

Resubmission

lidocaine 5% medicated plaster (Versatis®) **No. (334/06)**
Grunenthal GmbH

04 July 2008

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 resubmission

lidocaine 5% medicated plaster (Versatis®) is accepted for restricted use within NHS Scotland for the treatment of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia).

There are only limited comparative data available for lidocaine plasters, the comparative clinical effectiveness remains unclear. It is restricted to use in patients who are intolerant of first-line systemic therapies for post-herpetic neuralgia or where these therapies have been ineffective.

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.

This resubmission states that the efficacy of lidocaine 5% plasters has been assessed in eleven clinical trials including five randomised controlled trials discussed in the original submission. However none of these trials compared lidocaine 5% plasters with other drugs licensed for the treatment of PHN. This resubmission also presented additional, unpublished, interim results of a comparison with oral pregabalin. These data, however, remain commercial in confidence.

The clinical trials described below are therefore as per the original submission.

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 ≥ 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 5% plasters were administration site dermal reactions, which were mainly of mild to moderate intensity. Systemic adverse effects are unlikely as systemic absorption of lidocaine from the plasters is low.

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

Summary of clinical effectiveness issues

This resubmission advocates the use of lidocaine plasters after patients have failed to respond to or are unsuitable for amitriptyline and gabapentin; before the use of a strong opioid or capsaicin cream and before referral to a pain specialist. It is unclear from the submission which other therapies had been tried unsuccessfully before entry into the lidocaine clinical trials.

The submission provides interim results of a comparison with pregabalin. However these data are limited by their interim nature and the open-label design of the study, the relevant results involving a subgroup of enrolled patients resulting in small patient numbers. The results of the interim analysis suggest that lidocaine plasters are at least as effective in reducing pain scores as pregabalin. The comparative trial lasted for 4 weeks only.

A recent review by the Drug and Therapeutics Bulletin (February 2008) raised the issue of intermittent application, with the plaster applied for 12 hours in every 24 hours. It is not clear from the published trials whether this results in breakthrough pain during the 'plaster-free' time.

Due to the low systemic availability lidocaine plasters were associated with improved tolerability compared with pregabalin. However, there are no direct comparative data with other agents for PHN.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis using a Markov model for treatment pathways comparing lidocaine plasters to pregabalin 300mg/day, pregabalin 600mg/day and gabapentin 1800mg/day for the treatment of PHN. Indirect comparison was required to assess the efficacy compared to gabapentin, and this indirect comparison was limited by: comparing the open-label interim results from a comparative trial with pregabalin to double-blind trials of gabapentin and pregabalin versus placebo; the use of secondary outcome measures to compare results; the use of endpoints measured after different durations of treatment and; the small patient numbers.

The manufacturer used this analysis to support a case for the use of lidocaine plasters after amitriptyline and gabapentin has been considered or do not provide adequate pain relief but before a strong opioid, capsaicin cream or referral to a pain specialist. Therefore, a comparison has been made with pregabalin for third line use.

The base case cost per QALY was estimated at £507 for the comparison with pregabalin 600mg/day, with lidocaine plasters "dominating" pregabalin 300mg/day (i.e. higher cost, poorer outcome for pregabalin), and an incremental cost per QALY gained of £814 versus gabapentin. The additional QALYs estimated for lidocaine plasters were derived from a combination of better response rate, defined as patients achieving a >50% improvement in standard pain scale score, fewer discontinuations due to adverse events and higher utility values (due to a better systemic side effect profile) associated with maintenance treatment in responders to lidocaine plasters relative to the comparators.

While the economic model appears well constructed, the main weakness was the data available for the indirect comparison with pregabalin and gabapentin. A particular weakness was small patient numbers and very short follow-up for lidocaine plasters, with the only data used in the economic analysis for all comparisons being that from the interim analysis of the comparative study versus pregabalin.

Several alternative scenarios presented by the manufacturer were useful in addressing some of the concerns with the analysis. These demonstrated a cost per QALY of approximately £3000 v pregabalin assuming 1.03 plasters per day and £16000 based on a dose of 1.86 plasters per day for a scenario assuming no additional efficacy or differences in discontinuation rates for lidocaine plasters, but retaining benefits in utility due to a better side effect profile in responders.

Summary of patient and public involvement

Patient Interest Group Submission: Pain Concern

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.

In November 2006, the European Federation of Neurological Societies (EFNS) published guidelines on the pharmacological treatment of neuropathic pain. This recommends tricyclic antidepressants or gabapentin / pregabalin as first line agent for post-herpetic neuralgia. It states that topical lidocaine has been evaluated only in patients with allodynia in short-term studies which used an enrichment phase or were post hoc analyses from larger trials. However, due to excellent tolerability, this treatment may be preferred in the elderly, particularly in patients with allodynia and small area of pain.

Additional information: previous SMC advice

Following an independent review panel assessment, SMC published advice in August 2006: pregabalin (Lyrica®) 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®). The oral antiepileptic drugs, gabapentin and pregabalin, are licensed for the treatment of peripheral neuropathic pain and can therefore be used for PHN. However pregabalin has not been recommended by SMC for this indication. The antiepileptic carbamazepine and the tricyclic antidepressant amitriptyline are used to treat PHN but are not licensed for this indication.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Lidocaine 5% plaster	One to three plasters	881 to 2643
Pregabalin	150 to 600mg	840 to 1259*
Gabapentin	900 to 1800mg	335 to 1161 [#]
Carbamazepine	400 to 1600mg	39 to 154 [#]
Carbamazepine S/R	400 to 1600mg	64 to 251 [#]
Amitriptyline	25 to 75mg	9 to 22 [#]
Capsaicin 0.075% cream	Apply three to four times	158**

[#] costs of generic gabapentin, carbamazepine, carbamazepine SR and amitriptyline from eVadis accessed on 6 May 2008; * any dose of pregabalin (150 to 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 £12.15) lasts 28 days; doses are for general comparison and do not imply therapeutic equivalence.

Additional information: budget impact

The estimated gross budget impact of lidocaine plasters was £14k in 2008 for 30 patients treated, based on an estimated 4% market share of current patients treated for PHN, rising to £74k in 2012, for 20% of treated patients (163 patients).

The manufacturer provided figures on current uptake of lidocaine plasters in Scotland, raising concerns that the budget impact may represent an underestimate. After taking potential savings from reduced use of pregabalin, the net budget impact was estimated at £1k in 2008 rising to £6k in 2012. However, these estimates are based on an assumption of a dose of 1.03 plasters per day which may represent a low estimate for practice in Scotland.

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 **13 June 2008**.*

** 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 reference, shaded grey, was in addition to information supplied with the submission.

Anon. Lidocaine plasters for postherpetic neuralgia. Drug and Therap Bull 2008; 46: 14-16.