²). Capsaicin is extremely lipophilic, having little affinity for the aqueous blood phase and is readily absorbed into the epidermal and dermal layers. To determine systemic capsaicin exposure after single 60 or 90 minute applications, plasma samples were collected in 173 patients with PHN at varying intervals after patch removal (0, 1, 3, 6, and 24 hours). Overall, the majority of plasma concentrations of capsaicin were lower than 10 ng/ml; capsaicin plasma levels were found to decline rapidly, with a mean elimination half-life after patch removal of 1.64 hours. After a 60-minute application, the mean area under the plasma concentration time curve was 7.42 ng.h/ml and the maximum plasma concentration (Cmax) value was 1.86 ng/ml. The primary metabolites of capsaicin, hydroxy- and dehydrocapsaicin, were not detected in patients in this study.

Capsaicin is metabolized readily in the liver by various cytochrome P450 enzymes. During in vitro incubation with human skin, capsaicin was metabolized slowly over 20 hours. As only small quantities of drug reach the systemic circulation, there are no recommendations for dose adjustments in cases of hepatic or renal failure.

Clinical Experience
The capsaicin 8 % patch clinical development program comprised phase I, II, and III studies and is summarized in Tables 1, 2, and 3, respectively. For treatment of PHN, the capsaicin 8 % patch is applied for 60 minutes and then removed. In order to more fully blind patients in the trials, a low-concentration capsaicin 0.04% patch was used as an active control; this dose was selected because it induced erythema and a sensation of heat.
multicenter, randomized controlled trial (RCT), 42 % of PHN patients treated with the capsaicin 8 % patch reported a ≥30 % reduction in pain intensity compared with 32 % in the active control group (odds ratio [OR] 1.56, 95 % confidence interval [CI] 1.03 to 2.37; p=0.03; see Table 2). In this same study, the mean percent change in numerical pain rating scale (NPRS) score between baseline and weeks 2–12 was −29.9 % in the capsaicin 8 % patch group versus −20.4 % in the active control group. In another multicenter RCT in PHN, the mean percent change in NPRS score between baseline and weeks 2–8 was −32.0 % in the capsaicin 8 % patch group versus −24.4 % in the active control group (p=0.011). In the same study, a ≥30 % reduction in NPRS score was achieved in 46 % of capsaicin 8 % patch-treated patients compared with 34 % of active controls (p=0.02; see Table 3).

A meta-analysis that included seven RCTs of similar design investigated the capsaicin 8 % patch (1,120 with PHN; 338 with HIV-associated neuropathy [AN]). This meta-analysis was based on pooled individual patient data, for identical end-points, as if all patients were part of one large study. The percent change from baseline to weeks 2–12 was −30.7 % in the capsaicin 8 % patch and −22.7 % in the control group, which yielded a group difference of 8.0 % (95 % CI 4.6, 11.5) (p<0.001); the proportion of patients achieving a ≥30 % reduction in pain intensity was 44 % for the capsaicin 8 % patch-treated patients compared with 34 % for control-treated patients. In a separate meta-analysis of combined individual patient data (1,313 participants with PHN) from seven double-blind RCTs, 44 % of patients had a ≥30 % reduction in pain intensity, and 11 % of patients achieved complete pain relief 2–12 weeks after capsaicin 8 % patch treatment. In those responding to treatment, analgesia started within a few days of treatment and was sustained for an average of 8 months. In a Cochrane review of six studies involving 1,272 participants with PHN and 801 with HIV-AN, it was concluded that capsaicin 8 % patch treatment generated greater levels of pain relief than the active control in both PHN and HIV-AN. Point estimates of the numbers needed to treat were 8.8 (95 % CI 5.3–26) at 8 weeks and 7.0 (95 % CI 4.6–15) at 12 weeks.

The Qutenza Safety and Effectiveness in Peripheral Neuropathic Pain (QUEPP) study evaluated 1,044 patients without diabetes with peripheral neuropathic pain, who received a single application of the capsaicin 8 % patch, PHN was the most frequent diagnosis (31.9 %) followed by postsurgical neuralgia (22.8 %), post-traumatic neuropathy (12.4 %), polyneuropathy (14.3 %), and mixed pain syndromes (16.6 %). Mean relative pain intensity during weeks 1–12 decreased by 24.7 % (1.1 standard error of the mean [SEM]) and significant improvements in pain attacks (p<0.001), sleep duration (p<0.001), and sleep quality (p<0.001) were reported in the peripheral neuropathic pain patients. The ≥30 % responder rate was 42.7 % and the ≥50 % responder rate was 23.7 %. The use of opioids and anti-convulsants decreased significantly (p<0.001) in capsaicin 8 % patch-treated patients. In the QUEPP study, 146 adverse drug reactions were reported in 106 of 1,063 patients of the safety population (10.0 %); the most common among these were application site reactions, such as erythema and pain. In total, 27 serious adverse event (SAE) drug reactions were reported in 17 patients (1.6 %) and five SAEs resulted in death, none of which were treatment-related. The highest treatment response, relative change of numeric pain rating score on days 7–14 to week 12 compared with baseline, was seen in patients with a history of pre-existing peripheral neuropathic pain of <6 months, suggesting that early initiation of treatment may be advantageous. In patients with pre-existing peripheral neuropathic pain for <6 months, the mean relative change of the NPRS score on days 7–14 to week 12 versus baseline was −36.6 % (4.6 SEM; n=105).

Longitudinal analysis from four double-blind RCTs of the topical capsaicin 8 % patch has suggested that there are different response groups to treatment, which may be related to different pain mechanisms despite a presumed common underlying disease process. In this analysis, five distinct response subgroups were detected from data of 1,248 patients treated with the capsaicin 8 % patch, including a group of nonresponders, a group with partial response, and a group exhibiting full analgesic effect.

Overall, the clinical studies showed the capsaicin 8 % patch to be generally safe and well-tolerated (see Tables 1–3). The most commonly reported side effects were dermal irritation, erythema, and pain at the site of application. These effects were transient and mild to moderate in severity. This was emphasized by an integrated analysis of tolerability data from the capsaicin 8 % patch clinical program, including 1,696 patients with peripheral neuropathic pain related to PHN, HIV-AN, and painful diabetic neuropathy. Almost all (≥98 %) of the patients completed ≥90 % of the full treatment duration, regardless of the number of treatments given. NPRS score increases returned, on average, to baseline within 85 minutes following treatment. Transient patch application-related pain with the capsaicin 8 % patch was managed with local cooling or oral analgesics in nearly all cases. This indicated that patch application-related pain was not a barrier to use.

Role of Lidocaine Pre-treatment
To mitigate any discomfort, prior to treatment with the capsaicin 8 % patch, the product prescribing information states that patients should be pre-treated with topical anesthetic cream, such as lidocaine, for 60 minutes. Lidocaine reduces pain transmission through inhibition of sodium ion channels; sodium channels act independently of the TRPV1 receptors. Capsaicin can induce axonal depolarization and dysfunction even in the presence of sodium channel blockade. There are potential advantages in avoiding pre-treating patients with topical lidocaine including a reduction in total treatment time and a potential cost benefit. This was supported by a comparison of 32 pre-treated patients with 26 non-pre-treated patients receiving capsaicin 8 % patch treatment in which there was no significant

**Table 1: Phase I Studies Investigating the Capsaicin 8 % Patch**

<table>
<thead>
<tr>
<th>Study/Reference</th>
<th>Design</th>
<th>Parameter Investigated</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malmberg et al., 2004</td>
<td>Randomized controlled open-label study comparing C8P with capsaicin 0.04 % patch and control patch (n=20)</td>
<td>Epidermal nerve fiber density</td>
<td>Significant reduction in epidermal nerve fiber density observed in the C8P</td>
</tr>
<tr>
<td>Kennedy et al. 2010</td>
<td>Randomized controlled open-label study of long-term effects (n=36)</td>
<td>Epidermal nerve fiber density and quantitative sensory testing</td>
<td>Significant reduction in epidermal nerve fiber density</td>
</tr>
</tbody>
</table>

C8P = capsaicin 8 % patch.
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**Table 2: Phase II Studies Investigating the Capsaicin 8 % Patch**

<table>
<thead>
<tr>
<th>Reference</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Design</th>
<th>Treatment (Patient Numbers)</th>
<th>Main Efficacy Outcomes</th>
<th>Key Safety/Tolerability Outcomes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backonja et al., NCT0034710 2010²</td>
<td></td>
<td>Randomized, double-blind, controlled study with an open-label extension in PHN</td>
<td>C8P (n=32) or control patch* (n=12)</td>
<td>During days 8–28 after the double-blind treatment, C8P-treated patients had a mean change in NPRS score from baseline of –32.7 % versus –4.4 for control (p=0.003). Open-label extension: mean change from baseline morning and evening NPRS score during weeks 2–12 was –33.8 % for C8P and +4.9 % for control</td>
<td>TEAEs occurred in 42 % of C8P group and 17 % of control group</td>
</tr>
<tr>
<td>Webster et al., NCT00916942 2011¹</td>
<td></td>
<td>Open label in PNP</td>
<td>54 PHN patients, 52 with HIV-DSP</td>
<td>96 % of patients reported ≥1 TEAE. Most-frequently reported TEAEs were transient, mild-to-moderate application site erythema, pain, edema, and papules</td>
<td></td>
</tr>
<tr>
<td>Webster et al., NCT00082316 2010¹</td>
<td></td>
<td>Open label, randomized repeat treatments up to four patches, in PNP</td>
<td>117 patients (25 with PHN, 91 PDN, and 1 HIV-DSP) with three topical anesthetic formulations: (L.M.X.4®, Topoicaine® Gel or Betacaine Enhanced Gel 4)</td>
<td>Treatment with any of the topical anesthetics tested appeared to have a good safety profile and generally well tolerated. &gt;97 % of patients completed ≥90 % of the planned treatment</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Phase III Studies Investigating the Capsaicin 8 % Patch**

<table>
<thead>
<tr>
<th>Reference</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Design</th>
<th>Treatment (Patient Numbers)</th>
<th>Main Efficacy Outcomes</th>
<th>Key Safety/Tolerability Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backonja et al., NCT00115310 2008¹</td>
<td></td>
<td>Multicenter, double-blind, parallel-group in PHN</td>
<td>C8P (n=206) or control patch* (n=196)</td>
<td>From baseline to weeks 2–8, a ≥30 % reduction in pain intensity was achieved in 42 % of the C8P group versus 32 % of the control group (p=0.03). Mean change in NPRS score: –29.6 % in C8P group versus –19.9 % in control group (p=0.001)</td>
<td>TEAEs occurred in 99 % of C8P group versus 88 % of control group</td>
</tr>
<tr>
<td>Webster et al., NCT00061776 2010¹</td>
<td></td>
<td>Multicenter, randomized, double-blind, controlled dose finding study in PHN</td>
<td>C8P (n=222) or control patch* (n=77)</td>
<td>Mean percent reductions in NPRS score from baseline to weeks 2–8 was significantly greater in the total C8P group (26.5 %; p=0.0286) and the 90-minute C8P group (27.8 %; p=0.0438) compared with the pooled control group (17.3 %)</td>
<td>99 % completed ≥90 % of the intended patch application. 59 % of the C8P group reported an TEAE versus 56 % of the control group</td>
</tr>
<tr>
<td>Irving et al., NCT0030222 2011¹</td>
<td></td>
<td>Multicenter, randomized double-blind study in PHN</td>
<td>C8P (n=212) or patch control* (n=204)</td>
<td>From baseline to weeks 2–8, a ≥30 % reduction in NPRS score seen in 46 % of the C8P group versus 34 % of the control group Overall, there was a 32.0 % mean reduction from baseline in NPRS score in the C8P group versus a 24.4 % reduction in the control group</td>
<td>Most TEAEs were application site specific (notably erythema and pain), transient, and generally mild to moderate in severity</td>
</tr>
<tr>
<td>Webster et al., NCT00068081 2011¹</td>
<td></td>
<td>Multicenter, randomized double-blind, controlled study in PHN</td>
<td>C8P (n=102) or control patch* (n=53)</td>
<td>36.5 % mean reduction in NPRS scores from baseline to weeks 2–8 in the C8P group versus 29.9 % reduction in controls (p&lt;0.05)</td>
<td>Reported in 75 % of C8P patients and 53 % of control patients. Most TEAEs were application-site specific</td>
</tr>
</tbody>
</table>

C8P = capsaicin 8 % patch; HIV-DSP = human immunodeficiency virus-associated distal sensory polyneuropathy; NPRS = numerical pain rating scale score; PDN = painful diabetic neuropathy; PHN = post-herpetic neuralgia; PNP = peripheral neuropathic pain; TEAE = treatment-emergent adverse event. *Control patch = capsaicin low dose (0.04 %) patch.

difference in mean NPRS at any time during or after capsaicin patch treatment. Furthermore, the same proportions (57 %) of pre-treated and non-pre-treated patients were willing to receive capsaicin re-treatment. Topical lidocaine-induced analgesia itself is transient (lasting 1–2 hours); statistically significant pain relief compared with the vehicle patch was not achieved in clinical trials until 4 hours post-application. This suggests
Repeat Application of the 8 % Capsaicin Patch

The effects of repeated 8 % capsaicin patch treatment were shown in an open label extension of a PHN trial.15 Fifteen patients who received at least two treatments had similar reductions in their pain score from baseline, 28.4 % after the first treatment; 29.7 % after the second treatment. Nine patients who received three treatments achieved a mean reduction from baseline in NPRS score of 34.1 ± 24.2 (95 % CI 52.7–15.6). These results demonstrated that a mean decrease of approximately 30 % was maintained during each treatment cycle of the capsaicin 8 % patch regardless of the number of treatments received.

Cost-effectiveness

A review of high-concentration topical capsaicin for the treatment of chronic neuropathic pain highlighted that although the treatment is similar to other available therapies in terms of efficacy, it is likely to be used with other available therapies have failed owing to reasons of cost.16 However, in a cost-effectiveness analysis using a 1-year Markov model that compared the 8 % capsaicin patch to existing PHN therapies, measures showed that 8 % capsaicin and topical lidocaine patches had significantly higher rates of effectiveness than oral agents.17 The analysis also found that the 8 % capsaicin patch was comparable to the topical lidocaine patch and within an accepted cost per quality-adjusted life-year gained threshold compared with the oral treatments.

Concluding Remarks

Initially the topical administration of capsaicin, a highly selective agonist for TRPV1, resulted in localized burning sensations, hyperalgesia, allodynia, and erythema.18 Over time, TRPV1-expressing cutaneous nociceptors become less sensitive to a variety of stimuli, including capsaicin itself, and exhibit a protracted decrease in spontaneous and evoked firing known as defunctionalization.19–21 Capsaicin-induced defunctionalization of cutaneous nociceptors results in a reversible retraction of epidermal nerve fibers while leaving the majority of the neuron and cell body in the dorsal root ganglion unaffected.22–23

At present, it is unclear why only a proportion of patients respond to capsaicin treatment and how response to treatment may be predicted. Questions also persist as to whether lidocaine pre-treatment is beneficial, how deep the capsaicin from the capsaicin 8 % patch penetrates the skin layers, and how much capsaicin reaches the nociceptors.

Overall, the clinical evidence indicates that the capsaicin 8 % patch has a good safety and tolerability profile and offers effective topical therapy in PHN. The episodic treatment application of every 3 months or longer makes the capsaicin 8 % patch a convenient option for patients. The capsaicin 8 % patch is therefore a valuable addition to the armamentarium of analgesic options for PHN.
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