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Capsaicin 8% Dermal Patch: A Review in Peripheral Neuropathic Pain

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Abstract

The adhesive capsaicin dermal patch (Qutenza®) delivers a high concentration (8% w/w) of synthetic capsaicin, a highly selective agonist of transient receptor potential vanilloid-1 (TRPV-1), directly to the site of pain. The capsaicin 8% dermal patch is indicated in the EU for the treatment of peripheral neuropathic pain (PNP) in adults, either alone or in combination with other medicinal products for pain. In patients with painful diabetic peripheral neuropathy, a single 30-min application of the capsaicin 8% dermal patch provided 12 weeks of pain relief and improved sleep quality compared with placebo. Repeat treatment with the capsaicin 8% dermal patch plus standard of care over 52 weeks provided sustained pain relief, with no negative neurological effects compared with standard of care alone. The capsaicin 8% dermal patch was non-inferior to oral pregabalin in relieving pain in patients with non-diabetic PNP, with a faster onset of action and greater treatment satisfaction. A single 60-min application of the capsaicin 8% dermal patch provided rapid and sustained pain relief in patients with postherpetic neuralgia. Results in patients with HIV-associated neuropathy were equivocal, with a significant improvement in pain intensity observed in one trial, but not in the other. The capsaicin 8% dermal patch was generally well tolerated; transient application-site reactions were the most common adverse events. In conclusion, the capsaicin 8% dermal patch is a useful addition to the treatment options currently available for patients with PNP.

Capsaicin 8% dermal patch: clinical considerations in peripheral neuropathic pain

Potent, highly selective agonist of TRPV-1
Relieves pain and improves sleep quality in patients with painful diabetic peripheral neuropathy
Provides rapid, sustained pain relief in patients with postherpetic neuralgia
Non-inferior to oral pregabalin in relieving pain in patients with non-diabetic peripheral neuropathic pain

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1 Introduction

Neuropathic pain occurs as a direct consequence of a lesion or disease affecting the somatosensory system [1]. It can be classified as central or peripheral, based on the site of the lesion or disease causing the pain [1, 2]. Important causes of peripheral neuropathic pain (PNP) include painful diabetic peripheral neuropathy (PDPN), postherpetic neuralgia (PHN), HIV-associated neuropathy (HIV-AN) and chemotherapy-induced peripheral neuropathy [2]. Clinical features of PNP may include burning, stinging or stabbing pain, tingling, numbness, allodynia and hyperalgesia. Chronic neuropathic pain is associated with significantly impaired quality of life (QOL) and is often unresponsive to available treatments [2].

Transient receptor potential vanilloid-1 (TRPV-1), a thermal nociceptor, plays an important role in the detection of painful stimuli such as heat, acids and irritant chemicals [3, 4]. Capsaicin, the main active ingredient of hot chilli peppers, is a potent, highly selective TRPV-1 agonist [3, 5]. Capsaicin initially activates TRPV-1-expressing nociceptors on the skin, resulting in erythema [6]. With continued exposure, these nociceptors become less sensitive and no longer respond to capsaicin or various other stimuli [4, 6].

Low-concentration (0.025–0.075%) capsaicin creams have demonstrated moderate efficacy in the topical treatment of PNP [2, 3]. However, these creams must be applied multiple times a day for several weeks and the initial burning sensation is often not well tolerated [2, 3].

A high-concentration (8% w/w) capsaicin dermal patch (Qutenza®) has been developed which aims to provide long-lasting pain relief following a single application. In the EU, the capsaicin 8% dermal patch is indicated for the treatment of PNP in adults, either alone or in combination with other medicinal products for pain [6]. This article reviews the pharmacological properties of the capsaicin 8% dermal patch and its clinical efficacy and tolerability in patients with PNP.

2 Pharmacodynamic Properties of Capsaicin

Capsaicin is a ligand-gated cation channel that is highly expressed in nociceptive nerve fibres (mainly C and Aδ fibres) [3]. Activation of TRPV-1-expressing nociceptors causes erythema due to the release of vasoactive peptides [6]. Multiple mechanisms are involved in capsaicin-induced 'defunctionalization' of the sensory nerve fibres [5]. These include inactivation of voltage-gated sodium channels, high levels of intracellular calcium (and the subsequent enzymatic, cytoskeletal and osmotic changes), interruption of fast axonal transport via microtubule depolymerization, and loss of mitochondrial function via direct inhibition of electron chain transport [5]. The mean half maximal effective concentration (EC_{50}) of capsaicin at mechanoheat-sensitive C fibres is ≈350 nmol/L [7].

Capsaicin reduced epidermal nerve fibre (ENF) density and diminished sensitivity to heat stimuli in volunteers [8, 9]. Relative to placebo-treated sites, a single application of the capsaicin 8% dermal patch for 60 or 120 min significantly ($p < 0.001$) reduced ENF immunostaining by ≈60% (4.8 and 4.4 vs. 11.8 neurites/mm) and significantly ($p < 0.05$) increased the warmth detection threshold (+1.9 and +1.1 vs. −0.1 °C). A shorter application time (30 min) had no significant effect on ENF density or sensitivity to warmth. None of the treatments produced a significant change in cold sensation detection thresholds [8]. In a similar study, a single 60-min application of the capsaicin 8% dermal patch significantly ($p < 0.0001$) reduced ENF density by ≈80% compared with unexposed sites 1 week after exposure (10.4 vs. 48.7 counts/mm) [9]. ENF density in capsaicin 8% dermal patch-exposed areas was almost fully (93%) restored by week 24 (41.1 vs. 44.7 counts/mm; $p = 0.02$) [9].

Reduced ENF density following capsaicin exposure is usually associated with impairment of sharp mechanical-pain and heat-pain sensations [9]. Relative to control sites, a single application of the capsaicin 8% dermal patch for 60 min significantly ($p < 0.0001$) reduced the proportion of stimuli perceived as sharp mechanical pain (72.5 vs. 88.2%) and significantly ($p = 0.02$) increased the tactile threshold (4.39 vs. 3.9 mN) 1 week after exposure. Sensations returned to normal by week 12. No changes in thermal sensation were observed; this may have been due to the employed detection methods lacking the required sensitivity [9].

3 Pharmacokinetic Properties of Capsaicin

The pharmacokinetics of capsaicin in patients with PNP can be described using a one-compartment model, with first-order absorption and linear elimination [10].

In vitro data indicate that the rate of release of capsaicin from the patch is linear over the duration of application [6]. During a 60-min application of the capsaicin 8% dermal patch, ≈1% of capsaicin is estimated to be absorbed into the epidermal and dermal layers of the skin [6]. A sufficient cutaneous bioavailability of capsaicin was reached following a 30-min application of the capsaicin 8% dermal patch on ex vivo thin (mamma) and thick (plantar) human skin under physiological conditions (32 °C) [7]. The bioavailability of capsaicin was not improved with longer application times (60 or 90 min) or with changes in the ambient temperature. There were no relevant changes in the concentration–time profile when thick skin was heated to 42 °C, while cooling thin skin to 10 °C reduced the bioavailability of capsaicin in all skin layers [7].

In patients with PHN ($n = 96$), HIV-AN ($n = 44$) or PDPN ($n = 33$), systemic exposure to capsaicin was low and transient following a single 60- or 90-min application of the capsaicin 8% dermal patch [10]. Only 20% of patients treated with the capsaicin 8% dermal patch had quantifiable plasma concentrations of capsaicin at one or more time points (0, 1, 3, 6 or 24 h after patch removal). Most quantifiable plasma concentrations were observed at the time of patch removal, with a trend towards disappearance by 3–6 h post-patch removal. In a population pharmacokinetic analysis, the mean maximum plasma concentration of capsaicin following a 60-min application of the capsaicin 8% dermal patch was 1.38 ng/mL after a mean time of 1.46 h. The area under the plasma concentration–time curve was 4.36 ng·h/mL [10]. Capsaicin is 93–94% bound to plasma proteins [11].

Capsaicin is rapidly metabolized in vitro by hepatic enzymes, predominantly CYP2C19, to form three major metabolites (16-hydroxycapsaicin, 17-hydroxycapsaicin and 16,17-dehydrocapsaicin) [11, 12]. These metabolites were not detected in the plasma of patients with peripheral neuropathy [6, 10] and are unlikely to be pharmacologically active at TRPV-1 receptors [10]. In contrast, in vitro biotransformation of capsaicin in human skin is very slow [12]. During incubation with human skin, radiolabeled

capsaicin was slowly metabolized over 20 h. Unchanged drug accounted for most (74–79%) of the radioactivity, with a small fraction being metabolized to vanillylamine and vanillic acid [12]. The mean elimination half-life of capsaicin is ≈ 130 min [6].

Given the transient, low systemic exposure to capsaicin following patch application, no formal drug interaction studies have been performed [6].

4 Therapeutic Efficacy of Capsaicin 8% Dermal Patch

The therapeutic efficacy of a high-concentration (8% w/w) capsaicin dermal patch for the treatment of PNP has been assessed in patients with PDPN (Sect. 4.1) and in non-diabetic patients with PNP of various aetiologies (Sect. 4.2), including PHN (Sect. 4.2.2) and HIV-AN (Sect. 4.2.2). This section focuses on data from large ($n > 300$), randomized, phase III trials, with the efficacy of the capsaicin 8% dermal patch in the real-world setting also briefly discussed (Sect. 4.3).

4.1 Painful Diabetic Peripheral Neuropathy

The efficacy of the capsaicin 8% dermal patch in patients with PDPN was evaluated in two randomized, multicentre, phase III trials: the 12-week, double-blind STEP trial [13] and the 52-week, open-label PACE safety trial [14]. Both trials enrolled patients aged ≥ 18 years with PDPN due to type 1 or type 2 diabetes mellitus for ≥ 1 year, a glycated haemoglobin (HbA_{1c}) level of ≤ 9% [14] or ≤ 11% [13] and an average daily Numeric Pain Rating Scale (NPRS) score of ≥ 4 on question 5 of the Brief Pain Inventory-Diabetic Neuropathy (BPI-DN) [13, 14].

4.1.1 Versus Placebo

In STEP, patients were randomized to receive a single 30-min application of the capsaicin 8% dermal patch or a placebo patch to painful areas of the feet [13]. At baseline, the mean age of patients was 63 years, the mean duration of PDPN was 5.8 years and the average daily pain score (BPI-DN question 5) was 6.5. The primary endpoint was the percentage change in average daily pain score from baseline to the mean score over weeks 2–8 [13].

The capsaicin 8% dermal patch provided pain relief and improved sleep quality in patients with PDPN [13]. The capsaicin 8% dermal patch was significantly more effective than placebo in reducing the average daily pain score between weeks 2–8 and weeks 2–12 (Table 1); improvements in pain were observed from week 2 onwards. Prespecified subgroup analyses of the primary endpoint using baseline average daily pain score (< 7 or ≥ 7), HbA_{1c} (< 6.5 or ≥ 6.5%) and duration of PDPN (< 3 years or ≥ 3 to < 10 years) supported the results seen in the overall study population [13].

Significantly more capsaicin 8% dermal patch than placebo recipients achieved a ≥ 30% reduction from baseline in average daily pain scores between weeks 2 and 12, but not between weeks 2 and 8 (Table 1) [13]. There were no significant between-group differences (BGDs) in the proportion of patients achieving a ≥ 50% reduction from baseline in average daily pain scores. The capsaicin 8% dermal patch was significantly more effective than placebo in reducing the mean sleep interference score between weeks 2–8 and weeks 2–12 (Table 1). Reductions from baseline in sleep interference scores were greater in the capsaicin 8% dermal patch group than the placebo group from week 5 onwards ($p \leq 0.05$, except at week 10) [13].

At week 12, treatment satisfaction favoured the capsaicin 8% dermal patch over placebo for two questions on the Self-Assessment of Treatment II questionnaire ($p < 0.05$) [13]. Improvements in health-related QOL (HR-QOL), as assessed by the European Quality of Life Questionnaire in 5 Dimensions (EQ-5D), were not significantly different between the capsaicin 8% dermal patch and placebo groups at any time point [13].

4.1.2 Versus Standard of Care

Patients in PACE were randomized to treatment with the capsaicin 8% dermal patch for 30 min or 60 min plus standard of care, or standard of care alone, to painful areas of the feet [14]. Standard of care was optimized for each patient. Throughout the study, patients could receive up to seven patch treatments (≥ 8 weeks apart). At baseline, the mean age of patients was 60 years, the mean duration of PDPN was 4.3 years and the mean Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score was 41.5. The primary endpoint was the percentage change in the Norfolk QOL-DN total score from baseline to study end (discussed in Sect. 5.1). Key secondary efficacy endpoints included the mean change from baseline in BPI-DN pain scores and Patient Global Impression of Change (PGIC) response rates. Formal statistical testing was not performed [14]. Discussion in this section focuses on the recommended application time of the capsaicin 8% dermal patch in patients with PDPN (i.e. 30 min) [6]; however, for completeness, data for all treatment groups are included in Table 2.

Compared with standard of care alone, the capsaicin 8% dermal patch plus standard of care reduced average daily pain, pain severity and pain interference (assessed by BPI-DN scores) (Table 2) [11, 15]. The proportion of patients achieving a ≥ 30% reduction in average pain score (BPI-DN question 5) was 67% with the capsaicin 8% dermal patch plus standard of care and 41% with standard of

Table 1 Efficacy of capsaicin 8% dermal patch in patients with painful diabetic peripheral neuropathy in the STEP trial

Endpoint [13]	CAP ($n=186$)	PL ($n=183$)
Mean change from BL in BPI-DN average daily pain score (%)		
Weeks 2–8[a]	− 27.4*	− 20.9
Weeks 2–12	− 28.0*	− 21.0
≥ 30% reduction from BL in BPI-DN average daily pain score (% of pts)		
Weeks 2–8	40	33
Weeks 2–12	41*	32
Median time to treatment response (days)[b]	19	72
≥ 50% reduction from BL in BPI-DN average daily pain score (% of pts)		
Weeks 2–8	21	18
Weeks 2–12	22	19
Mean change from BL in BPI-DN sleep interference score (%)		
Weeks 2–8	− 33.1*	− 24.2
Weeks 2–12	− 34.0*	− 24.7
PGIC improvement[c] (% of pts)		
Week 8	39	30
Week 12	41	30

BL baseline, *BPI-DN* Brief Pain Inventory-Diabetic Neuropathy, *CAP* capsaicin 8% dermal patch, *PGIC* Patient Global Impression of Change, *PL* placebo, *pts* patients

*$p \leq 0.05$ vs. PL

[a]Primary endpoint

[b]Time required for 50% of pts to achieve a ≥ 30% reduction from BL in BPI-DN average daily pain score

[c]Very much or much improved

Table 2 Efficacy and safety of capsaicin 8% dermal patch in patients with painful diabetic peripheral neuropathy in the PACE trial

Mean change from BL at study end[a] [11, 14, 15]	CAP + SOC		SOC ($n=155$)
	30 min ($n=156$)	60 min ($n=157$)	
Norfolk QOL-DN total score (%)[b]	− 27.6	− 32.8	− 6.7
UENS total score	− 2.1	− 3.0	− 1.2
BPI-DN pain scores			
Average daily pain	− 2.0	− 2.3	− 1.1
Pain severity index	− 1.9	− 2.2	− 0.9
Pain at its worst in last 24 h	− 2.3	− 2.6	− 1.2
Pain at its least in last 24 h	− 1.5	− 1.8	− 0.7
Pain right now	− 1.7	− 2.0	− 0.8
Pain interference index	− 1.9	− 2.0	− 0.8
EQ-5D VAS	+ 10.4	+ 11.2	+ 5.5

BL baseline, *BPI-DN* Brief Pain Inventory-Diabetic Neuropathy, *CAP* capsaicin 8% dermal patch, *EQ-5D* European Quality of Life Questionnaire in 5 Dimensions, *QOL-DN* Quality of Life-Diabetic Neuropathy, *SOC* standard of care, *UENS* Utah Early Neuropathy Scale, *VAS* visual analogue scale

[a]No formal statistical testing was performed to calculate *p*-values for the difference between CAP + SOC and SOC

[b]Primary safety endpoint; a reduction in score represents no deterioration

care alone [11]. Similar results were seen with regard to the proportion of patients achieving a ≥ 50% reduction in average pain score (45 vs. 24%). At study end, ≈ 70% of patients receiving the capsaicin 8% dermal patch plus standard of care were very much, much or minimally improved on the PGIC versus 39% with standard of care alone [11].

The capsaicin 8% dermal patch plus standard of care was also associated with improvements in HR-QOL (Table 2) and treatment satisfaction relative to standard of care alone

(available as an abstract) [15]. More patients receiving the capsaicin 8% dermal patch plus standard of care versus standard of care alone had no problems with pain or discomfort, mobility, self-care, usual activities and anxiety or depression, reported improvements in pain level, activity level, QOL and willingness to undergo treatment again, and preferred the study treatment to their previous treatment (numerical data not reported) [15].

4.2 Non-Diabetic Peripheral Neuropathic Pain

The 8-week randomized, multicentre, open-label ELEVATE trial investigated the efficacy of the capsaicin 8% dermal patch compared with oral pregabalin in patients with non-diabetic PNP [16]. The trial enrolled patients aged 18–80 years with a documented diagnosis of probable or definite PNP due to post-traumatic nerve injury (51% of patients), non-diabetic painful peripheral polyneuropathy (25%) or PHN (24%); patients with HIV-AN were excluded. All patients had an average baseline NPRS score of ≥4 over a period of ≥4 consecutive days. Patients were randomized to receive the capsaicin 8% dermal patch (a single 30-min application to the feet or a single 60-min application to any other part of the body; $n=282$) or an optimized dosage of oral pregabalin (initiated at 75 mg/day and increased by 75 mg every 3–4 days, up to a maximum of 600 mg/day; $n=277$). The primary endpoint was the proportion of patients achieving a ≥30% reduction in the mean NPRS score from baseline to week 8. Non-inferiority was established if the two-sided 95% confidence interval (CI) for the odds ratio (OR) of the capsaicin 8% dermal patch versus pregabalin was >0.693 in both the full analysis set (FAS) and per-protocol set (PPS) [16].

The capsaicin 8% dermal patch was non-inferior to oral pregabalin in providing pain relief in patients with PNP, with a faster onset of action [16]. At week 8, the proportion of patients with a ≥30% reduction from baseline in the mean NPRS score was 56% in the capsaicin 8% dermal patch group and 55% in the pregabalin group. The BGD (capsaicin 8% dermal patch-pregabalin) was 1.2% (OR 1.03; 95% CI 0.71–1.50) in the FAS and 0.3% (OR 1.03; 95% CI 0.70–1.52) in the PPS. The median time to pain relief (where 50% of patients had a 30% reduction in NPRS scores over 3 consecutive days) was 7.5 days in the capsaicin 8% dermal patch group and 36.0 days in the pregabalin group ($p<0.0001$; FAS). The change in mean NPRS score from baseline to between weeks 2–8 was −37.1% in the capsaicin 8% dermal patch group and −27.5% in the pregabalin group (FAS) [16].

The proportion of patients in the FAS who achieved optimal therapeutic effect (defined as no change in background chronic pain medication; no discontinuation of study drug due to lack of efficacy or tolerability prior to week 8; ≥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) was 52% in the capsaicin 8% dermal patch group and 45% in the pregabalin group [16].

The capsaicin 8% dermal patch was associated with a higher level of treatment satisfaction than pregabalin, as assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM) [16]. At week 8, TSQM scores were significantly (p-values not stated) higher for the capsaicin 8% dermal patch versus pregabalin for patient perception of effectiveness (59.1 vs. 54.8; BGD 4.3; 95% CI 0.4–8.1), side effects (95.3 vs. 74.1; BGD 21.2; 95% CI 17.5–24.9) and global satisfaction (59.6 vs. 52.9; BGD 6.7; 95% CI 2.3–11.2). The TSQM score for convenience was not significantly different between treatment groups (71.8 vs. 72.8). The proportion of patients willing to continue treatment at week 8/end of study was 78% in the capsaicin 8% dermal patch group and 66% in the pregabalin group [16].

In a post hoc analysis of ELEVATE, the capsaicin 8% dermal patch was superior to pregabalin in reducing the intensity and area of dynamic mechanical allodynia (DMA), a typical symptom of PNP [17]. Analyses were based on patients with DMA at baseline, defined as an NPRS score of >0 and a sensitive area of allodynia of >0 cm^2 ($n=488$). The least square (LS) mean change in DMA intensity (assessed on the NPRS scale) from baseline to week 8/end of study significantly ($p=0.002$) favoured the capsaicin 8% dermal patch over pregabalin (−2.98 vs. −2.35). The capsaicin 8% dermal patch was also significantly ($p=0.009$) more effective than pregabalin in reducing the area of DMA from baseline to week 8/end of study (LS mean change −76.2 vs. −33.1 cm^2). Significantly ($p=0.001$) more capsaicin 8% dermal patch than pregabalin recipients had complete resolution of allodynia at week 8/end of study (24 vs. 8%) [17].

4.2.1 Postherpetic Neuralgia

The efficacy of the capsaicin 8% dermal patch in patients with PHN was evaluated in two 12-week, randomized, multicentre, double-blind, phase III trials: study C116 [18] and study C117 [19]. Both trials enrolled patients aged 18–90 years with PHN for ≥6 months and an average baseline NPRS score of 3–9. Patients were randomized to receive a single 60-min application of the capsaicin 8% dermal patch or a low-concentration (0.04% w/w capsaicin) control patch to the painful area(s). The primary endpoint of both trials was the percentage change in NPRS score from baseline to weeks 2–8 [18, 19].

The capsaicin 8% dermal patch provided rapid and sustained pain relief in patients with PHN [18, 19]. In both trials, the capsaicin 8% dermal patch reduced the mean NPRS score from baseline to a significantly greater extent

than the control patch during weeks 2–8 (Table 3) [18, 19]. The difference favouring the capsaicin 8% dermal patch over the control patch was observed from the first [18] or second [19] week and was significant ($p < 0.05$) at every subsequent week. The proportion of patients with a ≥30% reduction from baseline in mean NPRS score during weeks 2–8 was significantly higher in the capsaicin 8% dermal patch group than in the control group (Table 3) [18, 19]. Similarly, the proportion of patients with a reduction from baseline in mean NPRS score of ≥2 points during weeks 2–8 was significantly ($p < 0.01$) greater in the capsaicin 8% dermal patch group than the control group in study C116 (40 vs. 25%) [18] and in study C117 (42 vs. 26%) [19]. In study C116, the change from baseline in mean NPRS score during weeks 2–8 was significantly ($p < 0.01$) greater with the capsaicin 8% dermal patch than the control patch regardless of whether or not patients were receiving concomitant neuropathic pain medications (post hoc analysis) [18].

In both trials, the proportion of patients with PGIC improvement (Table 3) was significantly higher in the capsaicin 8% dermal patch group than in the control group [18, 19]. In study C117, significantly more capsaicin 8% dermal patch than control recipients were judged by the study investigators to be improved on the Clinical Global Impression of Change (Table 3) [19]. In study C116, 4.9% of capsaicin 8% dermal patch recipients and 4.6% of control patch recipients withdrew from the study early because of unsatisfactory therapeutic response [18]; corresponding rates in study C117 were 0.5 and 2.5% [19].

Longer term, pain reductions were maintained with repeated applications of the capsaicin 8% dermal patch in patients with PHN [20, 21]. Study C106 was a 40-week, open-label extension of a 4-week pilot study (C102) [20],

Table 3 Efficacy of capsaicin 8% dermal patch in patients with postherpetic neuralgia or HIV-associated neuropathy

Study	Treatment [duration (min)]	No. of pts	Mean change from BL in NPRS score (%)	Response rate[a] (% of pts)	PGIC improvement[b] (% of pts)	CGIC improvement[b] (% of pts)
PHN						
Study C116 [18]	CAP (60)	206	− 29.6***[c]	42*	55*	
	CON (60)	196	− 19.9	32	43	
Study C117 [19]	CAP (60)	212	− 32.0*[c]	46*	61**	63**
	CON (60)	204	− 24.4	34	47	48
HIV-AN						
Study C107 [22]	Pooled CAP	225	− 22.8**[c]	34**	67***	66**
	Pooled CON	82	− 10.7	18	31	37
	CAP (30)	72	− 27.7***	42**	66***	65**
	CAP (60)	78	− 15.8	24	70***	63*
	CAP (90)	75	− 24.7**	36**	65*	70**
Study C119 [23]	Pooled CAP	332	− 29.5	43	67*	66**
	Pooled CON	162	− 24.5	36	55	52
	CAP (30)	167	− 26.2	39	65†	65††
	CON (30)	73	− 19.1	26	45	39
	CAP (60)	165	− 32.8	48	69	66
	CON (60)	89	− 30.0	45	63	63
Integrated analysis [24]	Pooled CAP	482	− 27.4**	40**	67***	
	Pooled CON	215	− 20.0	31	49	
	CAP (30)	239	− 26.9†	40†	65††	
	CON (30)	100	− 15.8	23	41	
	CAP (60)	243	− 27.9	40	69‡	
	CON (60)	115	− 24.2	37	57	

BL baseline, *CAP* capsaicin 8% dermal patch, *CGIC* Clinical Global Impression of Change, *CON* low-concentration (0.04% w/w capsaicin) control patch, *HIV-AN* HIV-associated neuropathy, *NPRS* Numeric Pain Rating Scale, *PGIC* Patient Global Impression of Change, *PHN* postherpetic neuralgia, *pts* patients

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. CON; †$p < 0.01$, ††$p < 0.001$ vs. CON (30); ‡$p < 0.05$ vs. CON (60)

[a]A ≥30% reduction from BL in NPRS mean score during weeks 2–8 in PHN [18, 19] or weeks 2–12 in HIV-AN [22–24]

[b]Very much, much or slightly improved at week 12

[c]Primary endpoint (i.e. mean change from BL during weeks 2–8 in PHN [18, 19] or weeks 2–12 in HIV-AN [22–24])

and study C118 was a 48-week, open-label, phase II trial in patients with PHN ($n=54$) or HIV-AN ($n=52$) [21]. Eligible patients received up to three additional 60-min applications of the capsaicin 8% dermal patch at intervals of ≥ 6 [20] or ≥ 12 [21] weeks based on pain recurrence. In study C106, the mean reductions from baseline in NPRS score following the first ($n=21$), second ($n=15$) and third ($n=9$) retreatments were 31.4%, 30.0% and 34.1%, respectively [20]. At week 48 in study C118, the mean reduction from baseline in NPRS score in patients with PHN was 35.6%, with 75% of patients reporting improvement on the PGIC scale [21].

4.2.2 HIV-Associated Neuropathy

The efficacy of the capsaicin 8% dermal patch in patients with HIV-AN was evaluated in two randomized, double-blind, phase III trials: study C107 [22] and study C119 [23]. Eligible patients had painful HIV-associated distal sensory polyneuropathy for ≥ 2 months and an average baseline NPRS score of 3–9. The capsaicin 8% dermal patch or a low-concentration (0.04% w/w capsaicin) control patch was applied to painful areas of the feet for 30 min, 60 min or 90 min in study C107 [22] and 30 or 60 min in study C119 [23]. The primary endpoint of both trials was the percentage change in NPRS score from baseline to weeks 2–12 [22, 23]. Discussion in this section focuses on the recommended application time of the capsaicin 8% dermal patch in patients with HIV-AN (i.e. 30 min) [6]; however, for completeness, data for all treatment groups are included in Table 3.

In study C107, a 30-min application of the capsaicin 8% dermal patch reduced the mean NPRS score from baseline to a significantly greater extent than the control patch during weeks 2–12 (Table 3) [22]. This result was seen regardless of whether or not patients were receiving other neuropathic pain medications. A 30-min application of the capsaicin 8% dermal patch was also significantly better than the control patch in terms of response rate, PGIC improvement and CGIC improvement (Table 3) [22]. In study C119, there was a large difference between the 30- and 60-min control groups in the mean percentage change from baseline in NPRS score (−19.1 vs. −30.0%; Table 3), preventing the intended pooling of the control groups according to prespecified criteria [23]. Therefore, comparisons were performed between the individual capsaicin 8% dermal patch groups and their respective control groups; these comparisons were of low power for detecting treatment differences and did not reach statistical significance for the primary endpoint or most secondary endpoints, except for PGIC and CGIC improvement with the 30-min application (Table 3). Of note, post hoc non-parametric analyses of the primary endpoint demonstrated statistically significant differences between the pooled and 30-min capsaicin 8% dermal patch groups and their respective control groups (both $p<0.05$) [23].

An integrated analysis of study C107 and study C119 demonstrated that the capsaicin 8% dermal patch was significantly more effective than the control patch in reducing the NPRS score from baseline during weeks 2–12 (Table 3) [24]. Rates of treatment response and PGIC improvement were significantly higher with the capsaicin 8% dermal patch than the control patch (Table 3). For both the primary endpoint and responder analysis, a 30-min application of the capsaicin 8% dermal patch was more effective than the control patch regardless of gender, median baseline NPRS score (< 6.07 or ≥ 6.07), median duration of HIV-associated distal polyneuropathy (< 5.1 or ≥ 5.1 years) and use of concomitant neuropathic pain medications (defined as receiving an antiepileptic, non-selective serotonin reuptake inhibitor antidepressant or opioid on day –1 and for ≥ 7 consecutive days) [24].

The efficacy of the capsaicin 8% dermal patch was maintained for up to 1 year with repeated applications in patients with HIV-AN, according to a 40-week, open-label extension of study C107 [25] and study C118, a 48-week, open-label, phase II trial in patients with HIV-AN ($n=52$) or PHN ($n=54$) [21]. Eligible patients received up to three additional 60-min applications of the capsaicin 8% dermal patch ≥ 12 weeks apart [21, 25]. In the extension phase of study C107, the mean reductions in NPRS score from baseline to weeks 2–12 following the first ($n=57$), second ($n=50$) and third ($n=28$) retreatments were 27.1, 24.6 and 22.7%, respectively [25]. Among patients who responded to the first treatment ($n=122$), the median time of maintained response was 17 weeks. Approximately one-third of these patients maintained their response at week 52 after only a single application of the capsaicin 8% dermal patch [25]. At week 48 in study C118, the mean reduction from baseline in NPRS score in patients with HIV-AN was 12.4%, with 80% of patients reporting improvement on the PGIC scale [21].

4.3 In the Real-World Setting

Real-world experience has confirmed the efficacy of the capsaicin 8% dermal patch for the treatment of PNP [26–42]. Some data are available as abstracts [34–39]. In several large ($n>400$), prospective, observational, non-interventional studies conducted in Germany [26, 27], Scandinavia [28] and seven European countries [29], the capsaicin 8% dermal patch provided effective pain relief and improved QOL in non-diabetic patients with PNP of various aetiologies.

The largest of these studies (QUEPP) recruited 1044 patients with PNP, including those with PHN (32% of patients), post-surgical neuralgia (23%), mixed pain syndromes (17%), polyneuropathy (14%) and post-traumatic neuropathy (12%) [26]. A single application of the

capsaicin 8% dermal patch (for 30 min to the feet or 60 min to other parts of the body) significantly ($p \leq 0.001$) reduced the mean NPRS score from baseline at the first assessment (7–14 days), with this improvement maintained through 12 weeks. From day 7–14 to week 12, the proportions of patients with a ≥ 30 and ≥ 50% reduction from baseline in mean NPRS score were 41 and 24%, respectively. The capsaicin 8% dermal patch significantly (all $p \leq 0.001$) reduced the frequency and intensity of pain attacks and the proportion of patients receiving long-term concomitant antiepileptics or opioids, improved sleep duration and sleep quality, and reduced the number of days absent from work due to neuropathic pain [26]. A retrospective subgroup analysis of the QUEPP study demonstrated that the extent of pain relief following application of the capsaicin 8% dermal patch decreased with increasing duration of pre-existing pain, suggesting greater benefits from early initiation of therapy [27].

The QUEPP findings are further supported by results from a phase IV, multicentre study (ASCEND; $n = 429$) [29] and a combined analysis of three studies conducted concurrently in Denmark, Norway and Sweden ($n = 412$) [28]. For instance, in ASCEND, the reduction in mean NPRS score from baseline to weeks 2–8 (co-primary endpoint) following the first application of the capsaicin 8% dermal patch was 26.6%; pain relief was sustained until week 52 [29]. The median time from first to second patch application (co-primary endpoint) was 191 days [29].

A number of small ($n < 100$), observational studies (of prospective [32–34, 38–40] or retrospective [30] design, where specified) have also confirmed the efficacy of the capsaicin 8% dermal patch in patients with various types of PNP, including PHN [30, 37, 40], post-traumatic neuropathic pain [30, 40], post-surgical neuropathic pain [30, 36–40], polyneuropathy [37, 40], chemotherapy-induced neuropathy [31, 35], lumbosacral neuropathic pain [34], pelvic neuralgia [32], neuropathic pain from critical ischaemia [33], refractory neuropathic pain due to neurofibromatosis type 1 [41] and phantom limb pain [42].

5 Tolerability of Capsaicin 8% Dermal Patch

The capsaicin 8% dermal patch was generally well tolerated in patients with PNP. Treatment-related adverse events (AEs) were reported by 60% of 1826 patients who received the capsaicin 8% dermal patch in randomized controlled trials [6]. AEs leading to discontinuation occurred in 2% of patients treated with the capsaicin 8% dermal patch and 1% of patients treated with the control patch [6]. Across controlled trials, the overall incidence of serious AEs was 6% in capsaicin 8% dermal patch recipients and 4% in control patch recipients [11]. One serious AE (increased BP during and after patch application) was considered to be possibly related to the capsaicin 8% dermal patch. The most commonly reported AEs with the capsaicin 8% dermal patch were application-site reactions, including dryness, erythema, oedema, pain, papules and pruritus. Most application-site reactions were generally non-serious, mild to moderate in severity and resolved spontaneously within 7 days [11].

In an integrated analysis of tolerability data from the clinical trial program in patients with PHN ($n = 920$), HIV-AN ($n = 685$) and PDPN ($n = 91$), increases in application-site pain were transient and generally resolved following removal of the capsaicin 8% dermal patch [43]. Repeated applications of the capsaicin 8% dermal patch did not affect the intensity of application-site pain. Most (99%) patients were able to tolerate the capsaicin 8% dermal patch to complete ≥ 90% of the full intended treatment duration [43].

The capsaicin 8% dermal patch was associated with fewer systemic AEs than oral pregabalin in the ELEVATE trial [16]. Drug-related treatment-emergent AEs (TEAEs) occurred in 61% of capsaicin 8% dermal patch recipients and 55% of pregabalin recipients. However, the nature of AEs differed between treatment groups. Transient application-site pain (24%), erythema (21%), burning sensation (16%) and application-site erythema (9%) were the most commonly reported TEAEs with the capsaicin 8% dermal patch, while systemic AEs such as dizziness (18%), somnolence (16%), nausea (11%) and headache (9%) were the most commonly reported TEAEs with pregabalin [16]. These results were confirmed in a 'burden of therapy' analysis, which demonstrated an initial peak followed by a rapid decline in TEAEs per day in the capsaicin 8% dermal patch group [44]. Conversely, in the pregabalin group, there was a gradual increase and relatively consistent burden followed by a minor decrease in TEAEs per day. The overall burden estimate (based on the number and severity of TEAEs) was significantly ($p = 0.0001$) higher with pregabalin than with the capsaicin 8% dermal patch (61.2 vs. 23.5) [44]. AEs leading to discontinuation occurred in 0% of patients in the capsaicin 8% dermal patch group and 9% of patients in the pregabalin group [16].

The tolerability profile of the capsaicin 8% dermal patch patients with PDPN was consistent with that seen in the non-diabetic population [6]. In the STEP trial, TEAEs were reported in 47% of capsaicin 8% dermal patch recipients and 34% of placebo recipients, with application-site reactions reported in 34 and 8% of patients [13]. No patients discontinued treatment due to drug-related TEAEs [13]. In the PACE trial, the most commonly reported TEAEs associated with a 30-min application of the capsaicin 8% dermal patch were application-site pain (28%), burning sensation (9%) and application-site erythema (8%) [14].

Longer term, the capsaicin 8% dermal patch continued to be generally well tolerated in patients with PNP. The incidence of AEs did not increase with repeated applications of

the capsaicin 8% dermal patch for up to 52 weeks [11, 14, 20, 21, 43].

5.1 Adverse Events of Special Interest

Across controlled trials, the overall incidence of cardiac AEs was 3% with the capsaicin 8% dermal patch and 3% with the control patch [11]. Cardiac AEs were classified as severe or serious in 1.1% and 1.2% of capsaicin 8% dermal patch recipients compared with 0.3% and 0.5% of control patch recipients. There were no ECG changes related to treatment with the capsaicin 8% dermal patch. Hypertension was the most commonly reported systemic AE, occurring in 3% of capsaicin 8% dermal patch recipients and 1% of control patch recipients. Four cases (< 1%) of hypertension and six cases (< 1%) of increased BP were considered to be at least possibly related to the capsaicin 8% dermal patch [11]. Transient increases in BP (< 8.0 mmHg) associated with increases in application-site pain have occurred during and shortly after exposure to the capsaicin 8% dermal patch [6]. Therefore, BP should be monitored during the treatment procedure [6].

There have been reports of generally minor and transient reductions in sensory function following application of the capsaicin 8% dermal patch [6]. However, in the STEP and PACE trials, application of the capsaicin 8% dermal patch was not associated with worsening sensory function, with respect to sharp, warm, cold and vibration sensations [13, 14]. Most patients demonstrated no change or improvement from baseline to study end in sensory perception and reflex testing [13, 14]. In the PACE trial, repeat treatment with the capsaicin 8% dermal patch plus standard of care over 52 weeks had no negative functional or neurological effects compared with standard of care alone. A 30-min application of the capsaicin 8% dermal patch plus standard of care was associated with no deterioration in Norfolk QOL-DN and Utah Early Neuropathy Scale (UENS) total scores versus standard of care alone (Table 2). Similar results were seen in the subgroup of patients ($n = 167$) who received the maximum of seven capsaicin 8% dermal patch treatments. No deterioration in any of the Norfolk QOL-DN or UENS subscale scores was observed with the capsaicin 8% dermal patch plus standard of care versus standard of care alone [14]. Caution is advised in patients with reduced sensation in the feet and in patients at increased risk for changes in sensory function [6]. Treatment with the capsaicin 8% dermal patch should be reconsidered if sensory loss develops or worsens [6].

5.2 In the Real-World Setting

Tolerability data from the real-world setting were generally consistent with those from clinical trials. In the largest real-world studies (QUEPP and ASCEND), treatment-related AEs were reported in 11–12% of patients [26, 29]. The most commonly reported AEs were application-site reactions, including pain (5–8%) and erythema (2–8%) [26, 29]. In QUEPP, the tolerability of the capsaicin 8% dermal patch was rated by physicians as 'very good' (37%),'good' (43%) or 'bad' (2%) [26]. The majority (> 92%) of patients in ASCEND completed ≥ 90% of the suggested patch application duration at first or subsequent treatments [29].

The long-term (52 weeks) safety and tolerability of the capsaicin 8% dermal patch in patients with non-diabetic PNP was also investigated in the phase IV, prospective, observational STRIDE trial ($n = 306$) [45]. The capsaicin 8% dermal patch was generally well tolerated, with no accumulation of AEs after multiple applications. The most commonly reported (≥ 5% incidence) drug-related TEAEs were application-site pain (37%), erythema (20%), application-site erythema (17%), burning sensation (14%) and pain (10%). Treatment with the capsaicin 8% dermal patch resulted in variable sensory alteration; both improvement and worsening of sensation were observed, with a minimal risk of complete sensory loss [45].

6 Dosage and Administration of Capsaicin 8% Dermal Patch

The capsaicin 8% dermal patch is indicated in the EU for the treatment of PNP in adults, either alone or in combination with other medicinal products for pain [6]. The capsaicin 8% dermal patch is 280 cm^2 in size and contains 179 mg of capsaicin (i.e. 640 µg/cm^2; 8% w/w). The recommended dosage is a single, 30-min application of up to four patches when applied to the feet (e.g. in patients with PDPN or HIV-AN) or a single, 60-min application of up to four patches when applied to other locations (e.g. in patients with PHN). Treatment may be repeated every 90 days, as warranted by the persistence or return of pain [6].

The efficacy and tolerability of the capsaicin 8% dermal patch in children and adolescents ≤ 18 years has not been established [6]. No dosage adjustments are necessary in patients with renal or hepatic impairment. Due to a lack of data, the capsaicin 8% dermal patch should be used with caution in pregnant women. It is unknown whether capsaicin metabolites are excreted in human milk. However, it is advised that women do not breastfeed during treatment with the capsaicin 8% dermal patch [6].

Local prescribing information should be consulted for detailed information regarding patch application, contraindications, warnings and precautions, and use in special patient populations.

7 Place of Capsaicin 8% Dermal Patch in the Management of Peripheral Neuropathic Pain

Clinical practice guidelines for the treatment of PNP generally recommend first-line therapy with antiepileptics (e.g. gabapentin, pregabalin) and antidepressants (e.g. tricyclic antidepressants, duloxetine, venlafaxine), with tramadol, opioids and topical preparations (e.g. lidocaine, capsaicin) recommended as second-line therapy [46–49]. Due to its topical route of administration and low systemic exposure (Sect. 3), the capsaicin 8% dermal patch may offer some advantages over systemic therapies, including a more rapid and longer duration of effect, fewer tolerability issues and a lower risk of drug–drug interactions.

The efficacy of the capsaicin 8% dermal patch in patients with PNP has been demonstrated in several randomized, phase III trials (Sect. 4). In patients with PDPN, a single 30-min application of the capsaicin 8% dermal patch provided 12 weeks of pain relief and improved sleep quality compared with placebo (Sect. 4.1.1). Of note, an appreciable 'placebo effect' was observed, with an improvement in mean daily pain scores of ≈20%. Repeat treatment with the capsaicin 8% dermal patch plus standard of care over 52 weeks provided sustained pain relief and improved HR-QOL (Sect. 4.1.2), without negative functional or neurological effects compared with standard of care alone (Sect. 5.1). However, the use of 'bedside' sensory testing in these trials instead of Quantitative Sensory Testing may have provided less sensitivity in detecting small variations of thermal or mechanical deficits [13, 14].

The capsaicin 8% dermal patch provided non-inferior pain relief to oral pregabalin in patients with non-diabetic PNP in the ELEVATE trial, with a faster onset of action and greater treatment satisfaction (Sect. 4.2). Of note, the capsaicin 8% dermal patch was superior to pregabalin in reducing the intensity and area of DMA, a common clinical manifestation of PNP. In patients with PHN, a single 60-min application of the capsaicin 8% dermal patch provided rapid and sustained pain relief, with pain reductions maintained over the longer term with repeated patch applications (Sect. 4.2.1). Results in patients with HIV-AN were equivocal, with a significant improvement in pain intensity observed in one trial, but not in the other (Sect. 4.2.2). Nevertheless, data from these two trials led to the capsaicin 8% dermal patch receiving a level A efficacy rating in the European Federation of Neurological Sciences guidelines for HIV-AN [24, 46].

Data from real-world studies of the capsaicin 8% dermal patch in patients with various types of PNP, in particular from large, prospective studies conducted in Europe, were consistent with those seen in clinical trials, suggesting that the capsaicin 8% dermal patch is an effective therapy beyond PHN and HIV-AN in non-diabetic patients (Sect. 4.3). However, it should be noted that most of these studies were limited to a single patch application. Longer-term, large-scale observational studies investigating the efficacy of repeated applications of the capsaicin 8% dermal patch in the real-world setting would be of interest.

The capsaicin 8% dermal patch was generally well tolerated in patients with PNP (Sect. 5). The most common AEs were application-site reactions; these were generally transient, non-serious and of mild to moderate severity. According to an integrated analysis of tolerability data from the clinical trial program, patient adherence to the full intended treatment duration indicated that application-site pain was not a barrier to use of the capsaicin 8% dermal patch (Sect. 5). In most cases, patch application-related pain can be adequately managed with oral analgesics and/or local cooling measures [43].

To date, few randomized controlled trials have directly compared the capsaicin 8% dermal patch with other medications for pain, particularly other topical agents such as the lidocaine 5% medicated plaster, which is indicated for the symptomatic relief of neuropathic pain associated with herpes zoster infection (i.e. PHN) [50]. A network meta-analysis demonstrated that the capsaicin 8% dermal patch was as effective as oral centrally acting agents (i.e. pregabalin, duloxetine and gabapentin) in patients with PDPN, with systemic tolerability benefits [51]. However, results of these indirect comparisons should be interpreted with caution. Further comparative efficacy and tolerability trials of the capsaicin 8% dermal patch relative to other analgesics would be of great interest.

Patients with neuropathic pain use substantially more healthcare resources (including office visits and medications) than patients with non-neuropathic pain or no pain [52]. Cost-effectiveness analyses published to date in patients with PNP suggest that the capsaicin 8% dermal patch is cost-effective compared with oral agents, including tricyclic antidepressants, duloxetine, gabapentin and pregabalin [52, 53]. In a modelled pharmacoeconomic study conducted in Scotland (model inputs taken from the ELEVATE trial), the probability of the capsaicin 8% dermal patch being cost-effective versus pregabalin was 97% at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year gained [52].

In conclusion, the high-concentration (8% w/w) capsaicin dermal patch is an effective and well tolerated treatment in patients with PNP, including PDPN, PHN and HIV-AN. It can be used alone or in combination with other medicinal products for pain. The capsaicin 8% dermal patch is designed to provide rapid, long-lasting pain relief following a single application, and is a useful addition to

the treatment options currently available for patients with PNP.

Data Selection Capsaicin 8% Dermal Patch: 267 records identified	
Duplicates removed	52
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	126
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	36
Cited efficacy/tolerability articles	34
Cited articles not efficacy/tolerability	19
Search strategy: EMBASE, MEDLINE and PubMed from 2016 to present. Previous Adis Drug Evaluation published in 2016 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were capsaicin 8%, Qutenza, NGX4010, Transacin, Transdolo. Records were limited to those in English language. Searches last updated 10 September 2018.	

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Compliance with Ethical Standards

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