

**lidocaine 5% plaster (Versatis)**

**No (334/06)**

**Grunenthal GmbH**

8 December 2006 (*issued February 2007*)

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 NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**lidocaine 5% plaster (Versatis<sup>®</sup>)** is not recommended for use within NHS Scotland for the treatment of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia).

The comparative clinical and cost effectiveness have not been demonstrated.

Overleaf is the detailed advice on this product.

**Chairman  
Scottish Medicines Consortium**

**Indication**

Treatment of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia)

**Dosing information**

One to three plasters applied to cover the painful area once daily for up to 12 hours within a 24-hour period.

**Product availability date**

8 January 2007

**Summary of evidence on comparative efficacy**

Lidocaine is a local anaesthetic that produces a local analgesic effect in patients with post-herpetic neuralgia (PHN). This is thought to occur by stabilisation of neuronal membranes and down regulation of neuronal sodium channels thereby impairing conduction of signals, which would be associated with the perception of pain.

A study recruited 265 patients aged at least 50 years with PHN for at least 3 months after healing of the rash who had a pain score at least 4 on an 11-point categorical scale (0-10). They were initially treated with up to three open-label lidocaine 5% plasters for eight weeks. Approximately 50% of patients responded to treatment and 71 of these patients were then randomised to receive either placebo or lidocaine 5% medicated plaster for 2 to 14 days. The primary endpoint was defined as lack of efficacy on two consecutive days leading to withdrawal of treatment. Fewer patients in the lidocaine plaster group than the placebo group withdrew due of lack of treatment benefit: 25% (n=9/36) vs. 46% (n=16/35). The difference between the groups was not reported as significant.

A double-blind cross-over study recruited 32 patients with PHN who had used lidocaine 5% plasters for at least one month in an open-label trial, rated their pain relief from the plasters as at least 'moderate' and experienced pain prior to each new patch application. They underwent two 14-day treatment sessions in random order where lidocaine 5% or placebo plasters were applied over a 12-hour period. The primary outcome was median time-to-exit due to lack of efficacy, defined as a reduction of at least 2-points on a 6-point categorical verbal rating scale of pain relief. This was significantly longer with lidocaine plasters compared to placebo: >14 vs. 3.8 days, with no patients exiting during the active-treatment phase.

A double-blind study recruited 150 adults aged at least 21 years who had PHN for at least one month after healing of skin lesions. They were randomised in a 2:1 ratio to application of up to three lidocaine 5% or placebo plasters to the painful area for no more than 12 hours in a 24-hour period for 21 days, with dosing frequency at the discretion of the patient. All other medications for PHN were to remain constant during the study and patients also recorded their daily use of analgesics. Plasters were applied for 10 hours in two clinic sessions, at least 48 hours apart, prior to the 21-day home-treatment phase and in a third clinic session after it. The primary outcomes included pain intensity, assessed via 100mm visual analogue scale (VAS), and pain relief, assessed via 6-point categorical scale. There were no significant differences between lidocaine and placebo in mean reduction from baseline VAS pain intensity averaged from six assessments over 1-10 hours in clinic session 1 (9.6 vs. 8.3mm) and session 2 (12 vs. 7.8mm) or for VAS pain scores assessed at 4 hours in the third clinic session (38 vs. 41mm) and averaged over the 21-day home-treatment phase from daily

scores (45 vs. 47mm). In similar analyses there were no significant differences between the lidocaine and placebo groups in mean pain relief over 1-10 hours at clinic session 1 (2.0 vs. 1.8) and session 2 (2.2 vs. 1.9). However, this was significantly greater with lidocaine compared to placebo at 4 hours in the third clinic session: 2.6 vs. 2.1 (p=0.023). For allodynia, a secondary outcome, mean reductions from baseline, assessed via 4-point categorical scale during temporary removal of test patches at 6 hours, were significantly greater with lidocaine compared to placebo in clinic session 1 (0.6 vs. 0.1) and session 2 (0.4 vs. 0.1). Results for allodynia at session 3 were not reported.

A double-blind cross-over study recruited patients similar to those in the previous study who had PHN pain  $\geq 25$ mm on a 100mm VAS. They received in random order four treatments each separated by at least three days: two 12-hour applications of lidocaine 5% plasters to the area of greatest PHN pain; one 12-hour application of placebo plaster to this area; and one observation period. The protocol did not clearly identify the primary outcome. The efficacy analyses included data from 35 patients who completed the study. Lidocaine plaster was associated with significantly greater mean reductions from baseline in pain assessed on 100mm VAS at 0.5, 1, 2, 4, 6, 9 and 12 hours compared to observation alone (9.0 to 12.3 vs. -4.7 to 3.6mm) and at 4, 6, 9 and 12 hours compared to placebo plaster (9.1 to 12.3 vs. -3.1 to 5.8mm). There were significant differences between lidocaine plaster (10.2mm) and both observation (0.24mm) and placebo plaster (4.23mm) in mean reductions averaged over the study period 0.5-12 hours. The placebo plaster was associated with significantly greater reductions in pain compared to observation at 2 hours (9.4 vs. 1.2mm) and 6 hours (4.7 vs. -1.8mm). Pain relief, assessed on a 6-point categorical scale, was significantly greater with lidocaine plaster compared to observation at all time points (1.9 to 2.4 vs. 1.1 to 1.4) and averaged over the study period (2.2 vs. 1.3). This was significantly greater than placebo plaster averaged over the study period (2.2 vs. 1.8), but not at individual time points (1.9 to 2.4 vs. 1.6 to 2.2). The placebo plaster was associated with significantly greater pain relief than observation averaged over the study period (1.8 vs. 1.3) and at 0.5, 2, 4, and 6 hours (1.8 to 2.2 vs. 1.1 to 1.4).

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

## **Summary of evidence on comparative safety**

The most common adverse effects with lidocaine plasters were administration site reactions, which were mainly of mild to moderate intensity. Systemic adverse effects are unlikely as systemic absorption of lidocaine from the plasters is low.

## **Summary of clinical effectiveness issues**

The significant results in the smaller of the studies, which recruited an “enriched” population of patients who had previously responded to lidocaine plasters, should be interpreted with caution as the adequacy of blinding was not assessed and previous exposure to lidocaine plasters combined with the cross-over design may have compromised this.

The submission advocates the use of lidocaine plasters after patients have failed to respond to conventional analgesics and tricyclic antidepressants. Many of the patients included in the studies described had been referred to tertiary centres after failure of multiple treatments for PHN and their mean duration of pain was approximately 4 years (range 0-26 years). Therefore, it is possible that many of the patients in these studies would have failed to respond to tricyclic antidepressants. However, these studies examined effects mainly over

≤12 hours and had a duration of 14 – 21 days. Longer-term data on the benefits of lidocaine plaster over placebo are not available.

The lidocaine patch may reduce PHN pain and allodynia through a local analgesic effect of lidocaine and by creating a physical barrier that protects the sensitive area. The latter may account for the significant pain reductions with placebo plaster compared to observation in the third study (crossover design) described previously and some of the non-significant differences between placebo plaster and lidocaine plaster for pain reductions and pain relief in the parallel group study. The benefits in mean pain reduction with lidocaine plaster over placebo plaster were less than 5mm on 100mm VAS in the larger parallel group study and, in the smaller crossover study, in assessments up to 2 hours after plaster application. However, in the latter study the benefit over placebo was between 6 and 12 mm at assessments between 4 and 12 hours.

No trials directly compare lidocaine plasters with other drugs licensed for the treatment of PHN, therefore, efficacy and safety relative to these are unknown. An indirect comparison of lidocaine plasters with oral gabapentin included in the submission was limited by the inclusion of open-label trials to support the treatment effects of lidocaine plasters compared with double-blind trials for gabapentin; the use of secondary outcomes measured on different scales to compare results; and the inclusion of doses of gabapentin exceeding those licensed for PHN. The most relevant data for an indirect comparison were obtained from a 7-week randomised double-blind trial. In this the maximum licensed daily dose of gabapentin (1800mg) was associated with a significant mean reduction in the primary outcome of average daily pain intensity (assessed on 11-point categorical scale, 0-10) from baseline of 2.2 compared to 1.1 with placebo. This represents a treatment effect of about 1 point over placebo. Treatment effects with lidocaine plasters on similar scales (100mm VAS) in the double-blind trials described previously appear similar. There is no robust evidence that lidocaine plasters will produce clinical benefits in practice greater than those with gabapentin.

## **Summary of comparative health economic evidence**

The manufacturer submitted a cost utility analysis using a Markov model for treatment pathways of lidocaine plasters compared to gabapentin for the treatment of PHN in patients who have insufficient pain relief with standard analgesics and who do not tolerate, or have a contra-indication to, tricyclic antidepressants. The model duration was 6 months. The base case cost per quality adjusted life year (QALY) gained for lidocaine plasters was estimated at £3,800. A comparison with gabapentin appears appropriate.

The main weakness of the economic evaluation was that the indirect comparison between lidocaine plasters and gabapentin was based on only two trials with very different study designs, and the use of different pain improvement scales to assess outcomes (see clinical effectiveness). This meant the reliability of the “sufficient pain relief” estimates supporting the Markov model was limited and may not be representative of the clinical benefits of lidocaine plasters in practice. Where there were gaps in the clinical data, an expert panel of 8 general practitioners (GPs) and a pain specialist working in Scotland was used to identify transition probabilities for movements between health states in the Markov model. Whilst well conducted, there was a heavy reliance on the expert panel. Utility data were derived from a published study but were subject to several adjustments that increased the complexity of this analysis. Sensitivity analysis was well presented but did not include variations to the gabapentin price, which could be expected to have an impact on the QALY. However, the limitations in relation to the clinical data included in the indirect comparison mean that the economic case is not demonstrated.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: guidelines and protocols

The February 2006 NHS Quality Improvement Scotland best practice statement on the management of chronic pain in adults recommends that the following drugs should be considered for the treatment of neuropathic pain: tricyclic antidepressants (the best available evidence is for amitriptyline); anticonvulsants (gabapentin is thought to be effective); and tramadol. Tricyclic antidepressants should be the preferred initial treatment for neuropathic pain.

## Additional information: previous SMC advice

Following an independent review panel assessment, the SMC issued advice on 7<sup>th</sup> July 2006 that pregabalin (Lyrica<sup>®</sup>) is not recommended for use within NHS Scotland for the treatment of peripheral neuropathic pain in adults. Comparative clinical and cost effectiveness have not been demonstrated. Further controlled data are needed to establish its place in therapy in patients refractory to or intolerant of other pharmacological treatments.

## Additional information: comparators

The other topical preparation licensed for treatment of PHN is capsaicin (Axsain<sup>®</sup>). The oral antiepileptic drugs, gabapentin and pregabalin, are licensed for the treatment of peripheral neuropathic pain and can therefore be used for PHN. The antiepileptic carbamazepine and the tricyclic antidepressant amitriptyline are used to treat PHN but are not licensed for this.

## Additional information: costs

Drug	Daily dose range	Annual cost (£)
Lidocaine 5% patch	One to three patches	883-2650
Pregabalin	150-600mg	840-1259*
Gabapentin	900-1800mg	73-146 <sup>#</sup>
Carbamazepine	400-1600mg	96-408 <sup>#</sup>
Carbamazepine s/r	400-1600mg	69-270
Amitriptyline	25-75mg	17-38 <sup>#</sup>
Capsaicin 0.075% cream	Apply three to four times	138**

<sup>#</sup> costs of generic gabapentin, carbamazepine and amitriptyline from eVadis accessed on 6<sup>th</sup> October 2006; \* any dose of pregabalin (150-600mg) prescribed in two divided doses costs £840 annually and prescribed in three divided doses costs £1259 annually; \*\*costs for capsaicin cream based on the assumption that a 45g tube (costing £10.63) lasts 28 days; doses are shown for general comparison and do not imply therapeutic equivalence;

## **Additional information: budget impact**

The manufacturer estimated that the gross budget impact of lidocaine plasters was £71k in 2006/07 rising to £319k in 2010/11. After taking potential savings from reduced use of gabapentin into account the net budget impact was estimated at £22k in 2006/07 rising to £97k in 2010/11. The gross cost may be the more realistic estimate of budget impact given the fluctuating costs of generic medicines. These estimates assumed 86 patients in 2006/7 rising to 387 in 2010/11 and market shares varying from 5% in 2006/7 to 20% in 2010/11.

**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.*

*This assessment is based on data submitted by the applicant company up to and including 19 January 2007.*

*\* 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/>*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*The undernoted references were supplied with the submission.*

*Rowbotham MC, Davies PS, Verkempinck C and Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain 1996; 65: 39-44.*

*Galer BS, Rowbotham MC, Perander J and Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain 1999; 80: 533-8.*