APPENDIX H

Evidence Review for NHS Surrey Area Prescribing Committee

Treatment: Capsaicin cutaneous patch (Qutenza®) for treatment of peripheral neuropathic pain in non-diabetic adults

Prepared by: Mandeep Allingham

Topic Submitted by: Mandeep Allingham

Date:

1. Purpose of the Review

To investigate the evidence available for the effectiveness of Qutenza® for treatment of peripheral neuropathic pain in non-diabetic adults and suggest its place in therapy within Surrey.

2. Appropriateness

2.1 The patient: Qutenza® is licensed for the treatment of peripheral neuropathic pain in non-diabetic adults. The patients may continue with concomitant neuropathic pain medication use.

2.2 The problem: This is a new therapy and data on repeated use are limited. There have been no comparative trails against standard therapies for neuropathic pain.

Definition: Peripheral neuropathic pain is an ongoing shooting, stabbing or burning pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system[1]. Peripheral neuropathy may be either inherited or acquired. Causes of acquired peripheral neuropathy include physical injury (trauma) to a nerve, tumours, toxins, autoimmune responses, nutritional deficiencies, alcoholism, and vascular and metabolic disorders. Acquired peripheral neuropathies are caused by systemic disease, trauma from external agents, or infections or autoimmune disorders affecting nerve tissue. Inherited forms of peripheral neuropathy are caused by inborn mistakes in the genetic code or by new genetic mutations[2].

Effects and prognosis:
No medical treatments exist that can cure inherited peripheral neuropathy. However, there are therapies for other forms. In general, adopting healthy habits - such as maintaining optimal weight, avoiding exposure to toxins, exercise, eating a balanced diet, correcting vitamin deficiencies, and limiting or avoiding alcohol consumption -- can reduce the physical and emotional effects of peripheral neuropathy. In acute neuropathies, such as Guillain-Barré syndrome, symptoms appear suddenly, progress rapidly, and resolve slowly as damaged nerves heal. In chronic forms, symptoms begin subtly and progress slowly. Some people may have periods of relief followed by relapse. Others may reach a plateau stage where symptoms stay the same for many months or years. Some chronic neuropathies worsen over time, but

very few forms prove fatal unless complicated by other diseases. Occasionally the neuropathy is a symptom of another disorder[2].

2.3 The Intervention:

How does it work: Capsaicin is a transient receptor potential vanilloid 1 (TRPV1) receptor agonist. Topical application causes initial excitation of primary sensory TRPV1 neurons, followed by prolonged desensitisation[3].

Care setting: Capsaicin patches cause pain and erythema at the application site in the majority of patients. A local anaesthetic should be applied for 60 minutes prior to application. Pre- and post-treatment with an opioid may be required. Blood pressure should be monitored during the treatment process as transient increases may occur Patches need to be applied in a clinic setting by suitably trained staff. This would mean initially in specialist pain clinics in secondary care and then if appropriate special clinics held in primary care[3].

Risk Management Issues:
Wear nitrile, NOT latex, gloves when handling the patch and treatment area.
Apply patches to clean, intact skin, not mucous membranes. Do not apply to the face.
Hairs can be clipped (not shaved) if necessary.
Used patches should be disposed of according to the instructions.
The cleansing gel provided may cause local skin reactions or irritation of eyes or mucous membranes.

Frequency: The patches are applied to the affected area for 30 or 60 minutes (depending on body site and indication) as a single application and can be repeated every 90 days as necessary. Up to 4 patches can be applied at any one time. The mean treatment area for trials for post-herpetic neuralgia equated to the use of two patches per application[3].

2.4 Alternative treatments:

As per Surrey PCTs 'Guildelines for management of Neuropathic pain in primary care', if symptoms are not controlled with paracetamol then patients are usually prescribed a tricyclic antidepressant (first line amitriptyline) and/or an anti-convulsant (first line gabapentin). Strong opioids may also be useful.

3. Effectiveness

One trial[4] included 402 patients who had had post-herpetic neuralgia (PHN) for at least 6 months and had an average numeric pain rating scale (NPRS) score of 3-9 [NPRS is an eleven point scale from 0-10 where 0 is no pain and 10 is worst pain possible]. After a 14 day baseline screening period patients were assigned to either a high-strength (8% Qutenza®) or a low-strength (0.04% control) capsaicin patch. As

topical capsaicin causes erythema and burning, use of a placebo would have unmasked participants to treatment allocation. Efficacy was assessed by daily NPRS scores ("average pain for the past 24 hours") for 12 weeks after patch application. Patient Global Impression of Change (PGIC) assessments, in which patients compare how they feel before and after treatment on a scale of –3 points (very much worse) to +3 (very much improved), were taken in addition to other quality of life and pain measurements.
The primary endpoint was the percentage change in mean NPRS score during weeks two to eight compared with baseline. A 29.6% reduction in NPRS score was found with Qutenza® compared with a 19.9% reduction in the control group. A reduction in NPRS score of at least 30% is considered a clinically moderately important improvement and a reduction of 10-20% a clinically minimally important improvement. In the Qutenza® group 42% of patients achieved at least 30% reduction in NPRS score in the first eight weeks compared with 32% of the control group (P=0.03). There were no statistically significant differences in the percentages of patients who achieved a 50% reduction in pain score, in changes in the majority of quality of life scores or in the proportion of patients with changes in concomitant neuropathic pain medication use although actual results were not reported.

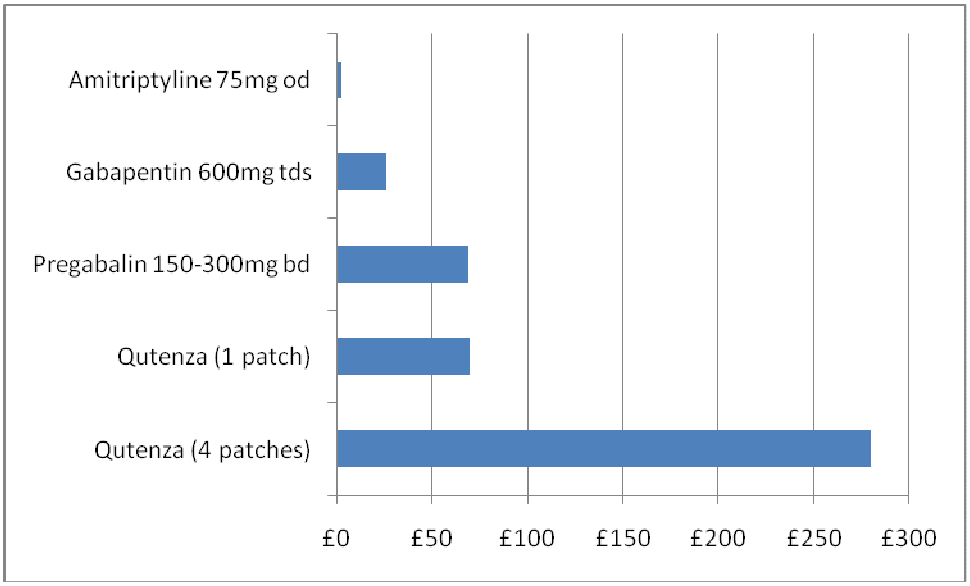
A further trial[5] randomised 307 patients with painful HIV-associated distal sensory polyneuropathy to either Qutenza® or control capsaicin patch applied to painful areas of the feet for 30, 60 or 90 minutes. The primary endpoint was the percentage change in the mean NPRS score during weeks two to twelve compared with baseline.
Results for all patients receiving Qutenza® showed a 22.8% reduction in NPRS score during weeks 2-12 compared with a reduction of 10.7% with control (P=0.0026). The 30- and 90-minute, but not the 60-minute application, resulted in a statistically significant reduction in NPRS score compared with control. In the Qutenza® group 34% achieved at least 30% reduction in NPRS score compared with 18% of the control group (P<0.01).

Data on repeated use of capsaicin patch are limited. Forty-week open-label extensions to 12 week studies in PHN (n=24) and HIVN (n=272, unpublished) have allowed up to 3 further applications. Pain relief appears to have been maintained although details are very limited[1,6.]
Comparative studies against other therapies are not available and would be methodologically difficult.
A Cochrane systematic review and meta-analysis pooled data from the two published studies to calculate an NNT of 12 to provide a 30% or greater improvement in pain over 12 weeks.[7] This compares with a NNT of approximately 5 for at least 50% pain relief with duloxetine or pregabalin over 10-18 weeks. However, capsaicin was compared against an active control rather than placebo, and the patient population, in terms of previous agents already tried, may not be comparable

4. Summary of Key Points for Consideration

Peripheral neuropathic pain is usually a chronic condition that can be difficult to treat. In the UK, the incidence of PHN is estimated to be 28 per 100,000 person-years.11 HIVN is reported to affect 30-60% of patients with HIV infection or AIDS[1].

Cost Comparisons: Cost for 30 days treatment (prices from MIMs and Drug Tariff July 2010)



N.B. Doses shown for general comparison and do not imply therapeutic equivalence. Costs of clinic time, monitoring, PBR tariff and local anaesthetic or opioids not included for Qutenza®

5. Conclusions and Recommendations

There is some evidence to indicate that Qutenza® may be useful in treatment of peripheral neuropathy in patients who have not responded satisfactorily to recommended oral therapy, although there is no comparative data. The trails have not been performed in patients without concomitant oral therapy and they do not clarify if treatment with Qutenza® leads to reduced oral therapy use.

APPENDIX H

The trails have not been performed with a 'true placebo' due to unmasking risk so it is hard to determine true benefit of treatment.
There is limited data on repeated use so long term effects of treatment are not known.
Not only should cost of the patches be considered but also the cost of clinic time, monitoring, PBR tariff and local anaesthetic or opioids need to be considered.

Points for discussion:

1. The Scottish Medicines Consortium (SMC) has accepted capsaicin (Qutenza®) for use within NHS Scotland for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain. Treatment should be under the supervision of a specialist in pain management.
   The use of this product is restricted to adults with post-herpetic neuralgia who have not achieved adequate pain relief with or who have not tolerated conventional first- and second-line agents. The company did not submit evidence relating to its use in other neuropathies and therefore the SMC was unable to approve its use in these patient groups.

2. In March 2010, NICE published guidance, "Neuropathic pain: The pharmacological management. The use of these patches has not been covered by this review.

3. The marketing authorisation restricts use of the patches to skilled healthcare professionals under the supervision of a physician. The patient needs to be accommodated for 2-3 hours per visit, allowing for the use of a maximum of 4 patches per visit. Treatment may be repeated every 90 days as warranted by the persistence or return of pain and a maximum of 4 patches may be used at any one time. This means the annual cost of treatment can vary from £840-£3360[8] per year. This would be included in the current tariff price as the patches are not PbR excluded.

4. The long-term effects of repeated applications, particularly on sensation are not yet known. For this reason it may be more appropriate to support the use of capsaicin patch in patients with PHN as a part of a clinical trial only.

5. The patch would be unsuitable for some types of neuropathic pain such as deafferentation pain so making it available as a "last resort" for all neuropathic pains could lead to some costly failures

Currently it would seem that the patches are only suitable for specialist pain clinic settings in non-diabetic patients with post-herpetic neuralgia, where all other standard treatment has failed, as a clinical trial due to the lack of long term safety data.

Appendix 1: Evidence search

Search terms used:

Resource	Used in this review?
National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.	✓
National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/ NICE produces national guidance in three areas of health: 1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.	✓ (through NHL)
Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.	x
Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/ CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of	x

Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database	
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/ Scottish equivalent of NICE	x
Medical Services Advisory Committee (Australia) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1 The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.	x
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.	x

Evidence retrieved

Reviews:

Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007393. DOI: 10.1002/14651858.CD007393.pub2 Accessed 8th April 2010

Appendix 2: References

1. Noto C, Pappagallo M & Szallasi A. NGX-4010, a high-concentration capsaicin dermal patch for lasting relief of peripheral neuropathic pain. Curr Opin Invest Drugs 2009; 10: 702-710

2. www.ninds.nih.gov

3. www.ukmi.nhs.uk

4. Backonja M, Wallace MS, Blonsky ER et al, for the NGX-4010 C116 Study Group. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. Lancet Neurol 2008; 7: 1106-1112)

5. Simpson DM, Brown S & Tobias J for the NGX-4010 C107 Study Group. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy Neurology 2008; 70: 2305-2313

6. Backonja MM, Malan TP, Vanhove GF et al for the C102/106 Study Group NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: A randomised, double-blind, controlled study with an open-label extension. Pain Med 2010; 11: 600-608

7. Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007393. DOI: 10.1002/14651858.CD007393.pub2 Accessed 8th April 2010