Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-Submission

capsaicin, 179mg, cutaneous patch (Qutenza®) SMC No. (673/11)
Astellas Pharma Ltd

05 September 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCS) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a re-submission

capsaicin (Qutenza®) is accepted for restricted use within NHS Scotland.

Indication under review: For the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.

SMC restriction: to use in patients who have not achieved adequate pain relief from, or have not tolerated, conventional first and second line treatments.

A phase IV, open-label, randomised, controlled study showed that capsaicin patch was non-inferior to an oral analgesic in adult patients with peripheral neuropathic pain.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

Capsaicin (Qutenza®) cutaneous patch is indicated for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.

Dosing Information

Capsaicin patches should be applied by a physician, or by a healthcare professional under the supervision of a physician, to the most painful skin areas (using up to a maximum of 4 patches). The painful area should be determined by the physician and marked on the skin. The patch(es) must be applied to intact, non-irritated, dry skin, and allowed to remain in place for 30 minutes for the feet (e.g. HIV-associated neuropathy) and 60 minutes for other locations (e.g. post-herpetic neuralgia). Treatment may be repeated every 90 days, as warranted by the persistence or return of pain.

The treatment area may be pre-treated with a topical anaesthetic or the patient might be administered an oral analgesic prior to application of the capsaicin patch(es) to reduce application related discomfort.

Product availability date

Capsaicin patch was launched in the UK in 2011.

Summary of evidence on comparative efficacy

Capsaicin is a highly selective agonist for the transient receptor potential vanilloid 1 receptor (TRPV1) found on cutaneous nociceptors. The initial effect of capsaicin results in pungency and erythema. Following exposure to capsaicin, cutaneous nociceptors become less sensitive to a variety of stimuli, which is thought to be the mechanism of the analgesic effect of the drug.[1]

Capsaicin cutaneous patch has previously been accepted for use within NHS Scotland, restricted to use in adults with post-herpetic neuralgia (PHN) who have not achieved adequate pain relief from, or who have not tolerated conventional first-and second-line treatments. In the current submission, the company has requested that SMC considers the use of capsaicin patch in a broader population of patients with peripheral neuropathic pain (PNP), who have not achieved adequate pain relief from, or have not tolerated, conventional first- and second-line treatments.

The clinical evidence derives from a phase IV open-label, randomised, multi-centre, non-inferiority study (ELEVATE)[2,3,4] comparing the efficacy and tolerability of capsaicin cutaneous patch with pregabalin in adult patients with PNP. Patients were eligible for the study if they were aged between 18 and 80 years with a documented diagnosis of probable or definite non-diabetic PNP in a localised and well-defined area suitable for treatment with capsaicin patch, including: post-herpetic neuralgia (PHN) with pain persisting at least six months since shingles vesicles crusting; peripheral nerve injury (PNI) including post surgical or post traumatic neuropathic pain, persisting for at least three months; or non-diabetic painful peripheral polyneuropathy (PPN) with pain that had persisted for a minimum of three months. Patients must have had an average pain score ≥4 during the screening period over at least four consecutive days using the “average pain for the past 24 hours” Numeric Pain Rating Scale (NPRS) score, and be naive to treatment with pregabalin or gabapentin or have had an inadequate trial of either of these medicines.

The primary endpoint was the proportion of patients in each group who achieved at least 30% decrease in the average NPRS score from baseline to week 8 (defined as "responders"), assessed in both the per protocol population and the full analysis set (FAS; which included all randomised patients who started study treatment). In the per protocol population, this was achieved in 58% (147/254) of patients receiving capsaicin patch and 58% (145/252) of patients in the pregabalin group; a difference (capsaicin minus pregabalin) of 0.3% (95% confidence interval [CI] -8.3% to 8.9%); odds ratio (OR) 1.03 (95% CI 0.70 to 1.5). In the FAS, the proportion of responders was 56% (157/282) for capsaicin patch and 55% (151/227) for pregabalin, a difference (capsaicin minus pregabalin) of 1.2%; OR 1.03 (95% CI: 0.72 to 1.50). Since the lower bound of the 95% CI of the OR was greater than the predetermined value of 0.693, non-inferiority of capsaicin versus pregabalin was demonstrated.

Interim results from an ongoing phase IV, prospective, multicentre, non-interventional study (ASCEND) of routine practice using capsaicin patch in seven European countries have been published in abstract form.[5] Up to 30 July 2013, 296 patients had been enrolled in the study. Capsaicin patch was used as primary, secondary and tertiary treatment for PNP in 16%, 45% and 39% of patients respectively. The average number of patches used in the first treatment was 1.5. At 8 weeks, 108 patients (43%) were classified as responders (≥30% improvement in average pain). Up to the cut-off point for the interim analysis, 65 patients (22%) had been retreated, with a median time to retreatment of 179 days.

A prospective, non-interventional study on the tolerability and analgesic effectiveness of capsaicin patch in German centres (QUEPP[6]) recruited 1063 non-diabetic adult patients with PNP. Of these there was safety and effectiveness data for 1,044 patients. The most frequently reported diagnoses were post herpetic neuralgia (32%), post-surgical neuralgia (23%, post-traumatic neuropathy (12%), polyneuropathy (14%) and mixed pain syndromes (17%) with a mean NPRS score at baseline of 6.3. The mean number of patches applied at the first visit was 1.4. The 30% responder rate for the period day 7-14 to week 12 was 41% (n=446).

Summary of evidence on comparative safety

Safety data from the ELEVATE study have not been published and are taken from the clinical study report.

In the ELEVATE study, the proportion of patients with any treatment-emergent adverse event (TEAE) was higher for capsaicin patch than pregabalin (74% versus 64%). Adverse events (reported by ≥5%) that were more frequent in the capsaicin patch compared with pregabalin included application site pain (24% versus 0%), erythema (21% versus 0.4%), burning sensation (16% versus 0.4%) and application site erythema (8.9% versus 0%). Adverse events that were reported less frequently with capsaicin patch compared with pregabalin included dizziness (2.5% versus 20%), somnolence (0.7% versus 16%), headache (14% versus 18%) and nausea (5% versus 13%).[2]

Adverse events reported for capsaicin patch in the ELEVATE study were consistent with the summary of product characteristics for capsaicin patch.[1]

In the QUEPP study, adverse events considered related to capsaicin patch by the investigator were reported in 10% of patients (n=106), of which the most frequent were pain or erythema at the application site.

Summary of clinical effectiveness issues

Capsaicin cutaneous patch has previously been accepted for restricted use within NHS Scotland for PHN in patients who have not achieved adequate pain relief from, or who have not tolerated, conventional first and second-line treatments. This submission provided new clinical data to support its use in other forms of non-diabetic PNP, in line with its licensed indication. The submitting company has requested that SMC considers capsaicin patch for use in patients who have not achieved adequate pain relief from, or who have not tolerated, conventional first and second-line treatments. The treatment pathway in the current SIGN guideline on chronic pain recommends initial treatment with amitriptyline or gabapentin for neuropathic pain, with pregabalin as an alternative in patients who have found no benefit from or not tolerated amitriptyline or gabapentin. Other oral medicines included in the treatment pathway are alternative tricyclic antidepressants and duloxetine. Lidocaine plaster is an option for patients with localised neuropathic pain who prefer a topical treatment.[7]

The main clinical evidence was from the ELEVATE study, which demonstrated non-inferiority of capsaicin cutaneous patch compared with oral pregabalin in non-diabetic adult patients with a variety of types of PNP. The primary outcome of ≥30% decrease in the "average pain for the past 24 hours", assessed by the NPRS scale was achieved in 58% of patients in both treatment groups. The European Medicines Agency considers patients who experience a 30% to 50% reduction in the assessment scale from baseline as responders.[10] The ELEVATE study was open-label, with both patients and treating physicians aware of treatment allocations, which is a potential source of bias; however, given the different methods of administration and the occurrence of treatment-related effects with both capsaicin patch and pregabalin, blinding of the study was not considered feasible. The ELEVATE study was of a short duration (8 weeks), so longer term efficacy is uncertain and time to retreatment was not determined. In the supportive ASCEND study, the median time to retreatment was 179 days.

The patient population in the ELEVATE study is broader than that suggested by the positioning sought by the company (i.e. patients who have not achieved adequate pain relief from or have not tolerated conventional first- and second-line treatments). Patients with HIV were excluded. Therefore the comparative efficacy of capsaicin versus pregabalin in patients with HIV associated neuropathy is not known. The ELEVATE study included patients with PHN (22% in the capsaicin group and 26% in the pregabalin group).

SMC clinical experts indicated that there is unmet need in the treatment of neuropathic pain and there are difficulties with current treatment options largely due to their poor tolerability. It was suggested that capsaicin patches would be a useful treatment option for specialist use when other therapies have been ineffective or not tolerated.

The comparator in the ELEVATE study was pregabalin, but Scottish prescribing guidelines[7] indicate that pregabalin may be used earlier in the treatment pathway than capsaicin patch in clinical practice. There are no comparative data of capsaicin patch with any other systemic or topical treatments for PNP.

Capsaicin patch is applied topically, and therefore avoids the central adverse effects and potential for drug-drug interactions that may occur with existing systemic treatments for PNP. It is applied as a single application to be repeated after 90 days, so may have an advantage in terms of compliance over systemic treatments administered daily.

Capsaicin patch must be administered by a physician or healthcare professional under the supervision of a physician. Patients require monitoring for application site pain and increase in blood pressure after application, and patients experiencing increased pain should be provided with supportive treatment such as local cooling or oral analgesics.[1] There are considerations for the service in terms of clinic time and staff resources required for administration of the patch, monitoring the patient after application and management of application site reactions.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis over a 2-year time horizon comparing capsaicin cutaneous patch to pregabalin for the treatment of PNP in non-diabetic adults either alone or in combination with other medicinal products for pain. The submitting company requested SMC consider capsaicin cutaneous patch for use in patients with PNP who have not achieved adequate pain relief from or have not tolerated conventional first and second line treatments.

Pregabalin was selected by the submitting company as the comparator on the basis that it may typically be used if other first- and second-line pharmacological treatments have failed as noted in the SIGN guidance.

The economic model was a simple decision tree in which patients would either be administered capsaicin or pregabalin. If a patient did not respond to treatment or experienced intolerable adverse events, the patient would progress to a last line treatment with duloxetine (which the submitting company used only as a proxy for available last line treatments). Treatment response/non-response was determined by the primary outcome (e.g. reduction in pain score was ≥30% in the past 24 hours from baseline to week 8).

The clinical data were primarily taken from the ELEVATE study and from supportive studies. In the base case, it was assumed that capsaicin cutaneous patch had equivalent efficacy in terms of treatment response rate. However, a difference in the rate of intolerable adverse events was assumed between treatments.

The utilities resulted from the data collected from ELEVATE study. Patients on capsaicin cutaneous patches achieved a faster increase in quality of life from a quicker onset of action and had an additional utility gain on response compared to a responder on pregabalin.

Medicines costs, follow up costs, resource use costs, and the treatment of intolerable adverse events costs, were included. Capsaicin cutaneous patches were assumed to be administered in an outpatient setting by a nurse and 1.38 patches assumed per patient with retreatment after 179 days.

The base case results show that capsaicin cutaneous patches dominated pregabalin based on incremental savings of £11 and a quality adjusted life year (QALY) gain of 0.049. This QALY gain was mainly derived from the time of onset differences, the small utility advantage associated with a response on capsaicin cutaneous patches and from the intolerable adverse event (AE) differences between both interventions.

One-way and two-way sensitivity analysis, threshold analysis, scenario analysis, and probabilistic sensitivity analysis (PSA) were undertaken. The analyses showed that the major driver was the time to capsaicin retreatment and this raised the incremental cost effectiveness ratio (ICER) to £7,951 if reduced from 179 days to 117 days. Scenario analysis which removed differences in terms of time to response, discontinuations and utility gain on response showed the treatment was still dominant (zero

utility gain but a saving of £36). If 1.51 patches were assumed to be used, the ICER changed from dominant to £1,188.

A number of uncertainties were identified as follows:

- The base case assumes that pregabalin patients would be treated in the secondary care setting. This may overestimate the pregabalin resource use costs given that pregabalin is also prescribed in primary care.
- There were some further concerns relating to the impact of assuming a reduction in pain relief over time with capsaicin and the submitting company provided some scenario analysis which took this into account, alongside changed assumptions to account for the potential use of pregabalin in primary care and capsaicin in secondary care settings. This produced a revised base case ICER of £4,297 per QALY. Increasing the number of patches to 1.51 increased this figure to £8,498, or £25,331 if it was assumed that the retreatment interval fell to 117 days. There was some further upward uncertainty in the ICERs if the use of topical anaesthesia was allowed for in the analysis; however, the submitting company indicated that this is no longer a requirement of the product licence.
- The New Drugs Committee debated the choice of comparator as current guidelines suggest that pregabalin may be used earlier in the treatment pathway therefore other comparators may be relevant.

Despite these weaknesses, the economic case was demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specific patient group.

- A submission was received from Pain Concern, which is a registered charity.

- Pain Concern has received funding from two pharmaceutical companies in the past two years, but not from the submitting company.

- Neuropathic pain can be hard to tolerate, and is often described as burning, shooting and stabbing. People strive to avoid pain by avoiding normal activities of daily living, leading often to isolation, disability and poor quality of life. This can lead to depression, anger, and damage to personal relationships and a financial burden on family members.

- This type of pain can be very difficult to treat so it is important to have a range of options to treat it. Existing oral treatments are associated with side effects, particularly problematic in the elderly, including confusion, drowsiness, swollen legs, jerking limbs, and falls. Existing topical treatments may not be sufficiently effective or long lasting.

- Advantages of the new medicine include: topical so avoids systemic side-effects; longer lasting than other topical pain relief; avoids worries about addiction to oral medication which may lead to abandoning treatment; offers an alternative to existing treatments.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline 136: Management of chronic pain was published in 2013.[7] A treatment pathway is included and is based on evidence identified in the guideline, information extrapolated in the research for the guideline and the clinical experience and consensus of the guideline development group. The treatment pathway recommends either amitriptyline (daily dose; 25mg to 125mg) or gabapentin (1200mg/day) as initial pharmacological treatment for neuropathic pain. Pregabalin is an alternative in patients who have found no benefit from or not tolerated amitriptyline or gabapentin. If treatment with these agents is ineffective, an alternative tricyclic antidepressant (e.g. imipramine or nortriptyline) or duloxetine may be used. Carbamazepine may also be used and this should be used first-line in patients with trigeminal neuralgia. Topical lidocaine plasters are recommended for patients with localised neuropathic pain in patients who prefer a topical treatment. Capsaicin patches (8%) and ketamine are treatment options after specialist referral when first line pharmacological therapies have been ineffective.

The National Institute for Health and Care Excellence (NICE) guideline 173: Neuropathic pain-pharmacological management: the pharmacological management of neuropathic pain in adults in non-specialist settings[8] recommends amitriptyline or pregabalin as first line treatment (except in the case of diabetic neuropathy when duloxetine should be used first line). If pain reduction is not satisfactory with the first treatment, then another first line treatment of a different drug type should be offered, either in place of or in combination with the initial therapy. If pain in still not adequately controlled, referral to a specialist is recommended and treatment options while waiting include tramadol, nortriptyline, imipramine or duloxetine. Topical lidocaine is an option for localised pain or for patients unable to take oral medication. Capsaicin patch should not be started to treat neuropathic pain in non-specialist settings.

The European Federation of Neurological Societies (EFNS) guidelines on the pharmacological treatment of neuropathic pain: 2010 revision[9] recommends tricyclic antidepressants (TCA), gabapentin, pregabalin and serotonin norepinephrine reuptake inhibitors (SNRI) (duloxetine, venlafaxine) as first line treatment in painful polyneuropathy. Tramadol is recommended second line except for patients with co-existing non-neuropathic pain. Third line therapy includes opioids. The guidelines state that capsaicin patches are promising for painful HIV neuropathies or post-herpetic neuralgia.

Additional information: comparators

There are a number of medicines recommended in treatment guidelines for the treatment of neuropathic pain, including: amitriptyline, gabapentin, pregabalin, imipramine, nortriptyline, duloxetine*, carbamazepine, lidocaine plaster, ketamine$^{\Delta}$.

*SMC advice restricts the use of duloxetine to patients with diabetic PNP, so it is not considered a comparator for the indication under review in this submission.

$^{\Delta}$Oral ketamine is an unlicensed “special”, so is not included in the cost table below.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Capsaicin patch	**One to four patches applied every three months as needed.**	**840 to 3360**
Lidocaine plaster	One to three plasters daily	878 to 2635
Pregabalin	150mg to 600mg daily (given as divided dose, twice or thrice daily)	837 to 1256*
Nortriptyline‡	25mg to 125mg daily	87 to 437
Gabapentin	300mg to 1200mg three times a day	79 to 301
Carbamazepine+ prolonged release	400mg to 1,600mg daily (given as divided dose, twice daily)	68 to 266
Imipramine‡	25mg to 125mg daily	15 to 75
Amitriptyline‡	25mg to 125mg daily	11 to 34

Doses are for general comparison and do not imply therapeutic equivalence. Cost for capsaicin patch from MIMS online on 19/06/14; all other costs from eVadis on 17/06/14.

* Any dose of pregabalin (150mg to 600mg daily) prescribed in two divided doses costs £64/28 days and £97/28 days when prescribed in three divided doses.

‡not licensed for neuropathic pain; dose as recommended for amitriptyline in SIGN guideline.

+licensed for trigeminal neuralgia only.

Additional information: budget impact

The manufacturer estimated the population eligible for treatment to be 91 patients in year 1 and 699 in year 5.

Based on an estimate uptake of 3% in year 1 and 23% in year 5, the impact on the medicines budget was estimated at £54k in year 1 and £414k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be savings of £22k in year 1 and of £173k in year 5

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Astellas Pharma Ltd. Capsaicin (Qutenza®) 179mg cutaneous patch, Summary of Product Characteristics, last updated 27/03/2013.

2. *Commercial In Confidence**

3. ClinicalTrials.gov. NCT01713426. A study to compare Qutenza® with pregabalin for the treatment of peripheral neuropathic pain (PNP) after 8 weeks of treatment (ELEVATE). A Study to Compare QUTENZA With Pregabalin for the Treatment of Peripheral Neuropathic Pain (PNP) After 8 Weeks of Treatment - Full Text View - ClinicalTrials.gov

4. Haanpaa M, Ernault E, Siciliano T et al. Local or systemic treatment for neuropathic pain? ELEVATE: an open-label, randomised, multicentre, non-inferiority efficacy and tolerability study. Presented at 14th Asian Australasian Congress of Anaesthsiologists. 21- 15 February, Auckland, New Zealand.

5. Poole C, Chambers C, Odeyemi I, Currie C. Evaluation of pain outcome using the capsaicin patch Qutenza® : A prospective, non-interventional study of routine practice.Presented at 8th Congress of the European federation of IASP Chapters (EFIC)-Pain in Europe VIII, 9-12 October 2013, Florence, Italy, Poster number 455. 2013.

6. Maihofner C, Heskamp M-L. Prospective, non-interventional study on the tolerability and analgesic effectiveness over 12 weeks after a single application of capsaicin 8% cutaneous patch in 1044 patients with peripheral neuropathic pain: first results of the QUEPP study. Current Medical Research & Opinion 2013, 29 (6): 673-83.

7. Scottish Intercollegiate Guidelines Network (SIGN) Guideline 136. Management of Chronic Pain (December 2013). SIGN 136: Management of Chronic Pain

8. National Institute for Health and Care Excellence (NICE) guideline 173: Neuropathic pain-pharmacological management: the pharmacological management of neuropathic pain in adults in non-specialist settings. Neuropathic pain – pharmacological management Introduction CG173

9. Attal N, Cruccu G, Baron R et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. European Journal of Neurology 2010; 17:1113-23.

10. European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain. CPMP/EWP/252/03 Rev.1. January 2007. Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain.pdf

This assessment is based on data submitted by the applicant company up to and including 15 August 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.