AWMSG Secretariat Assessment Report – Advice no. 0412
Capsaicin (Qutenza®▼) 179 mg cutaneous patch

This assessment report is based on evidence submitted by Astellas Pharma Ltd on 9 September 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Capsaicin (Qutenza®▼) is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain[1].
Dosing	Capsaicin patches should be applied to the most painful skin areas, using up to a maximum of 4 patches. Capsaicin patches should remain in place for 30 minutes for the feet and 60 minutes for other locations. Capsaicin patch treatments may be repeated every 90 days, as warranted by the persistence or return of pain. Capsaicin patches should be applied by a physician or by a health care professional under the supervision of a physician. Refer to the Summary of Product Characteristics (SPC) for further information regarding pre-treatment and treatment following patch removal[1].
Marketing authorisation date	15 May 2009[1].
UK launch date	11 April 2011[2].

2.0 DECISION CONTEXT

2.1 Background

Peripheral neuropathic pain (PNP) is defined as pain caused by a lesion or disease of the peripheral somatosensory nervous system[3] and is commonly associated with conditions such as painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN) and HIV-associated neuropathy (HIV-AN)[4,5]. Clinical features of PNP can include disabling symptoms of burning, stinging, shooting pain or electrical sensations, paraesthesias, allodynia and hyperalgesia[4,6]. There is no definitive, accurate estimate for the population prevalence of neuropathic pain; considerable variability exists in estimates of both incidence and prevalence, possibly due to differences in the definitions of neuropathic pain, methods of assessment and patient selection[4]. Recent estimates suggest the prevalence of neuropathic pain as 7 to 8% in the European population[7,8].

In non-specialist settings (primary and general hospital care), commonly used pharmacological treatments for the treatment of neuropathic pain include antidepressants, anticonvulsant drugs, opioid analgesics and topical treatments such as capsaicin and lidocaine[4,6]. Current guidelines from the National Institute for Health and Clinical Excellence (NICE) suggest that oral amitriptyline (unlicensed indication) or

pregabalin should be offered as the first line treatment for neuropathic pain; as a second line therapy, it is suggested that amitriptyline-treated patient should switch to or combine with pregabalin, while pregabalin-treated patients should switch to or combine with amitriptyline. Patients requiring a third line of a therapy should be referred to a specialist pain service and offered oral tramadol instead of or in combination with the second line treatment or topical lidocaine[4].

Capsaicin is a highly selective agonist for the transient receptor potential vanilloid 1 (TRPV1) receptor, which is abundant on sensory neurons that transmit the sensations of pain (nociceptors)[1,6]. Persistent stimulation of TRPV1 receptors may result in desensitisation of nociceptors and an analgesic effect due to consequent decrease in sensitivity to relevant noxious stimuli. High concentrations of capsaicin are suggested to quickly desensitise cutaneous nociceptors, causing pain relief and less burning sensation than low concentrations of capsaicin. Capsaicin (Qutenza®▼) is a high concentration cutaneous patch containing 179 mg (8%) of capsaicin per patch[6]. Capsaicin patches are administered in a specialist clinic setting by healthcare professionals who have completed MHRA approved training on application, removal and disposal of the patches[2].

2.2 Comparators

The comparators requested by WMP were:

- lidocaine plaster (Versatis®)
- capsaicin (0.075%) cream (Axsain®)
- pregabalin (Lyrica®)
- gabapentin

The company submission does not include direct comparisons against these medicines. Instead the submission compares capsaicin patch use in addition to usual care versus usual care alone, where usual care is defined as a mixture of concomitant pain medication or observation (refer to section 4)[2]. The rationale for this decision is partly based upon a survey of six pain specialists in Wales, which indicated that medicines such as amitriptyline, lidocaine plaster, capsaicin cream, pregabalin and gabapentin are prescribed to patients with PNP in the non-specialist primary care setting[2,9]. As capsaicin patches require application in the specialist setting[2]; the company suggest that these patients reflect a refractory population who have previously failed to achieve satisfactory analgesia using other medications. Five of the pain specialists surveyed felt that capsaicin patches would be most likely used as a supplement to current pain therapies. However, one specialist felt that capsaicin patch use would displace lidocaine patch use and opiate therapies[2].

2.3 Guidance and related advice

- NICE clinical guidelines 96. Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings (2010)[4].
- European Federation of Neurological Societies (EFNS) guidelines on the pharmacological treatment of neuropathic pain: 2010 revision[10].
- British Pain Society. Recommended guidelines for Pain Management Programmes for adults (2007)[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes several studies that evaluated the efficacy of capsaicin cutaneous patches in two patient populations PHN (C102, C106, C108, C110, C116 and C117) and HIV-AN (C107, C109 and C119); one additional study

included patients with both conditions (C118)[2]. The company submission stated that the majority of neuropathies within PNP are accepted as comparable to PHN. The company did not include data for the HIV-AN studies as part of the Form B submission. The decision by the company was based on discussions between the company and pain specialists in Wales, which indicated that HIV-AN is not a condition seen or treated in specialist pain clinics in Wales[2].

The effectiveness of capsaicin 8% patches as demonstrated in the phase II study C118 is not discussed further in this report, as this study did not include a control arm and so does not add anything to the evidence of effectiveness which can be derived from other studies.

3.1 Overview of studies C108, C110, C116 and C117

These four phase II/III studies had very similar methods and study designs. Each were double-blind, randomised controlled studies evaluating the efficacy and tolerability of 8% capsaicin patch with that of a low concentration control 0.04% w/w capsaicin patch in patients with PHN[12–15]. Inclusion criteria incorporated patients with moderate to severe neuropathic pain secondary to PHN with an average numeric pain rating scale (NPRS) score of 3 to 9 and who had at least a 3 to 6 month gap after any vesicles due to shingles had crusted over prior to them commencing study treatment.

Following screening, patients were treated on day 0 and assessed at weeks 4, 8, and 12; study C108 also included a 40-week open-label extension phase for patients who completed the week 12 evaluation. Prior to placement of study patches, a 4% lidocaine cream (LMX 4®) was applied to the area, followed by application of the treatment patches for 60 minutes. In addition to local cooling, oxycodone solution (1 mg/ml) or equivalent could be administered at the onset of treatment-associated discomfort and as needed. Following discharge, patients could use opioid rescue medication (hydrocodone bitartrate 5 mg and paracetamol 500 mg) every eight hours for up to three (studies C108 and C110) or five (studies (C116 and C117) days following patch application for treatment-associated discomfort as needed. Topical pain medications were not permitted during the 12-week study period[12–15]. Permitted concomitant medications were limited to oral or transdermal opioids (≤ 60 mg/day morphine or equivalent), chronic pain medications (stable regimen for ≥ 21 days before study and maintained during study) or paracetamol (≤ 2 g/day)[16–19].

The primary efficacy endpoint was the percentage change in NPRS score for average pain for the past 24 hours from baseline to weeks 2 to 8[12–15]. A reduction of approximately two points or approximately 30% in the NPRS score usually represents a clinically important difference[20]. To avoid the potential confounding effect of allowed opioid rescue medications during days 0 to 3, NPRS scores from week 1 were not included in the primary analysis. Relevant secondary endpoints included Patient and Clinician Global Impression of Change (PGIC and CGIC), self-assessment of treatment (SAT), Short-form McGill Questionnaire (SF-MPQ), brief pain inventory (BPI) and percentage of patients with a ≥ 30% reduction in NPRS score from baseline to weeks 2–12. Refer to the Glossary for definitions of primary and secondary endpoints[12–15].

3.1.1 Results of studies C108, C110, C116 and C117

Table 1. Patient disposition and results from studies C108, C110, C116 and C117.

		C108[13,16]				C110[12,18]	C116[15,17]	C117[14,19]
		30 min	60 min	90 min	Pooled			
Eligible patients	Capsaicin	72	77	73	222	102	205	212
	Control	23	29	25	77	53	197	204
Application time	Capsaicin	30	60	90	N/A	60	60	60
	Control	30	60	90	N/A	60	60	60
Percentage of patients receiving one or more concomitant pain medications* at baseline	Capsaicin	75	83	84	81	76	50	55
	Control				79	79	38	58
Primary efficacy endpoint: percentage change in NPRS score for average pain for the past 24 hours from baseline to weeks 2–8	Capsaicin	-26.2	-25.6	-27.8	-26.5	-36.5	-29.6	-32.0
	Control	17.3				-29.9	-19.9	-24.4
	P value	0.088	0.104	0.0438	0.0286	0.296	0.001	0.011
* Concomitant pain medications included opioids, antidepressants, anticonvulsants and other types of pain therapies.								

Other information provided as academic in confidence.

As can be seen in Table 1, studies C116 and C117 met the primary endpoint. Although study C110 demonstrated that capsaicin patches reduced pain scores compared with the control patch, this did not reach statistical significance. Analysis of C108 primary endpoint data also demonstrated mean reductions in NPRS scores for capsaicin-treated patients when compared with the control patch group, but this was only statistically significant in the pooled group. Male patients reported smaller reductions in pain scores than female patients in both the capsaicin 8% and control groups[13]. As the 60-minute capsaicin 8% group contained a higher proportion of males (61%), a post hoc analysis of the primary endpoint data from C108 was undertaken using a gender-stratified ANCOVA model, which identified statistically significant reductions in pain scores for the 60-minute and pooled groups[13].

Analysis of secondary endpoints for these studies showed similar reductions in pain scores but only reached statistical significance for studies C116 and C117 (see Appendix 1 for further information).

Most patients received one capsaicin patch treatment during the open-label C108 extension phase; 101/299 received ≥ 2 applications[16]. Mean time to re-treatment was 268 days[2]. Although reductions in pain scores were similar in patients who received two or more treatments (mean pain scores were reduced from baseline by 21.7%, 23.3% and 19.8% after two, three and four treatments respectively), these tended to be less than those observed in subjects receiving only one treatment of capsaicin 8% (mean pain scores were reduced by 36.6%)[2,16]. Additionally, the proportion of patients that responded to treatment decreased with the number of treatments. The study investigators suggest that this could be due to the fact that those subjects who only received one treatment often did not receive additional treatments because the patient had a satisfactory initial response which had not decreased over time, and so did not qualify for additional treatment. It should be noted that patients that required more applications of capsaicin patches did tend to have higher average NPRS scores at baseline. Study C108 was prematurely terminated during the open-label extension phase following a failure to meet the pre-specified study endpoint during the double-blind study phase[2,16].

3.2 Phase II studies: C102 and C106

These studies compared the efficacy and tolerability of 8% capsaicin patch with that of a low concentration control 0.04% w/w capsaicin patch in patients with PHN[21]. Inclusion criteria, dosing and permitted concomitant medications were as described for C116 and C117 (see Section 3.1). To assess tolerability and implementation of the procedure six patients received an initial single 60 minute application of 8% capsaicin patch. Thirty-eight patients were randomised into a double-blind phase (C102) to receive either capsaicin 8% patch (n = 26) or a low-concentration capsaicin control patch (n = 12) for four weeks. Patients who completed either of these studies were eligible to enrol in the open-label extension study C106 (n = 24), during which up to three additional capsaicin 8% patch treatments could be administered. Each treatment was referred to as a cycle. Patients were followed for a maximum duration of 48 weeks from initial treatment.

The primary endpoint for C102 was change in mean morning and evening NPRS scores from baseline to days 8–28. Study 106 used primary endpoints defined as change in mean morning and evening NPRS scores from baseline to weeks 2–12 of initial treatment, from baseline to weeks 2–12 of individual cycles and from baseline to termination of study.

Baseline characteristics were broadly similar between the treatment groups in the double-blind phase; however, there were more males in the control group than the

treatment group (75% versus 23%). Patients that received the capsaicin 8% patch had a mean decrease of 32.7% from baseline in mean morning and evening NPRS scores during days 8–28, compared with a 4.4% decrease for the control group (p = 0.003). Additionally, similar reductions in mean pain scores were observed in patients during the open-label extension phase, and the magnitude of the effect remained the same irrespective of the number of treatments: -31.4% after the first open-label treatment (n = 21); -30.0% after the second open-label treatment (n = 15 receiving at least two cycles); -34.1% after the third open-label treatment (n = 9 receiving three cycles)[21].

3.3 Comparative safety

The Committee for Medicinal Products for Human Use (CHMP) provided an analysis of the safety profile of capsaicin patches, based on the 1,696 patients enrolled in clinical studies that received the capsaicin 8% patch[6].

The overall incidence of adverse events (AEs) reported in the capsaicin 8% patch-treated patients was higher (84%) when compared with the control patch group (77%). This was primarily due to a higher incidence of application site AEs, such as pain, erythema, papules, pruritus, dryness and swelling, among patients that received the capsaicin 8% patch. Application site reactions were mostly of short duration and mild to moderate intensity. Hypertension was reported as an AE in 3% of capsaicin 8% patch-treated patients, compared with 1% of control group patients; CHMP concluded this to be related to pain experienced during treatment, as blood pressure returned to levels observed in control group patient after patch removal. The only AE considered to be associated with duration of capsaicin exposure was application site pain[6].

The overall incidence of serious AEs (SAEs) was comparable between patients that received the capsaicin 8% patch (6%) and the control patch group (4%). Myocardial infarction was the only SAE reported in more than two patients: capsaicin 8% (5 cases; 0.4%) and control group (2 cases; 0.3%). Cardiac disorders were more commonly reported as SAEs in the capsaicin 8% patch group (16 cases; 1.2%) compared with the control group (4 cases; 0.5%). However, CHMP concluded that the imbalance of cardiac events is most probably not attributable to capsaicin treatment, as the event timing was varied and there was no common pathology, related dose response or association with detectable systemic capsaicin exposure[6]. As part of the Risk Management Plan (RMP), CHMP requested the establishment of an educational programme, which will address the need to evaluate the risk of adverse cardiovascular reactions due to the potential stress of the procedure in patients with unstable or poorly controlled hypertension or recent cardiovascular events prior to initiating capsaicin patch treatment[6]. This risk is listed as a precaution in the SPC for Qutenza®. This educational programme began in June 2010 and, as of August 2011, 24 UK pain centres have been accredited for use of capsaicin patches[2].

The overall incidence of AEs was not affected by patient age, number of re-treatments or the size of the area being treated. However application site dryness and swelling did occur at a higher incidence with increased patch surface area[6].

Long-term neurological assessment of patients treated with multiple applications of capsaicin has yet to demonstrate any evidence of accelerated nerve damage. However, CHMP noted that there were unsolved concerns regarding the risk of accelerated nerve damage and requested the undertaking of a long-term safety study, which is reflected in the RMP[6].

3.4 WMP critique

- CHMP concluded the initial analysis of efficacy data from the main clinical studies produced inconclusive results[6]. Although studies C116 and C117 met

the primary endpoint of reducing NPRS scores these findings were not confirmed by the results from C108 and C110. Additionally, CHMP questioned the clinical relevance of the small effect size in studies C116 and C107, as a two point reduction in pain was not achieved. Prior to licensing, the company submitted a new integrated analysis of the main studies to CHMP; this focussed on 60- and 30-minute treatment in PHN and HIV-AN patients respectively and evaluated change in NPRS score from baseline to weeks 2 to 12. Pain scores were significantly reduced in both PHN (29.6%, p = 0.0001) and HIV-AN patients (27%, p = 0.0026), while analysis of several secondary endpoints provided supportive evidence of efficacy. CHMP concluded that the results of the integrated analysis were acceptable and noted that the effect size could be small due to the use of a low concentration capsaicin patch as a control[6].

- The control treatment used in studies was a low strength 0.04% capsaicin patch that was used in place of placebo patches to provide effective blinding in the study, since topical capsaicin can produce local erythema and a burning sensation[6]. However, the control patches were designed to have minimal clinical efficacy[2]. Despite this, patients receiving the control patch exhibited a greater than expected response during controlled studies[12–15] and the company suggests that the control patch could potentially have caused an analgesic effect. The control patch was 200-fold less concentrated than the capsaicin patch but delivered approximately 29-fold less capsaicin[2]. Additionally, the company acknowledge that use of the low concentration capsaicin patch could have caused patients receiving the control to have a robust placebo effect, due to the visual and sensory cues from the application of the low-concentration capsaicin patch[2]. It is also worth noting that control patch-treated patients exhibited high rates of AEs (77%)[6], which could be masking the true incidence of AEs in the capsaicin group. CHMP noted that that the use of a traditional placebo arm would not permit studies to remain blinded[6]; however, the use of a low strength patch still has inherent limitations.
- The company submission highlights several benefits to capsaicin patch use, including few drug interactions due to negligible systemic absorption and few systemic side effects, which could potentially be advantageous for use in patients who poorly tolerate existing treatments or in patients receiving multiple medications[2]. The company also suggests that the incorporation of capsaicin patches into treatment regimens does not increase pill burden and potentially allows discontinuation or dose reduction of concomitant therapies, such as pregablin, lidocaine plasters and opioids, which may reduce systemic side effects from these medications. In support of this suggestion, the company submission includes an abstract from a forthcoming conference, which provides data from a single-arm study of 52 capsaicin-treated patients, which showed a 40% reduction in the mean number of concomitant medications taken. This treatment effect could not be tested as part of the clinical studies discussed in Section 3.1.1, as part of the inclusion criteria required that patients remained on the same dose of concomitant medication during the treatment period. An additional benefit described by the company is that analgesic effects are achieved within a few days and can potentially be maintained for 12 weeks. Clinical studies were included as part of the submission that demonstrate the maintenance of effect for 12 weeks (see Appendix 1) [2].
- Although the majority of capsaicin patch-treated patients in clinical trials stated that they would undergo treatment again, this was equivalent to patient preference rates in the control group[14,15].
- Administration of capsaicin patches is undertaken in a specialist setting, which means that patients are not able to self-medicate and must attend a specialist clinic, which requires clinic time and resources. The company suggest that this

means the use of capsaicin patches is easy to control, compliance is guaranteed and there is a low potential for non-rational prescribing.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes cost-utility analyses (CUA) of the addition of capsaicin patch (Qutenza®▼) to usual care in the treatment of PNP in non-diabetic adults[2]. The model is based on data relating only to the treatment of PHN, which the company considers to be a proxy for all PNP types. Although the licensed indication permits the use of the capsaicin patch alone or in combination with other medicines[1], the economic evidence presented by the company seems to relate only to use of capsaicin patches as an add-on treatment in patients who are refractory to or not tolerant of usual first or second line treatments[2].

The primary base case analysis is based on a meta-analysis of efficacy data derived from all patients included in the capsaicin patch phase III clinical trials described in Section 3, including those patients who used the capsaicin patch without other concomitant medicines. A secondary analysis has been provided using a post hoc analysis of efficacy data, relating only to those patients in the trials who used the capsaicin patch as an add-on to other medicines. It is assumed that patients who respond to treatment initially will continue to respond in the same way at each subsequent re-treatment. A re-treatment interval of 268 days is assumed. A ten-year time horizon of analysis is used. See Appendix 2 for further details.

4.1.2 Results

As both analyses assume that the capsaicin patch will be used as an add-on therapy, the company assumes there are no differences in the cost of usual care. The secondary analysis would seem the more relevant of the two analyses, as it is based on data that are more reflective of the use of the patches as add-on to other medicines. Results are summarised in Table 2.

Table 2. Company-reported CUA results of capsaicin patches versus usual care in the treatment of PNP in non-diabetic adults[2].

	Usual care	Capsaicin patches plus usual care	Incremental cost
Primary base case analysis			
Cost	£0	£1,527	£1,527
QALYs	3.763	3.859	0.096
ICER	£15,982		
Secondary analysis			
Cost	£0	£1,281	£1,281
QALYs	3.648	3.724	0.076
ICER	£16,870		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

The company reports that the probabilistic sensitivity analyses for the primary base case generated a 61% probability of the capsaicin patch being cost-effective at a threshold of £20,000 and 76% at a threshold of £30,000 per QALY gained. For the secondary analysis the probability of the capsaicin patch being cost-effective was reported as 55% at £20,000 and 66% at £30,000 per QALY gained. However, around 17% of the simulations of the secondary analysis indicated that capsaicin patches were less effective and more costly than usual care.

One-way sensitivity analyses indicate that the primary base case model is most sensitive to the probability of response to usual care, the use of the 95% confidence interval of the estimate generating model outputs including the possibility that usual care is both less costly and more effective than capsaicin patches. The next most influential parameters were: utilities for "pain relieved by treatment" (ICER ranged from £14,000 to £40,000 per QALY), utilities for "pain not relieved by treatment" and age-adjustment parameter for utilities (ICERs range from £12,000 to £25,000 per QALY) when explored in the range of +/-25%. For the secondary analysis the ICER was most sensitive to utilities for "pain relieved by treatment", followed by: the probability of response to usual care, utilities for "pain not relieved by treatment" and age-adjustment for utilities, the ICERs being similar to those in the base case model.

Each base case model assumes a re-treatment interval of 268 days and threshold analysis indicates that the ICER exceeds £30,000 per QALY when the interval reduces to less than 109 days in the primary base case model and 192 days in the secondary model.

Eight possible scenarios were considered to address variation in model parameters, such as treatment costs, probability of adverse events, onset of treatment, probability of spontaneous PHN resolution, changes in utility for response to capsaicin patch and removing age adjustment of utilities. Scenario analyses produced a variation in the ICER from £12,146 when age-adjustment parameter for utilities was removed to £28,837 when the utility increment for "pain relieved by treatment" was halved.

4.1.3 WMP Critique

Strengths of the economic evidence include:

- A systematic literature review was conducted to identify previous studies on modelling of cost-effectiveness of PHN treatments.
- Interviews and surveys with pain specialists in Wales were conducted by the company to identify current treatment strategies for PHN in Wales.
- A wide range of sensitivity analyses were conducted to address the uncertainty associated with several key model parameters.

Limitations of the economic evidence include:

- Efficacy data are derived from a meta-analysis of PHN trial data only.
- Evidence for re-treatment with the capsaicin patches is limited and the assumed interval between re-treatment has a significant impact on the model outputs. Threshold analysis indicates the ICER in the post hoc analysis increases to £30,000 per QALY when the interval to re-treatment is 192 days (by contrast, the SPC permits re-treatment every 90 days if required)[1]. The number of patches used per treatment in the clinical trials is greater than that modelled, as the company observes that the recorded treatment area sizes was smaller than the surface area covered by the patches provided. The actual number of patches to be used would therefore seem a source of uncertainty.
- Several sources of utility data were identified and the base case analyses use values that generate more favourable ICER estimates than alternative sources.

Sensitivity analyses demonstrate that the model outputs are particularly sensitive to the assumed utility values for treatment states.

- Although a wide range of scenario and sensitivity analyses have been conducted, all assume a ten-year time horizon of analysis. The company has not explored alternative time horizons and WMP analyses using the company's model indicate that the ICER increases using shorter time horizons.
- The comparator is defined by the company as usual care, but excludes lidocaine plasters, which company-sought expert opinion suggests is used in around 30% of PHN patients in specialist pain clinics. The lack of comparison against lidocaine plasters means the economic evidence is potentially incomplete.

4.1.4 Summary of published evidence on cost effectiveness

Standard literature searches have identified a published study comparing the cost-effectiveness of 8% capsaicin patch administered once every 12 weeks for the treatments of post-herpetic neuralgia versus antidepressants (TCAs), topical lidocaine patches, duloxetine, gabapentin and pregabalin in the USA. The cost-utility analysis was based on a Markov model with a different structure to that submitted by the company. Other notable differences include a one-year time horizon of analysis (c.f 10 years) and a ≥30% decrease in pain as the efficacy endpoint (c.f. 50%). It also appears that relative efficacy estimates have been made using unadjusted, naive comparisons for the published model. The incremental cost-effectiveness ratio (ICER) for capsaicin patch compared to TCA therapy was around $60,000 per QALY gained and, compared to duloxetine, pregabalin and gabapentin, the ICER ranged from $40,000 to $44,000 per QALY gained. There was no statistically significant difference in modelled effectiveness (0.606 QALYs vs. 0.602 QALYs) or costs ($5305 vs. $4988) between capsaicin and lidocaine plasters. Sensitivity analyses were conducted to evaluate the impact of treatment intervals with capsaicin patch of 14.5 and 17.7 weeks, based on open-label study extensions, and which are shorter than the 192 day (27.4 week) interval at which the company's model estimates an ICER of £30,000 per QALY gained. Due to differences in costs and health care settings it is not possible to translate the results of this published study to the Welsh setting; however, the model does highlight important differences in assumptions and approaches that would have the potential to impact upon the outputs of the company's model.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on a range of published prevalence and incidence data for PHN and PNP in the UK, and Welsh population statistics, the company estimates there are currently 9,657 patients with PHN and 45,096 people with PNP in Wales. After excluding people with diabetic neuropathy, the number of PNP patients who would be potentially eligible for treatment with capsaicin patch is estimated as 13,908. Based on published sources, the number of newly diagnosed PHN patients in Wales is 2,148 and the estimated number of PNP patients (excluding those with diabetic neuropathy) is 7,572. Assuming a population growth of 0.3% per annum, the mean annual risk of death for individuals aged 70 in Wales and the annual probability of PHN resolution taken from the company's economic model, the company estimates that the net population experiencing PHN in Wales will increase from 10,136 in year one to 11,513 in year five. The number of patients with PNP (excluding diabetic neuropathy), estimated using the method described above, is expected to increase from 18,442 to 31,184 in five years

time. The company used efficacy data from the capsaicin patch clinical studies to estimate the number of patients who might be treated with capsaicin patch over the next five years. The estimated numbers of patients and the associated costs over the 5 year period are shown in Table 3.

Table 3. Company-reported costs associated with capsaicin patch treatment[2].

	Year 1	Year 2	Year 3	Year 4	Year 5
PHN					
Number of eligible patients	94	98	99	98	95
Uptake†	1%	3%	5%	7%	9%
Number of treated patients*	1	3	6	9	12
Overall net costs**	£438	£1,491	£2,814	£4,322	£5,936
PNP (excluding diabetic neuropathy)					
Number of eligible patients	1,074	1,293	1,457	1,571	1,637
Uptake†	1%	3%	5%	7%	9%
Number of treated patients*	11	42	85	138	198
Overall net costs**	£4,986	£19,518	£40,602	£67,141	£97,747

*Includes newly treated individuals and those receiving maintenance therapy
**Include capsaicin patch costs and administration costs
†Based on company market projections

Univariate sensitivity analyses were conducted by the company to address the uncertainty associated with parameters included in the cost estimates (capsaicin unit costs, number of capsaicin patches per application, number of treated patients, adverse events and others). The analyses demonstrated that the number of capsaicin patches per application, the percentage of patients treated in secondary care and hazard ratio were the most influential parameters affecting net costs of treatment of patients with PHN. For patients with PNP these were the percentage of patients with diabetes, number of capsaicin patches per application and capsaicin patch unit costs.

5.1.2 WMP critique

There is an apparent lack of accurate epidemiological data for PNP and the company has made significant efforts to estimate relevant patient numbers. However, despite this there is significant uncertainty around the company estimates of the total number of PNP patients. The company has attempted to define a group of PHN patients and PNP patients (excluding diabetic neuropathy) separately. The cost estimates for capsaicin patches are derived from the economic model, and as a consequence the limitations and uncertainties of the economic model feed through to the budget estimates. No attempt has been made to determine a net budget impact, as the assumption is that capsaicin patches would be added to ongoing treatment with other medicines. Although a wide range of sensitivity analyses have been provided, it is unclear how informative or reliable the resulting cost estimates are.

5.2 Table of comparative unit costs

The comparison of unit costs for the treatment of PNP requires information about the surface area to be treated, which is highly variable among individuals. Therefore, a comparison of costs for patches, creams and oral preparations is problematic. Table 4 provides example annual acquisition costs for the capsaicin patch and lidocaine plaster, which may be used as an add-on to ongoing treatment with other medicines. It should be notes that both capsaicin patches and lidocaine plasters may be cut to size prior to application, and that one capsaicin patch covers a total surface area that is twice that of one lidocaine plaster.

Table 4. Examples of drug acquisition costs for capsaicin patches and lidocaine plasters used in the treatment of PNP.

	Example administration	Annual acquisition cost*
Capsaicin patch (Qutenza®▼) 14 × 20 cm	One patch applied once every 90 days if required	£840 †
Lidocaine plaster (Versatis®) 14 × 10 cm	Two plasters applied per day	£1762

**Costs are based on MIMS list prices[22].*
†Assumes four applications per year, which is the maximum frequency of use[1]. Excludes the cost of other consumables required for patch application and removal
This table does not imply therapeutic equivalence of drugs or the stated doses.
See relevant SPCs for full dosing and application details[1,23].

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

WMP is of the opinion that capsaicin (Qutenza®▼) cutaneous patches are not suitable for shared care within NHS Wales.

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6-12 months:

- A multicentre, single-arm, open-label study of the repeated administration of Qutenza®▼ for the treatment of peripheral neuropathic pain (STRIDE)[24,25]. This safety study will examine the effects of repeated application as required by the post-regulatory RMP[6].
- An ongoing retrospective analysis being undertaken at a pain clinic in Germany. The initial results are being presented at the EFNS Congress in Budapest in September 2011 and publication is planned for early 2012[2].
- Additional case series are in press for patients within the UK[2].

GLOSSARY

Brief pain inventory (BPI)
An index of pain severity, pain relief, and the effects of pain on ability to function. Subjects rated their pain on a scale of 0 (no pain) to 10 (worst possible pain) in response to these categories:

- Pain at its worst in the last 24 hours.
- Pain at its least in the last 24 hours.
- Pain on average in the last 24 hours.
- Pain right now.
- Pain-associated interference with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life in the last 24 hours[17].

Clinician Global Impression of Change (CGIC)
A survey that asks the investigator to indicate "how the subject appears to you now, compared to how they appeared to you before receiving treatment in this study" on a scale of −3 (subject very much worse) to +3 (subject very much improved)[19].

Numeric pain rating scale (NPRS)
An 11-point scale (0-10), with 0 indicating no pain and 10 indicating worst possible pain. A reduction of approximately two points or approximately 30% in the NPRS usually represents a clinically important difference[20].

Patient Global Impression of Change (PGIC)
A survey that asks the subject to "indicate how you feel now, compared to how you felt before receiving treatment in this study" on a scale of −3 (very much worse) to +3 (very much improved)[17].

Self-assessment of treatment (SAT)
A sponsor-derived survey where patients were asked to assess capsaicin patch treatment using a form which included the following questions:

- How do you assess your pain level after treatment in this study?
- How do you assess your activity level after treatment in this study?
- How has your quality of life changed after treatment in this study?
- Would you undergo this treatment again?
- How do you compare the treatment you received in this study to previous medication or therapies for your pain?

To answer these questions, the subject checked a box on a 3- or 5-point scale (with the middle option indicating a neutral response and the lower and higher options indicating a negative or positive response, respectively) [17,19].

Short-form McGill Questionnaire (SF-MPQ)
This questionnaire consists of 15 descriptors (11 sensory; 4 affective) which are rated on an intensity scale: 0 = none, 1 = mild, 2 = moderate or 3 = severe. Three pain scores (sensory, affective and total) are derived from the sum of the intensity rank values of the words chosen for specific descriptors[26].

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Appendix 1. Additional clinical information

Table 1. Analysis of primary and secondary efficacy endpoints for phase III clinical studies evaluating capsaicin 8% patches in postherpetic neuralgia patients.

		C108[13,16]				C110[12,18]	C116[15,17]	C117[14,19]
		30 min	60 min	90 min	Pooled			
Primary endpoint								
Percentage change in NPRS score for average pain for the past 24 hours from baseline to weeks 2–8	Capsaicin	-26.2	-25.6	-27.8	-26.5	-36.5	-29.6	-32.0
	Control	17.3				-29.9	-19.9	-24.4
	P value	0.088	0.104	0.0438	0.0286	0.296	0.001	0.011
Secondary and ancillary endpoints								
Percentage change in NPRS score for average pain for the past 24 hours from baseline to weeks 2–12	Capsaicin	-24.4	-24.4	-26.1	-25.0	-36.6	-29.9	-32.3
	Control	-14.7				-32.3	-20.4	-25.0
	P value	0.055	0.0491	0.0240	0.0120	0.509	0.002	0.017
Percentage of responders (>30% reduction in pain from baseline) during weeks 2–12	Capsaicin	38	35	40	37	49	44	47
	Control	29				45	33	35
	P value	0.147	0.348	0.1	0.103	0.574	0.05	0.021
Percentage of subjects with mean percent decrease from baseline ≥ 50% during weeks 2–12	Capsaicin	24	27	23	25	39	26	30
	Control	10				36	21	21
	P value	0.0185	0.0077	0.0235	0.0057	0.628	> 0.05	0.035
Patient Global Impression of Change (PGIC): percentage of patients feeling improved	Capsaicin	Week 8: 46 Week 12: 40	Week 8: 49 Week 12: 52	Week 8: 53 Week 12: 48	Week 8: 50 Week 12: 47	Week 8: 60 Week 12/termination: 61	Week 8: 57 Week 12/termination: 57	Week 8: 62 Week 12/termination: 61
	Control	Week 8: 43 Week 12: 36				Week 8: 40 Week 12/termination: 51	Week 8: 46 Week 12/termination: 46	Week 8: 51% Week 12/termination: 47
	P value	Week 8: 0.822 Week 12: 0.511	Week 8: 0.326 Week 12: 0.075	Week 8: 0.066 Week 12: 0.073	Week 8: 0.297 Week 12: 0.082	Week 8: 0.369 Week 12/termination: 0.053	Week 8: 0.0293 Week 12/termination: 0.0409	Week 8: 0.030 Week 12/termination: 0.005

Table 1 contd.

		C108[13,16]				C110[12,18]	C116[15,17]	C117[14,19]
		30 min	60 min	90 min	pooled			
Clinician Global Impression of Change (CGIC): percentage of patients judged by the investigator to have felt improved	Capsaicin	Week 8: 44 Week 12: 38	Week 8: 47 Week 12: 51	Week 8: 55 Week 12: 42	Week 8: 49 Week 12: 44	Week 8: 63 Week 12/termination: 64	-	Week 8: 63 Week 12/termination: 63
	Control	Week 8: 43 Week 12: 38				Week 8: 47 Week 12/termination: 49		Week 8: 52 Week 12/termination: 48
	P value	Week 8: 0.678 Week 12: 0.747	Week 8: 0.414 Week 12: 0.059	Week 8: 0.0154 Week 12: 0.293	Week 8: 0.263 Week 12: 0.172	Week 8: 0.220 Week 12/termination: 0.123		Week 8: 0.0298 Week 12/termination: 0.0033
Self-assessment of treatment (SAT): percentage of patients with improvement in pain relief, activity level, and quality of life (QoL) at week 12	Capsaicin	Pain relief: 36 Activity: 24 QoL: 30	Pain relief: 47 Activity: 30 QoL: 31	Pain relief: 45 Activity: 27 QoL: 36	Pain relief: 43 Activity: 27 QoL: 32	Pain relief: 61 Activity: 36 QoL: 44	Pain relief: 50 Activity: 30 QoL: 41	Pain relief: 55 Activity: 36 QoL: 43
	Control	Pain relief: 38 Activity: 22 QoL: 27				Pain relief: 49 Activity: 26 QoL: 42	Pain relief: 43 Activity: 25 QoL: 26	Pain relief: 41 Activity: 26 QoL: 35
	P value	Pain relief: 0.686 Activity: 0.672 QoL: 0.378	Pain relief: 0.338 Activity: 0.340 QoL: 0.528	Pain relief: 0.229 Activity: 0.295 QoL: 0.115	Pain relief: 0.294 Activity: 0.326 QoL: 0.216	Pain relief: 0.096 Activity: 0.362 QoL: 0.594	Pain relief: 0.087 Activity: 0.295 QoL: 0.008	Pain relief: 0.0026 Activity: 0.0900 QoL: 0.1148
Short-form McGill Questionnaire (SF-MPQ) mean change at week 8	Capsaicin	Sensory: -3.1 Affective: -1.0 Total: -4.2	Sensory: -2.8 Affective: -0.9 Total: -3.7	Sensory: -1.9 Affective: -1.1 Total: -3.1	Sensory: -2.6 Affective: -1.0 Total: -3.7	Sensory: -4.3 Affective: -1.5 Total: -5.8	Sensory: -3.8 Affective: -0.9 Total: -4.7	Sensory: -4.1 Affective: -1.2 Total: -5.3
	Control	Sensory: -1.4 Affective: -0.3 Total: -1.5				Sensory: -3.8 Affective: -1.0 Total: -4.9	Sensory: -2.8 Affective: -0.8 Total: -3.6	Sensory: -3.7 Affective: -0.8 Total: -4.4
	P value	Sensory: 0.137 Affective: 0.208 Total: 0.078	Sensory: 0.236 Affective: 0.209 Total: 0.142	Sensory: 0.661 Affective: 0.121 Total: 0.328	Sensory: 0.196 Affective: 0.086 Total: 0.080	Sensory: 0.743 Affective: 0.461 Total: 0.603	Sensory: 0.132 Affective: 0.895 Total: 0.209	Sensory: 0.3566 Affective: 0.2143 Total: 0.2404
Brief pain inventory (BPI): mean change in score for average pain in the last 24 hours	Capsaicin	Week 8: -1.4	Week 8: -1.4	Week 8: -0.9	Week 8: -1.3	Week 8: -1.7	Week 8: -1.3 Week 12:-1.3	Week 8: -1.5 Week 12:-1.4
	Control	Week 8: -0.7				Week 8: -1.9	Week 8: -1.0 Week 12:-1.0	Week 8: -1.1 Week 12:-1.0
	P value	Week 8: 0.0340	Week 8: 0.0233	Week 8: 0.501	Week 8: 0.0402	Week 8: 0.645	Week 8: 0.121 Week 12: 0.354	Week 8: 0.1311 Week 12: 0.1053

BPI: Brief Pain Inventory; CGIC: Clinician Global Impression of Change; NPRS: numeric pain rating scale; PGIC: Patient Global Impression of Change; QoL: quality of life; SAT: Self-assessment of treatment; SF-MPQ: Short-from McGill Questionnaire.

Appendix 2. Additional health economic information

Table 1. Health economic model detail[2]

	Base Case Model	Appropriate?
Comparator(s)	Capsaicin patch plus usual care is compared against usual care alone. Usual care is defined as 'a mixture of concomitant pain medication or observation with the control arms in capsaicin patch clinical trials taken to be a proxy for usual care alone[2]	Capsaicin patch is licensed for use alone or in combination with other medicines. WMP originally requested a comparison of capsaicin patch against lidocaine plaster (Versatis®); capsaicin (0.075%) cream (Axsain®); pregabalin (Lyrica®) and gabapentin. The company considers that capsaicin patches will be used in specialist care settings in patients who are refractory to first and second-line treatments. Based on expert opinion, the company considers that the capsaicin patch will be added to existing treatment (usual care), rather than be used as a direct replacement. The company presents two models: usual care in the 'primary' model is based on all patients in the capsaicin trials, around 50% of who were not receiving pain medications. The 'secondary' model uses efficacy data based on only those patients also taking other pain medications and so would seem the most relevant of the two models given the company's proposed positioning of capsaicin patches. Usual care in the clinical trials excluded lidocaine plasters; however, the views of expert clinicians contacted by the company seem to indicate that lidocaine plasters would be used in around 30% of patients[2]. A comparison against lidocaine plasters would seem relevant.
Population	Adults with peripheral neuropathic pain (PNP), excluding patients with diabetic neuropathy. All data relate to patients with postherpetic neuralgia (PHN).	The company has modelled the use of capsaicin in non-diabetic adults with PHN, which it considers to be a proxy for all forms of non-diabetic PNP. The economic evidence presented by the company would seem to relate to a restricted use of capsaicin patches as an add-on treatment in patients who are refractory to or not tolerant of usual first or second-line treatments.
Analysis type	Cost-utility analysis (CUA), based on a two stage model. The first 365 days are represented by a simple decision tree; thereafter, patient outcomes are modelled using a Markov model employing four health states: pain relieved by treatment, pain not relieved by treatment, spontaneous relief, or an absorbing state of death. A one-year cycle is assumed.	Yes, CUA is the preferred type of analysis.

Table 1. Continued.

	Base Case Model	Appropriate?
Perspective	The NHS in Wales and personal social services (PSS).	The analysis considered direct medical costs from the perspective of NHS Wales.
Time horizon	Analysis assumes a ten-year time horizon.	PNP (i.e. PHN) is potentially protracted. The company has assumed a ten-year time horizon based on expert opinion that 62% would be resolved by ten years. Importantly, no other time horizon has been explored and WMP analyses using the company's model indicate that shorter time horizons increase the reported ICERs significantly (e.g. the ICER from the post hoc analysis increases from £16,870 per QALY in the base case to £26,500 per QALY using a five-year time horizon).
Discount rate	A 3.5% p.a. discount rate is applied to both costs and outcomes.	Yes, as preferred.
Efficacy	Efficacy data were derived from meta-analysis of odds ratios of response (defined as a ≥ 50% improvement in pain from baseline at eight weeks) from capsaicin patch clinical trials. To estimate relative efficacy for usual care individual participant data for patients receiving usual care was synthesised using fixed-effects meta-analysis. Spontaneous resolution of pain was modelled using a regression model of a small published natural history study in elderly patients with PHN. Mortality data are based on published annual mortality rates for Wales.	Around 50% of patients in the clinical trials used the capsaicin patch alone. Therefore, the company provides a primary base case analysis using data from all trial participants (those using the patch with or without concomitant medicines) and a post hoc analysis using trial data only from those who received concomitant treatment. Usual care in randomised controlled trials included application of a control patch, containing a low concentration (0.04%) of capsaicin, which may favour the usual care arm. The company suggests that the actual area covered by the capsaicin patches in clinical trials was 63% greater than the painful area, and so has assumed smaller patch areas based on average painful area observed in clinical trials. It is not clear if/how this may influence observed effectiveness. . It is assumed that patients who respond to treatment in the first eight weeks will continue to respond to subsequent treatments. Those who do not respond in the first eight weeks are assumed not to receive further treatment with the capsaicin patch.

Table 1. Continued.

	Base Case Model	Appropriate?
Adverse effects	The probability of experiencing tolerable adverse events with capsaicin patches was estimated based on the number of patients experiencing administration site disorders in capsaicin patch clinical trials. The probability of experiencing intolerable adverse events with capsaicin patch was estimated based on the number of patient withdrawals. Since usual care in the clinical trials included control patch, the incidence of incremental adverse events in patients receiving usual care alone was considered to be zero.	Yes, seems a practical approach.
Utility values	Utility values were derived from published studies. Utility scores were adjusted to reflect lower quality of life in trial population based on their age (70 years at baseline). Disutilities associated with adverse events were assumed.	The company reports various potential sources of utility values, and those chosen for the base case analyses appear to be more favourable than those from alternative sources. Sensitivity analysis demonstrated that modelled ICERs were particularly sensitive to utility estimates for different health states.
Resource use and costs	Treatment costs included cost of capsaicin patch; topical analgesia prior to application; occlusive film; sterile gloves; medication for breakthrough pain; and nurse time associated with administration and patient monitoring. The assumed average number of capsaicin patches per patient per treatment was 1.72. A treatment interval of 268 days was estimated based on an open-label extension to one of the clinical trials (C108). Cost of monitoring was assumed to be equal in both arms. Costs associated with tolerable adverse events included the costs of opioid rescue medication. For intolerable adverse events an additional GP visit/pain management consultation was included. No usual care costs are applied as these are assumed to be the same for both arms of the model.	Yes. However, while the average use of capsaicin patches was estimated per surface of painful area +1cm^2, the treated area in clinical trials was 63% greater than the painful area. Sensitivity analysis demonstrated that modelled ICERs were sensitive to the number of capsaicin patches per application. A treatment interval of 268 days (95%CI 229 to 308) estimated from open-labelled study C108 is significantly longer than the treatment interval permitted by the licensed indication (90 days), and threshold analysis indicates the model is sensitive to the assumed re-treatment interval. Based on limited retrospective data analysis, the company has suggested that the use of capsaicin patch may reduce the need for concomitant analgesics; however, there are few data provided, and this is not further explored in the model.
Uncertainty and scenario analyses	Uncertainty of model estimates were addressed via deterministic sensitivity analyses, probabilistic sensitivity analyses, threshold analyses and eight possible scenario analyses.	Yes, a wide range of sensitivity analyses was performed; however, all assume a ten-year time horizon. The company suggests this is for conciseness, but WMP analyses indicate the model is very sensitive to the time horizon used.
Model provided?	Yes.	Yes.

CUA: Cost utility analysis; ICER: incremental cost effectiveness ratio; PHN: postherpetic neuralgia; PNP: peripheral neuropathic pain; PSS: personal social services; QALY: quality-adjusted life year; WMP: Welsh Medicines Partnership.