Drugs & Therapy Perspectives (2020) 36:47–56
https://doi.org/10.1007/s40267-019-00701-0

ADIS DRUG Q&A

Capsaicin 8% dermal patch in peripheral neuropathic pain: a profile of its use

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Published online: 24 December 2019

Abstract
A dermal patch containing a high (8%) capsaicin concentration (hereafter referred to as the capsaicin 8% dermal patch) [Qutenza®] is a useful option for the treatment of peripheral neuropathic pain (PNP). The patch, referred to as Qutenza 179 mg cutaneous patch in the EU summary of product characteristics, is indicated in the EU for the treatment of PNP in adults, either alone or in combination with other medicinal products for pain. Prolonged exposure to capsaicin (the main pungent component in hot chilli peppers) appears to engender analgesia/pain relief by inducing cutaneous nociceptor 'defunctionalisation' [i.e. a cascade of events, including a reduction in TRPV1 (transient receptor potential vanilloid-1) receptor sensitivity to various painful or noxious stimuli, resulting in impaired local nociceptor function for an extended period]. Across clinical and real-world studies in patients with painful diabetic peripheral neuropathy (PDPN) or non-diabetic PNP, including post-herpetic neuralgia (PHN) and HIV-associated neuropathy, single applications of the capsaicin 8% dermal patch generally relieved pain and improved health-related quality of life, patient status and/or treatment satisfaction. Pain relief was at least sustained following repeated applications for ≤ 52 weeks. As the capsaicin 8% dermal patch is associated with minimal systemic absorption, its use is expected to result in few systemic adverse events or drug–drug interactions.

Adis evaluation of the capsaicin 8% dermal patch in the management of peripheral neuropathic pain
Highly selective TRPV1 receptor agonist
Relieves pain and improves sleep quality in adults with PDPN
Noninferior to oral pregabalin in relieving non-diabetic PNP in adults
Provides rapid and sustained pain relief in adults with PHN
Adverse events (most commonly application-site pain and erythema) are transient, self-limiting and typically mild or moderate in intensity

Additional information for this Adis Drug Q&A can be found at https://doi.org/10.6084/m9.figshare.11099882.

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What is the rationale for using the capsaicin 8% dermal patch in peripheral neuropathic pain?

Neuropathic pain is defined by the International Association for the Study of Pain as 'pain caused by a lesion or disease of the somatosensory nervous system' and is classified as central or peripheral [1, 2]. Conditions associated with peripheral neuropathic pain (PNP) include painful radiculopathy, painful polyneuropathy, peripheral nerve injury, post-herpetic neuralgia (PHN) and trigeminal neuralgia [2]. Neuropathic pain typically presents with both positive [i.e. painful or altered sensations (e.g. burning or searing, tingling)] and negative [i.e. diminished or absent feeling (e.g. deadness, numbness)] sensory symptoms [3] and can have a substantial impact on quality of life (e.g. physical and psychological health, and economic and social wellbeing) [4].

The management of neuropathic pain is challenging owing to the heterogeneity of its aetiologies, underlying mechanisms and symptoms (indeed, ≈ 60% of patients present with localized pain) and can involve various pharmacological therapies, including antidepressants, antiepileptic drugs, opioids and topical preparations, with the latter well suited for the treatment of localized neuropathic

pain (LNP) [4, 5]. Among the pharmacological options is capsaicin, the main pungent component in hot chilli peppers and a highly selective agonist for the transient receptor potential vanilloid-1 (TRPV1) receptor [6]. TRPV1 receptors located in the skin are involved in the physiological response (e.g. burning, itching, stinging, warming) to painful or noxious endogenous and exogenous stimuli [e.g. acidosis (pH < 6), heat (temperature of > 43 °C) and irritant chemicals] [6–9]. While the initial activation of TRPV1 receptors by capsaicin replicates their activation by other stimuli, prolonged capsaicin exposure results in a cascade of events, including a reduction in the sensitivity of TRPV1 receptors to various stimuli (including capsaicin itself) [7, 8, 10, 11]. It is this 'defunctionalisation' of cutaneous nociceptors, rather than neuropeptide depletion, that is thought to underlie the analgesic/pain relief response to capsaicin therapy [7, 8, 10, 12].

Initial topical (cream) formulations of capsaicin 0.025–0.075% demonstrated only modest efficacy and required multiple daily applications for the treatment of PNP, resulting in adverse events (AEs; pain and erythema) and compliance issues [3, 6, 8]. A dermal patch formulation of capsaicin at a concentration of 8% (hereafter referred to as the capsaicin 8% dermal patch) [Qutenza®] was subsequently developed to address these shortcomings. The patch, referred to as Qutenza 179 mg cutaneous patch in the EU summary of product characteristics, is approved for the treatment of PNP in adults in the EU [10]. This article provides an overview of the use of the capsaicin 8% dermal patch in this patient population, with a summary of its prescribing information in the EU provided in Table 1.

How does the capsaicin 8% dermal patch work?

The TRPV1 receptor is a non-selective cation channel highly expressed on small diameter sensory neurons, particularly those that detect painful or noxious sensations (nociceptors) [7]. Its initial activation by capsaicin results in an influx of calcium ions and the subsequent release of vasoactive neuropeptides, ultimately inducing burning, itching, stinging and warming sensations [6, 10, 11, 13]. Prolonged capsaicin exposure induces a cascade of events (including reduced TRPV1 receptor sensitivity to various stimuli), thereby impairing local nociceptor function, and thus providing analgesia/pain relief, for an extended period; this 'defunctionalisation' effect is, however, reversible, with normal function (i.e. the detection of noxious sensations) returning within weeks in healthy volunteers [7, 8, 10, 11].

Therapy with capsaicin is not expected to alter sensations from non TRPV1-expressing cutaneous neurons, nor the ability to detect mechanical and vibrational stimuli [10]. However, a single 60-min application of the capsaicin 8% dermal patch to healthy volunteers participating in a randomized, open-label, phase I study [14] significantly ($p = 0.02$) increased the tactile threshold and significantly ($p < 0.0001$) reduced the detection of sharp mechanical pain relative to control 1 week after exposure. Both sensations returned to normal within 12 weeks. While no changes in thermal sensation were seen, this was possibly due to a lack of sensitivity in the detection methods [14].

In vitro, capsaicin had a linear rate of release from the capsaicin 8% dermal patch over the duration of application, with an estimated ≈ 1% absorbed into the epidermal and dermal layers of the skin during a 60-min application period [10]. In a 60 kg individual, the maximum potential capsaicin exposure from the capsaicin 8% dermal patch is ≈ 0.12 mg/kg once every 3 months; to put this in perspective, in the same weighted individual, the average oral intake of capsaicin is 0.025 mg/kg/day and the highest dietary exposure is up to 3.3 mg/kg/day [10].

What is the efficacy of the capsaicin 8% dermal patch in the clinical setting?

Several large ($n > 300$), randomized, multicentre, phase III [15–20] or IV [21] clinical studies have established the efficacy of the capsaicin 8% dermal patch in adults with painful diabetic peripheral neuropathy (PDPN) [15, 16] or non-diabetic PNP [17–21]. In the phase III studies, patients received a single 30-min, 60-min or 90-min application of the capsaicin 8% dermal patch to painful body areas [17, 18] or the feet [15, 16, 19, 20]. In the phase IV study, patients received a single 30-min application to the feet or a single 60-min application to any other body part [21].

PDPN

A single 30-min application of the capsaicin 8% dermal patch was associated with modest, but statistically significant, improvements in pain relief and sleep quality in adults with PDPN participating in the 12-week STEP study [15]. Relative to placebo, the capsaicin 8% dermal patch significantly reduced average daily pain from baseline to between weeks 2–8 (primary endpoint) [Table 2]. Improvements in this endpoint were seen from week 2 onwards ($p \leq 0.05$, except at week 6), and according to prespecified subgroup analyses occurred regardless of baseline average daily pain score (< 7 or ≥ 7), HbA_{1c} level (< 6.5% or ≥ 6.5%) and duration of PDPN (< 3 years or ≥ 3 to < 10 years). Statistically significant mean percentage reductions from baseline in the average daily pain score between weeks 8–12 (−28.0 vs −21.0; $p = 0.018$) and improvements in the proportion of patients achieving a ≥ 30% reduction from baseline in

Table 1 Summary of the application and use of the capsaicin 8% dermal patch (also referred to as Qutenza 179 mg cutaneous patch) in peripheral neuropathic pain in the EU [10]

What is the approved indication for the capsaicin 8% dermal patch?	
Treatment of peripheral neuropathic pain in adults; may be used alone or in combination with other medicinal products for pain	
How is the capsaicin 8% dermal patch available?	
A single-use 14 × 20 cm (280 cm^2) dermal patch containing a total of 179 mg of capsaicin (640 µg of capsaicin per cm^2 of patch)	
Each patch comprises a backing layer, a matrix and a removable protective layer (the release liner)	
Available in packs containing one or two patches (each individually sealed in a separate sachet) plus a 50 g tube of cleansing gel	
How should the capsaicin 8% dermal patch be stored?	
Store the patches (flat in the original packaging) and the cleansing gel below 25 °C	
How should the capsaicin 8% dermal patch be applied and used?	
Patches should be applied by a physician or a healthcare professional (under physician supervision) to the most painful area(s) on the skin (identified and marked by the physician)	
Apply a maximum of 4 patches during a single treatment; repeat treatments every 90 days if warranted by persisting or returning pain	
Prior to application	If required for patch adherence, clip (not shave) hairs in the treatment area(s), wash with soap and water and dry thoroughly
	Consider a topical anaesthetic (for the treatment area and surrounding 1–2 cm) or an oral analgesic (to reduce potential application-site reactions); remove the topical anaesthetic and wash and dry the skin thoroughly before applying the patch
Timing of application	Apply within 2 h of opening the sachet, but do not remove the release liner until just prior to application
	If required, cut the patches (before removing the release liner) to match the size and shape of the treatment area
Application precautions	To avoid unintentional drug contact (which may cause erythema, burning sensations, eye pain, cough and eye/throat irritation), apply the patches in a well ventilated area, avoid holding them near the eyes or mucous membranes, use nitrile (not latex) gloves, and consider wearing a mask and protective glasses when handling the patches and cleaning the treatment areas
Method of application	Peel and fold a section of the release liner and place the adhesive side of the printed patch on the treatment area, holding the patch in place
	Slowly and carefully peel the release liner from underneath while smoothing the patch onto the skin to ensure complete contact, with no air bubbles or moisture
	Allow the patches to remain in place for 30 min for the feet (e.g. HIV-associated neuropathy, painful diabetic peripheral neuropathy) and 60 min for other locations (e.g. post-herpetic neuralgia); use stretchable socks or rolled gauze to ensure contact is maintained
	Provide supportive treatment [e.g. local cooling or oral analgesics (i.e. short-acting opioids)] for patients in pain during or after patch application; use an alternative pain reduction strategy if high opioid tolerance is suspected (as patients may not response to oral opioids when used for acute pain)
How should the capsaicin 8% dermal patch be removed and disposed of?	
Remove gently and slowly by rolling inward (to minimize the risk of capsaicin aerosolisation); after removal, liberally apply cleansing gel to the treatment area and leave for ≥ 1 min before wiping it off with dry gauze (to remove any remaining capsaicin from the skin); finally, gently wash the treatment area with soap and water	
Dispose of used and unused patches and all other materials that have contacted the treated area immediately after use by sealing them in a polyethylene medical waste bag and placing them in an appropriate medical waste container	
Does the capsaicin 8% dermal patch have systemic effects?	
Systemic exposure	Transient (unquantifiable within 3–6 h of dermal patch removal) and low (< 5 ng/mL) capsaicin exposure following 60-min application
Drug interactions	No interactions with other drugs anticipated (due to transient low systemic exposure following application)

Consult local prescribing information for further details

average daily pain scores (i.e. ≥ 30% responder rate) between weeks 2–12 (40.9% vs 31.7%; $p = 0.05$) were also seen with the capsaicin 8% dermal patch versus placebo. However, the between-group differences (BGDs) in the ≥ 30% responder rate at weeks 2–8 and the ≥ 50% responder rates at weeks 2–8 and weeks 2–12 were not significant. The median time to a treatment response [defined as the time required for 50% of patients to achieve a ≥ 30% reduction from baseline in the Numeric Pain Rating Scale (NPRS) score for average daily pain] was 19 and 72 days in the capsaicin 8% dermal patch and placebo groups [15].

The capsaicin 8% dermal patch significantly ($p < 0.05$) reduced sleep interference (as assessed by question 9F of the Brief Pain Inventory-Diabetic Neuropathy) from baseline

Table 2 Efficacy of the capsaicin 8% dermal patch in adults with peripheral neuropathic pain

Study	Comparators	Primary endpoint (unless otherwise stated)	CAP vs comparator
Painful diabetic peripheral neuropathy			
STEP [15]	CAP 30 min ($n=186$) vs PL ($n=183$)	Mean Δ from BL in the NPRS score for average daily pain[a] (%) [mean BL value]	Weeks 2–8: −27.4* vs −20.9 [6.4 vs 6.4]
PACE [7, 16, 22]	CAP 30 min + SOC ($n=156$) and CAP 60 min + SOC ($n=157$) vs SOC alone ($n=155$)	Mean Δ from BL in the NPRS score for average daily pain[a,b] [mean BL value]	Week 52: −2.0 and −2.3 vs −1.1 [5.6 ($n=468$)]
Non-diabetic peripheral neuropathic pain			
ELEVATE [21]	CAP 30 or 60 min ($n=282$) vs oral PRE 150–600 mg/day[c] ($n=277$)	≥30% reduction from BL in the mean NPRS score for average daily pain (% of pts) [mean BL value]	Week 8: 56 vs 55 [6.5 vs 6.7]; BGD of 1.2% (OR 1.03; 95% CI 0.71–1.50)
Post-herpetic neuralgia			
Study C116 [17]	CAP 60 min ($n=206$) vs CON ($n=196$)	Mean Δ from BL in the NPRS score for average daily pain (%) [mean BL value]	Weeks 2–8: −29.6*** vs −19.9 [6.0 vs 5.8]
Study C117 [18]	CAP 60 min ($n=212$) vs CON ($n=204$)	Mean Δ from BL in the NPRS score for average daily pain (%) [mean BL value]	Weeks 2–8: −32.0* vs 24.4 [5.7 vs 5.8]
HIV-associated neuropathy			
Study C107 [19]	CAP 30, 60 or 90 min ($n=225$) vs CON ($n=82$)	Mean Δ from BL in the NPRS score for average daily pain (%) [mean BL value]	Weeks 2–12: −22.8** vs −10.7 [5.9 vs 5.9]
Study C119 [20]	CAP 30 or 60 min ($n=332$) vs CON 30 or 60 min ($n=162$)	LSM Δ from BL in the NPRS score for average daily pain (%) [mean BL value]	Weeks 2–12: −29.5 vs −24.5 [6.1 vs 5.9]
Integrated analysis[d] [23]	CAP 30 or 60 min ($n=482$) vs CON 30 or 60 min ($n=215$)	LSM Δ from BL in the NPRS score for average daily pain (%) [mean BL value]	Weeks 2–12: −27.4** vs −20.1 [6.0 vs 5.9]

BGD between-group difference, *BL* baseline, *CAP* capsaicin 8% dermal patch, *CON* control (CAP 0.04% dermal patch), *LSM* least squares mean, *NPRS* Numeric Pain Rating Scale (which ranges from 0 to 10, with 0 indicating no pain and 10 indicating the worst possible pain), *OR* odds ratio, *PL* placebo, *PRE* pregabalin, *pts* patients, *SOC* optimized standard of care, Δ change

*$p \leq 0.05$, **$p < 0.01$, ***$p = 0.001$ vs comparator

[a]According to question 5 of the Brief Pain Inventory-Diabetic Neuropathy

[b]Other secondary endpoint

[c]Initiated at 75 mg/day and increased by 75 mg every 3–4 days up to a maximum of 600 mg/day; administered twice or thrice daily

[d]Of Studies C107 and C119

to weeks 2–8 and 2–12 [15]. Improvements were seen from week 5 onwards ($p \leq 0.05$, except at week 10). Overall patient status [Patient Global Impression of Change (PGIC) status of 'very much improved' or 'much improved'] at weeks 8 and 12 and health-related quality of life [HR-QOL; as assessed by the European Quality of Life Questionnaire in 5 Dimensions (EQ-5D)] at any timepoint did not significantly differ between the treatment groups [15].

Repeated therapy (≤7 applications, with a between-treatment interval of ≥8 weeks) with the capsaicin 8% dermal patch (30- or 60-min application period) plus optimized standard of care (SOC) over 52 weeks improved average daily pain (Table 2), according to the supportive 52-week, open-label PACE study [7, 16, 22]. Of note, formal statistical testing was not performed as PACE was primarily designed to evaluate tolerability endpoints [16]. Improvements in pain severity (mean changes from baseline of −1.9 and −2.2 vs −0.9) and pain interference (−1.9 and −2.0 vs −0.8) were also seen in the capsaicin 8% dermal patch 30- and 60-min plus SOC groups compared with the SOC alone group at week 52 [7, 16, 22]. At week 52, the ≥30% responder rates were 67.3%, 67.5% and 40.6% and the ≥50% responder rates were 44.8%, 48.4% and 23.8% in the respective groups [7, 16].

Improvements in overall patient status, HR-QOL and treatment satisfaction were seen with repeated capsaicin 8% dermal patch plus SOC therapy in PACE [7, 22]. A PGIC status of at least 'minimally improved' was achieved by ≈70% of patients in the combined capsaicin 8% dermal patch plus SOC group and 38.5% of those in the SOC alone group [7]. Moreover, the mean change from baseline to week 52 in the EQ-5D visual analogue scale was 10.4 and 11.2 in the capsaicin 8% dermal patch 30- and 60-min plus SOC groups and 5.5 in the SOC alone group [7]. At week 52, greater proportions of patients in the capsaicin 8% dermal patch plus SOC groups than in the SOC alone group had no problems with pain or discomfort, mobility, self-care, usual activities, and anxiety or depression; improvements in pain levels, activity levels, HR-QOL and willingness to undergo treatment again; and preferred the study treatment to their previous treatment (no quantitative data available) [22].

Non-diabetic PNP

A single (30- or 60-min) application of the capsaicin 8% dermal patch was an effective alternative to optimized oral pregabalin for pain relief in adults with non-diabetic PNP (post-traumatic nerve injury, non-diabetic painful peripheral polyneuropathy and PHN) participating in the 8-week, open-label, noninferiority, phase IV ELEVATE study [21]. The capsaicin 8% dermal patch was noninferior to oral pregabalin in terms of the ≥ 30% responder rate in both the full analysis set (FAS; Table 2) and the per-protocol set [odds ratio 1.03; 95% CI 0.70–1.52) [lower limits of the odds ratio 95% CIs were > 0.693 [21].

In the FAS, the proportion of patients achieving optimal therapeutic effect at week 8 (defined as no change in background chronic pain medication; no discontinuation of the study drug due to a lack of efficacy or tolerability prior to week 8; a ≥ 30% reduction in the NPRS score over ≥ 4 consecutive days from baseline to week 8; and no moderate or severe adverse drug reactions during the stable treatment period) did not significantly differ between the capsaicin 8% dermal patch and oral pregabalin groups (52 vs. 45%) [21]. The capsaicin 8% dermal patch group had a mean NPRS score change from baseline to between weeks 2–8 of − 37.1% (vs − 27.5% in the oral pregabalin group) and a faster onset of action than the oral pregabalin group [median time to pain relief (defined as 50% of patients achieving a 30% reduction in NPRS scores over 3 consecutive days) was 7.5 vs 36.0 days; $p < 0.0001$] [21].

The capsaicin 8% dermal patch generally provided better treatment satisfaction than oral pregabalin [21]. Least-squares mean (LSM) Treatment Satisfaction Questionnaire for Medication scores were significantly (based on 95% CIs for the LSM BGD) higher in the capsaicin 8% dermal patch group than in the oral pregabalin group for patient perception of effectiveness (59.1 vs 54.8), side effects (95.3 vs. 74.1) and global satisfaction (59.6 vs. 52.9), but not for convenience (71.8 vs. 72.8). Moreover, a significantly lower proportion of capsaicin 8% dermal patch than oral pregabalin recipients withdrew due to a lack of efficacy or tolerability (0.7 vs 9.7%), with a significantly higher proportion being willing to continue therapy at week 8/study end (78.4% vs 66.4%) [95% CIs for the BGDs not containing 0] [21].

The capsaicin 8% dermal patch was superior to oral pregabalin in relieving dynamic mechanical allodynia (DMA; a typical symptom of neuropathic pain) in ELEVATE participants with a baseline DMA (i.e. an NPRS score of > 0 and a sensitive area of allodynia of > 0 cm^2) [24]. In this post hoc analysis, LSM changes from baseline to week 8 were significantly more favourable with the capsaicin 8% dermal patch ($n = 253$) than with oral pregabalin ($n = 235$) for DMA intensity (− 2.98 vs − 2.35; $p = 0.002$) [mean baseline values of 6.60 and 6.71] and DMA area (− 72.6 vs − 33.1 cm^2; $p = 0.009$) [mean baseline values of 228.3 and 234.0 cm^2]. Moreover, at study end, a significantly higher proportion of capsaicin 8% dermal patch than oral pregabalin recipients had a complete resolution of allodynia (24.1% vs 12.3%; $p = 0.001$) [24].

PHN

When applied for 60 min, the capsaicin 8% dermal patch provided rapid and sustained pain relief compared with a capsaicin 0.04% dermal patch (hereafter referred to as control) in adults with PHN participating in two 12-week, double-blind, phase III studies (Study C116 [17] and Study C117 [18]). The capsaicin 8% dermal patch reduced the NPRS score for average daily pain from baseline by a significantly greater extent than control during weeks 2–8 (Table 2). Significant ($p < 0.05$) BGDs favouring the capsaicin 8% dermal patch over control in this endpoint were seen from week 1 [17] or 2 [18] onwards and occurred regardless of whether or not patients were receiving concomitant neuropathic pain medications in Study C116 [17] (post hoc analysis), but not Study C117 [18] (prespecified analysis).

The capsaicin 8% dermal patch was also significantly ($p < 0.05$) more favourable than control in terms of the mean percentage reduction from baseline in the average daily pain score between weeks 2–12 (− 29.9% vs − 20.4% [17] and − 32.3% vs − 25.0% [18]). Moreover, significantly ($p < 0.05$) more recipients of the capsaicin 8% dermal patch than of control achieved a clinically meaningful reduction in pain (i.e. ≥ 30% from baseline in the mean NPRS score for average daily pain) during weeks 2–8 (42% vs 32% [17] and 46% vs 34% [18]) and weeks 2–12 (44% vs 33% [17] and 47% vs 35% [18]) or a ≥ 2-point reduction from baseline in the mean NPRS score for average daily pain during weeks 2–8 (40% vs 25% [17] and 42% vs 26% [18]) and weeks 2–12 (42% vs 28% [17] and 43% vs 29% [18]).

Therapy with the capsaicin 8% dermal patch was associated with improvements in overall patient status in adults with PHN [17, 18]. Significantly ($p < 0.05$) greater proportions of patients using the capsaicin 8% dermal patch than those using control considered themselves to have at least 'slightly improved' (based on PGIC status) at both week 8 (53% vs 42% [17] and 62% vs 51% [15]) and week 12 (55% vs 43% [17] and 61% vs 47% [18]). Moreover, in study C117 [18], a significantly ($p < 0.05$) higher proportion of capsaicin 8% dermal patch than control recipients were judged by the study investigators to have improved ('very much', 'much' or 'slightly') on the Clinical Global Impression of Change (CGIC) at week 8 (63% vs 52%) and week 12 (63% vs 48%). It is worth noting that study withdrawal because of an unsatisfactory response occurred in 4.9% of capsaicin 8% dermal patch recipients and 4.6% of control recipients in study C116 [17] and in 0.5% and 2.5% of patients in Study C117 [18].

Repeated 60-min applications of the capsaicin 8% dermal patch (total 1–4, with a between-treatment interval of ≥ 6 [25] or ≥ 12 weeks [26]) maintained pain relief in adults with PHN participating in a 40-week, open-label extension (Study C106) of a 4-week, double-blind study (C102) [25], or a 48-week, open-label, phase II safety study (Study C118; PHN $n = 54$, who had completed a previous capsaicin 8% dermal patch study) [26]. In Study C102, the capsaicin 8% dermal patch ($n = 26$) significantly ($p = 0.003$) improved the NPRS score for average daily pain from baseline during weeks 2–4 (primary endpoint) relative to control ($n = 12$) [mean change of −32.7% vs −4.4%], with the effect magnitude maintained in Study C106 after a further one, two or three treatments (mean changes from baseline of −31.4%, −30.0% and −34.1%, respectively; $n = 21$, 15 and 9, respectively) [25]. In study C118 [26], the mean change from baseline at week 48 in the NPRS score was −35.6%, with 75% of patients considering themselves to have improved (with a PGIC status of 'slightly improved' or better).

HIV-associated neuropathy

A single 30-, 60- or 90-min application of the capsaicin 8% dermal patch reduced the pain of adults with HIV-associated distal sensory polyneuropathy (DSP; lasting ≥ 2 months) participating in a 12-week, double-blind, phase III study (Study C107) [19]. Relative to a capsaicin 0.04% dermal patch (i.e. control), the capsaicin 8% dermal patch significantly reduced the NPRS score for average daily pain from baseline to between weeks 2–12 (Table 2); significant ($p < 0.05$) BGDs favouring the capsaicin 8% dermal patch over control were seen from week 2 and occurred regardless of whether or not patients were receiving other neuropathic pain medications. Of note, no dose response was apparent, with the NPRS scores decreasing by 27.7%, 15.8% and 24.7% (mean values) in the individual 30-, 60- and 90-min capsaicin 8% dermal patch groups, respectively ($n = 72$, 78 and 75, respectively). The capsaicin 8% dermal patch was also significantly more favourable than control with regard to the proportions of patients with a ≥ 30% response during weeks 2–12 (34% vs 18%; $p = 0.009$), a PGIC status of at least 'slightly improved' at week 12 (67% vs 31%; $p < 0.001$) and a CGIC status of at least 'slightly improved' at week 12 (66% vs 37%; $p < 0.01$) [19].

In contrast, in another 12-week, double-blind, phase III study (Study C119) [20] in patients with HIV-DSP (lasting ≥ 2 months), the capsaicin 8% dermal patch and control (each applied for 30 or 60 min) did not significantly differ with regard to the NPRS score change for average daily pain from baseline to weeks 2–12 (primary endpoint; Table 2) or most secondary endpoints. However, a significant (p value not reported) difference in the NPRS score change between the 30- and 60-min control groups (−19.1% vs −30.0%) prevented their intended pooling for assessing each individual capsaicin 8% dermal patch group. Of note, post hoc nonparametric analyses of the primary endpoint demonstrated significant ($p < 0.05$) differences between the pooled and 30-min capsaicin 8% dermal patch groups and their respective control groups [20].

An integrated analysis [23] of Studies C107 and C119 found that a single 30- or 60-min application of the capsaicin 8% dermal patch significantly improved the change from baseline in the NPRS score for average daily pain during weeks 2–12 compared with control (Table 2). However, when this endpoint was assessed for the 30- and 60-min applications individually, the difference between the capsaicin 8% dermal patch ($n = 239$ and 243) and control ($n = 100$ and 115) was significant for the 30-min (−26.9 vs −15.8; $p = 0.002$), but not the 60-min (−27.9 vs −24.2), application. According to subgroup analyses, improvements in the NPRS score change occurred regardless of sex, baseline pain score, duration of HIV-DSP or use of concomitant neuropathic pain medication. Relative to control, the ≥ 30% responder rate during weeks 2–12 was significantly ($p < 0.05$) higher with the capsaicin 8% dermal patch in the combined group and the 30-min application group, but not the 60-min application group, with a PGIC status of at least 'slightly improved' at week 12 achieved by a significantly higher proportion of capsaicin 8% dermal patch recipients in all groups [23].

Pain relief in adults with HIV-associated neuropathy (HIV-AN) was maintained over up to 52 weeks following repeated applications (≤ 3, with a between-treatment interval of ≥ 12 weeks) of the capsaicin 8% dermal patch (60-min application period for nearly all applications) in a 40-week, open-label extension of C107 ($n = 272$) [27] or in Study C118 (HIV-DSP $n = 52$, who had successfully completed a previous capsaicin 8% dermal patch study) [26]. In the extension phase of study C107, the mean percentage change from baseline to between weeks 2–12 in the NPRS score for average daily pain (−25.8, −27.1, −24.6 and −22.7 after 0, 1, 2 and 3 retreatments, respectively; $n = 118$, 57, 50 and 28, respectively) [27] was similar to that seen following a single application of the capsaicin 8% dermal patch in the parent study [19] (Table 2). PGIC and CGIC benefits were seen regardless of the number of retreatments [27]. In Study C118, the mean change from baseline at week 48 in the NPRS score was −12.4%, with 80% of patients having a PGIC status of at least 'slightly improved') [26].

What is the efficacy of the capsaicin 8% dermal patch in the real-world setting?

Real-world experiences in large ($n > 300$), prospective, non-interventional studies conducted in France [28], Germany [29, 30], Scandinavia [31] and several European countries

[32, 33] have confirmed the findings of clinical studies investigating the efficacy of the capsaicin 8% dermal patch for the treatment of adults with PNP. For instance, in the largest study (QUEPP), a single 30-min (to the feet) or 60-min (to other parts of the body) application of the capsaicin 8% dermal patch to 1044 adults with non-diabetic PNP [most commonly PHN (32%) and post-surgical neuralgia (23%)] significantly ($p \leq 0.001$) reduced the mean NPRS score for average daily pain from baseline to the first assessment (1–2 weeks) [i.e. from 6.3 to 4.6], with this improvement maintained at each subsequent visit (weeks 4, 8 and 12: 4.5, 4.5 and 4.7, respectively) [29]. A ≥ 2-point reduction from baseline in the NPRS score had been achieved by 40.1% of patients at week 12; no change occurred in 22.6% of patients. At the first assessment and weeks 4, 8 and 12, respectively, the ≥ 30% responder rates were 40.4%, 44.7%, 42.9% and 37.7% and the ≥ 50% responder rates were 7.3%, 29.2%, 27.9% and 24.5%. Significant ($p \leq 0.001$) improvements in the frequency and intensity of pain attacks, sleep parameters (duration and quality), number of days absent from work due to neuropathic pain, and the proportion of patients requiring concomitant medication for PNP were seen with a single application of the capsaicin 8% dermal patch [29]. According to a retrospective subgroup analysis [30], the magnitude of the pain relief induced by capsaicin 8% dermal patch therapy was associated with the duration of pre-existing pain (i.e. patients with a ≤ 6-month history of PNP had the highest treatment response compared with those with higher pain durations), suggesting that the early initiation of topical therapy might be useful.

Single and repeated applications (1–5, with a between-treatment interval of 12–16 weeks) of the capsaicin 8% dermal patch were a successful analgesic therapy in almost one-quarter of patients in routine clinical practice in France [28]. In the QAPSA study, treatment was considered successful in 21.8% of 330 patients aged 15–92 years with non-diabetic PNP [most commonly post-traumatic/post-surgical neuropathic pain (76%)]. Success was defined as a ≥ 30% reduction from baseline in the NPRS score for average weekly pain at weeks 2–24 after the last application and a PGIC rating of at least 'slightly improved' at 24 weeks after the last application. The criteria for treatment failure (a < 30% reduction from baseline in the NPRS score for average weekly pain and a PGIC rating of 'unchanged' or worse) was fulfilled in 37.9% of patients, whereas in 40.3% of patients treatment success was considered as moderate. Clinically relevant improvements in HR-QOL were also seen at the end of the study [28].

The findings from QUEPP and QAPSA are supported by those from a multinational, phase IV study (ASCEND; $n = 412$) [32], a combined analysis of three studies conducted concurrently in Denmark, Norway and Sweden ($n = 382$) [31] and a multinational phase IV safety study ($n = 306$) [33]. For instance, in patients with non-diabetic PNP participating in ASCEND, a single application of the capsaicin 8% dermal patch reduced the mean NPRS score for average daily pain from baseline to weeks 2–8 (co-primary endpoint) by 26.6%, with pain relief sustained until week 52 (mean reduction from baseline in average daily pain of 37.0%) [32]. Moreover, the median time from first to second patch application (co-primary endpoint) was 191 days [32].

What is the tolerability profile of the capsaicin 8% dermal patch?

Single and repeated (≤ 7) applications of the capsaicin 8% dermal patch were generally well tolerated in adults with PNP, with their tolerability profiles consistent between clinical and real-world studies and between patients with PDPN and those with non-diabetic PNP. Based on data from clinical studies in patients with PDPN, PHN and HIV-AN, application-site erythema and application-site pain are the only adverse reactions reported as being very common (incidence ≥ 1/10) [10]. AEs in these studies were transient, self-limiting and typically mild or moderate in intensity [10].

In a pooled analysis of data from clinical studies in 2114 patients with PNP ($n = 590$ with PDPN and 1524 with non-diabetic PNP), application-site reactions occurred in 59.9% of capsaicin 8% dermal patch (30-, 60- or 90-min application period) recipients [7]. Treatment-related AEs (TRAEs) and serious TRAEs occurred in 59.2% and 0.2% of patients, with few patients discontinuing treatment because of adverse reactions or dying (0.7% and 0.1%) [7]. Moreover, in an integrated analysis [34] of 12 clinical studies in patients with painful diabetic neuropathy ($n = 91$), PHN ($n = 920$) and HIV-DSP ($n = 685$), increases in application-related pain were transient and generally resolved following removal of the capsaicin 8% dermal patch, with repeated applications having no effect on this pain. Almost all (99%) of the 1696 patients completed ≥ 90% of the full intended capsaicin 8% dermal patch application duration [34].

A transient increase in blood pressure (BP) [resulting from treatment-related increases in pain] is a well-known effect of capsaicin 8% dermal patch therapy [7] (Table 3). In the pooled analysis population, treatment-emergent AEs (TEAEs) related to BP changes within 7 days of patch application occurred in 38 (1.8%) capsaicin 8% dermal patch recipients (7 of whom had PDPN and were enrolled in STEP or PACE and 29 of whom had non-diabetic PNP). Cardiac disorder TEAEs within 7 days of patch application were reported in 9 (0.4%) patients (all of whom had non-diabetic PNP) using capsaicin 8% dermal patch and TEAEs related to vital signs in 117 (5.5%) patients [7]. BP should be monitored during the treatment procedure, with the risk of adverse cardiovascular events considered in patients with

Table 3 Summary of the warnings and precautions for the use of capsaicin 8% dermal patch in peripheral neuropathic pain in the EU [10]

How should the capsaicin 8% dermal patch be used in special populations?	
Pts with renal and/or hepatic impairment	Dosage adjustment is not required
Pts who are pregnant or breast-feeding	Use caution when prescribing to pregnant women and discontinue treatment in breast-feeding women
What are the contraindications to the use of the capsaicin 8% dermal patch?	
Hypersensitivity to capsaicin or any of the excipients	
What other special warnings/precautions pertain to the use of the capsaicin 8% dermal patch?	
Dermal assessment	Use the capsaicin 8% dermal patch only on dry, intact (unbroken) skin; do not use it on the face, above the hairline of the scalp and/or in proximity to mucous membranes
	Visually examine the feet of pts with painful diabetic peripheral neuropathy before each application and at subsequent clinical visits to detect skin lesions related to underlying neuropathy and vascular insufficiency
ASRs	ASRs are common/very common; remove the patch and evaluate the skin for chemical burns if severe pain occurs
Increase in BP	Monitor BP during the treatment procedure as treatment-related increases in pain may result in transient increases in BP (average < 8 mmHg) during and shortly after therapy
	Consider the risk of adverse CV events (due to the potential stress of the procedure) in pts with unstable or poorly controlled hypertension or a history of CV disease (particularly those with diabetes and coronary artery disease, hypertension and CV autonomic neuropathy) prior to initiating the treatment procedure
Reduced sensory function	Use with caution in pts with reduced sensation in the feet or those who are at risk of such sensory changes
	Evaluate for sensory loss before each patch application in pts with pre-existing sensory deficits
	Reconsider capsaicin 8% dermal patch therapy if sensory loss occurs/continues
Unintended exposure	Apply cleansing gel for 1 min to all skin that comes into contact with the dermal patch but is not intended for treatment, then wipe it off with dry gauze and gently wash the area with soap and water
	Remove any pt experiencing burning of the eyes, skin or airway from the vicinity of the dermal patch; flush or rinse the eyes and/or mucous membranes with water and provide appropriate medical care if shortness of breath develops

Consult local prescribing information for further details

ASRs application-site reactions, *BP* blood pressure, *CV* cardiovascular, *pt(s)* patient(s)

unstable or poorly controlled hypertension or a history of cardiovascular disease [7, 10] (Table 3).

Relative to oral pregabalin, the capsaicin 8% dermal patch was associated with fewer systemic adverse drug reactions in the ELEVATE study in adults with non-diabetic PNP [21]. TRAEs occurred in 61.3% of capsaicin 8% dermal patch recipients and 54.5% of oral pregabalin recipients, although the nature of the TRAEs differed between the groups. Patients using the capsaicin 8% dermal patch more commonly reported application-site pain, erythema, burning sensation and application-site erythema (23.8%, 20.9%, 15.6% and 8.9%, respectively), while those receiving oral pregabalin most frequently reported systemic TRAEs [e.g. dizziness (18.4%), somnolence (15.5%), nausea (10.8%) and headache (9.4%)]. Systemic adverse drug reactions were reported in ≤ 1.1% of capsaicin 8% dermal patch recipients [21]. It is worth noting that a 'burden of therapy' methodology analysis [35] of the ELEVATE study [21] found that capsaicin 8% dermal patch therapy was associated with an initial peak followed by a rapid decline in the safety burden estimate (based on the number and severity of TEAEs per day), while oral pregabalin was associated with a gradual increase in the burden estimate, with the high burden estimate persisting until study end, when it slightly decreased. In ELEVATE, 0% of 282 capsaicin 8% dermal patch recipients and 8.6% of 277 oral pregabalin recipients discontinued therapy because of AEs [21].

Reductions in sensation at the application site of the capsaicin 8% dermal patch are generally minor and temporary; there is no clear evidence for neurological impairment following multiple applications of the capsaicin 8% dermal patch, or dermal injuries that may be associated with sensory loss [7]. Indeed, no negative functional or neurological effects were seen with repeated (≤ 7) applications of the capsaicin 8% dermal patch plus SOC in adults with PDPN participating in the PACE study [16]. Moreover, the estimated LSM differences between 30-min and 60-min applications of the capsaicin 8% dermal patch plus SOC and SOC alone in the mean percentage change from baseline in the Norfolk QOL-Diabetic Neuropathy total score (primary endpoint) at week 52 were considered clinically meaningful (i.e. a ≥ 20% reduction) [16]. A case of hypoaesthesia persisting for 2 years after the end of the PACE study [16] was, however, reported in one patient with PDPN using the capsaicin 8% dermal patch [7]. A relationship between the hypoaesthesia and therapy with the capsaicin 8% dermal

patch could not be excluded, with caution recommended in patients with or at an increased risk of reduced sensation in the feet in the EU [10] (Table 3).

What is the current clinical role of the capsaicin 8% dermal patch in PNP?

Neuropathic pain is particularly difficult to manage and numerous treatment recommendations have been proposed over the previous decade [36]. Current guidelines [4, 37–40] are in broad agreement regarding the pharmacological options for the management of neuropathic pain, with antidepressants (e.g. duloxetine) and antiepileptic drugs (e.g. pregabalin) as first-line options and topical preparations (e.g. capsaicin 8% dermal patch) and opioids as second-line options. A recently published treatment algorithm (developed to guide primary physicians) has proposed six lines of therapy for managing neuropathic pain, with first-line treatment including multidisciplinary care in combination with non-opioid medications such as topical preparations (which are specifically recommended for LNP) [41]. Indeed, newly published German Society for Neurology guidelines have recommended capsaicin 8% dermal patch as a first-line option for LNP and a second-line option for neuropathic pain of any cause [42].

The capsaicin 8% dermal patch is a useful option for the treatment of PNP, and its inclusion alongside/among the other recommended options reflects the totality of evidence in clinical and real-world studies. Specifically, in the clinical setting, the capsaicin 8% dermal patch:

- *In adults with PDPN* Relieves pain and improves sleep quality following a single application; maintains pain relief and improves overall patient status, HR-QOL and treatment satisfaction after repeated applications over 52 weeks.
- *In adults with non-diabetic PNP* Following a single application, provides pain relief noninferior to, and treatment satisfaction higher than, that of oral pregabalin 150–600 mg/day.
- *In adults with PHN* Provides rapid and sustained pain relief and improvements in overall patient status following a single application; maintains pain relief after repeated applications over ≤ 48 weeks.
- *In adults with HIV-AN* Appears to reduce pain following a single application; maintains pain relief and demonstrates overall patient status benefits following repeated treatments over up to 52 weeks.

Real-world experiences in adults with PNP (including those with PHN and PNP following peripheral nerve injury) confirm the findings of the clinical studies.

It is worth noting that unlike most of the currently available therapies for neuropathic pain, the capsaicin 8% dermal patch is associated with minimal systemic absorption (Table 1) and thus few systemic AEs and drug–drug interactions. Indeed, AEs (most commonly application-site erythema and application-site pain) following therapy with the capsaicin 8% dermal patch are transient, self-limiting and usually mild or moderate in intensity. This includes reductions in sensation at the application site; no clear evidence for neurological impairment following multiple applications of the capsaicin 8% dermal patch has been identified. However, during the treatment procedure, BP should be monitored as a transient increase in BP (resulting from treatment-related increases in pain) is a well-known effect of capsaicin 8% dermal patch therapy. While the capsaicin 8% dermal patch must be applied by a healthcare professional, with appropriate care taken during application and removal to avoid unintentional contact with capsaicin, retreatment (if warranted by the persistence or return of pain) is every 90 days, potentially providing compliance benefits.

Acknowledgements The article was updated from *Drugs* 2018;78(14):1489–1500 [9], and was reviewed by: *A.R.T.S. Araújo*, Department of Pharmacy, School of Health Sciences, Polytechnic Institute of Guarda, Guarda, Portugal; *F. Araujo*, Department of Pharmacy, Virgen del Rocio Hospital, Seville, Spain; *G. Hans*, Multidisciplinary Pain Center, Antwerp University Hospital, Edegem, Belgium; *F. Rustemi*, Department of Pharmacy, Albanian University, Tirane, Albania. During the peer review process, Grünenthal, the marketing-authorization holder of the capsaicin 8% dermal patch, was also offered an opportunity to provide a scientific accuracy review of their data. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with ethical standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest Sheridan M. Hoy is an employee of Adis International Ltd./Springer Nature, is responsible for the article content and declares no conflicts of interest.

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