

## A review of lidocaine 5% medicated plasters for Post-herpetic Neuralgia

**Brief:** Lidocaine plasters are included in the NHS England document published in July 2017: Items which should not routinely be prescribed in primary care: a consultation on guidance for CCGs. This item is classified as 'an item of low clinical effectiveness, where there is a lack of robust evidence of clinical effectiveness or there are significant safety concerns'. This review has been prepared for NHS England in response to concerns raised by the manufacturer Grünental Ltd regarding inclusion of lidocaine plasters as an item that should not be routinely prescribed. The review aims to focus on the literature available on the licensed indication.

### Summary of clinical evidence

- Versatis® (lidocaine 5%) plasters are licensed for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection in adults (SPC) which is also referred to as Post-herpetic Neuralgia (PHN). They are not licenced for any other indication.
- Lidocaine plasters are not included as a treatment option in the NICE Clinical Guideline on neuropathic pain (CG173) and neither are they included in the 'treatments that should not be used' category. The full NICE guideline considered the evidence for topical lidocaine and only one small placebo cross-over study (n=28) for postsurgical incisional pain was reviewed, which showed no difference in effect of lidocaine patches compared to placebo on pain reduction. No studies for PHN were included in the review as one of the exclusion criteria were Randomised Controlled Trials (RCTs) with enriched enrolment. Overall, NICE concluded there was an absence of necessary effectiveness evidence.
- Other national organisations such as the SMC, PresQIPP and the Special Interest Group on Neuropathic Pain conclude that the evidence for the effectiveness of lidocaine plasters is limited, of low quality, and the clinical effectiveness remains unclear. Nevertheless, these organisations have approved use of lidocaine plasters in patients who are intolerant of first-line systemic therapies for PHN or where these therapies have been ineffective.
- Several systematic evidence reviews have been conducted on the use of topical lidocaine (any formulation) for PHN, including a Cochrane review and one published in the Lancet Neurology. Their conclusions are broadly similar and note that there is limited evidence from good quality (RCT's) to support the use of topical lidocaine. These reviews also suggest topical lidocaine as a treatment option in a select group of patients (i.e. second line).
- A number of small open-label studies suggest that lidocaine plasters are effective for PHN, but they did not meet the criteria for inclusion in the NICE and Cochrane review as only higher quality studies of a randomised, double-blind design were considered.
- The NICE Guideline Development Group have made a research recommendation to further investigate the use of topical lidocaine for localised peripheral pain as they could be a potential alternative treatment for people who do not wish to, or are unable to, take oral pain medications. There are several on-going clinical trials, as mentioned in the Cochrane review, which may help answer questions around clinical efficacy in a variety of pain indications. Although some of the studies have been completed the results have not been published; Grünental Ltd Medical Information were not able to provide further information in the timescale required for this review.
- Overall, the evidence base for lidocaine plasters is limited and there is no robust evidence for their use in PHN. However, there may be a place for use in patients with PHN who are intolerant of first-line systemic and topical therapies or where these therapies have been ineffective.

### Place in national guidance

The NICE Clinical Guideline (CG173) on neuropathic pain recommends amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment options for neuropathic pain. For people who wish to avoid, or are unable to take oral medication, topical capsaicin cream 0.075% is recommended as a treatment option. Lidocaine plasters are not included as treatment option in the Clinical Guideline on neuropathic pain and neither is it included in the 'treatments that should not be used' category (1). These guidelines were published in 2013 and review by NICE in September 2017, concluded that they found no new evidence that affects the recommendations in the guideline.

It is worth noting that in the full version of the NICE CG173, the evidence for topical lidocaine was considered under a specific review protocol which included randomised controlled trials (RCTs) and which excluded, for example, RCTs with enriched enrolment or single-blind placebo run-in period (2). The full review protocol is available as appendix D (<https://www.nice.org.uk/guidance/cg173/evidence/appendix-d-pdf-191621343>). Only one small placebo cross-over study (n=28) for lidocaine patches was included, which showed no effect on pain reduction post-surgery in patients with cancer. No studies for PHN were identified for inclusion in the review. Overall, it was concluded that there was an absence of necessary effectiveness evidence, and furthermore a health economic analysis could not be conducted. The Guideline Development Group felt that a research recommendation should be made to further investigate the use of this treatment for localised peripheral pain because it could be a potential alternative treatment for people who do not wish to, or are unable to, take oral pain medications.

The Scottish Medicines Consortium (2008) accepted lidocaine 5% medicated plaster (Versatis®) for restricted use within NHS Scotland for the treatment of neuropathic pain associated with previous herpes zoster infection (PHN) (3). They state, due to the limited comparative data available for lidocaine plasters, the comparative clinical effectiveness remains unclear. As such, it is restricted for use in patients who are intolerant of first-line systemic therapies for PHN or where these therapies have been ineffective.

Similarly, PrescQIPP considered the evidence in November 2013 and concluded that the effectiveness of lidocaine plasters is weak and limited (4). They recommend that prescribing of lidocaine plasters should be restricted to patients diagnosed with PHN, in whom alternative treatments have proved ineffective or where such treatments are contraindicated, and that patients being prescribed the lidocaine plasters for unlicensed indications should be reviewed and have their therapy discontinued.

### Licensing studies

The licence for Versatis® was based on two small studies including a 14 day placebo-controlled cross-over study (n=32) and an open-label study (n=265) in which patients who had previously responded to lidocaine patches were entered into the placebo-controlled randomised part of the trial (5,6). Both these studies were criticised by the [Medicines and Healthcare Products Regulatory Agency \[MHRA\]](#) for using “enriched populations” i.e. patients were only included if they had previously responded to lidocaine. The MHRA also noted that the manufacturer was not able to define prospectively which patients would respond to the plasters and it is not clear how many patients will derive benefit (7).

### Systematic reviews

Several systematic evidence reviews have been conducted on the use of topical lidocaine for neuropathic pain. This includes a Cochrane systematic review published in July 2014 (8). The review included double-blind RCTs of at least two weeks' duration comparing any formulation of topical lidocaine with placebo or another active treatment in chronic neuropathic pain. No evidence from good quality RCTs was found to support the use of topical lidocaine to treat neuropathic pain; all of the studies included were at high risk of bias because of small size or incomplete outcome assessment, or both. The Cochrane Collaboration acknowledge, however, that individual studies included in the review indicated that topical lidocaine was effective for relief of pain and clinical experience also supports efficacy in some patients. Limited information from single studies included in the review, mainly in PHN, indicate that topical lidocaine may be effective in treating neuropathic pain in a small number of patients, and is well tolerated, at least in the short term. They state several large ongoing studies, of adequate duration, with clinically useful outcomes should provide more robust conclusions about both efficacy and harm.

A more recent systematic review published in the Lancet Neurology (2015) was the basis of a revised Special Interest Group on Neuropathic Pain (NeuPSIG) recommendation (9). The systematic review only identified two enriched-enrolment studies in PHN due to an inclusion criteria of randomised, double-blind, placebo-controlled studies. A weak recommendation was assigned to lidocaine patches for neuropathic pain and as such these recommendations have been adopted by the [NeuPSIG guidelines](#): lidocaine patches 5% are recommended as a second line of treatment due to low quality of evidence (10).

### Other studies

In addition to the RCTs considered in the Cochrane review (5,6,11,12), the evidence base for lidocaine plasters for PHN include a number of open-label studies. In one open-label non-inferiority RCT of 4 weeks duration (n=96, PHN; n=204, diabetic peripheral neuropathy), more patients with PHN responded to lidocaine 5% plasters than to pregabalin; 62.2% vs. 46.5%, p value not given for the PHN group (13). However, this is a non-inferiority study so superiority of lidocaine cannot be extrapolated and the open-label design as well as the short duration and small size are limitations to the

findings. Similar limitations such as open-label design, short duration (2-8 weeks) and lack of control apply to the other studies investigating lidocaine plasters in PHN (14-17). The longest duration of the open-label studies is 12 months and 4 years over which the long-term efficacy and safety was evaluated (18,19). In the 12 month study, newly recruited patients (n=97) had a mean average pain intensity of  $5.9 \pm 1.4$  at baseline, which decreased to  $3.9 \pm$  at week 12 and remained stable  $3.9 \pm 2.3$  until the end of the 12 month period (18).

All the studies described above were published before recommendations were made by NICE, PrescQIPP and Cochrane. Although, individually some studies indicate that lidocaine plasters are effective for pain relief, they did not meet the criteria for inclusion in the NICE and Cochrane review as only higher quality studies of a randomised, double-blind design were considered.

We have also conducted an independent literature search of published primary papers (2013-2017) and were not able to identify any significant new evidence to the above to support the use of lidocaine plasters for PHN. Additional studies identified included small open-label or retrospective observational studies (20,21).

### Limitations

- This review has been prepared for NHS England in response to concerns raised by the manufacturer on categorising lidocaine plasters as an item that should not be routinely prescribed.
- The review includes evidence for the licensed indication only.
- Papers for individual studies were provided by the manufacturer.
- An independent literature search of further published studies was conducted post publication of PrescQIPP advice in 2013
- The review includes data on topical lidocaine formulations: patches and plasters. As such the terminology, plasters and patches, is used interchangeably throughout the document
- Grünental Ltd Medical Information were not able to provide further information requested in the timescale required for this review.

### Search Strategy

NICE [www.nice.org.uk](http://www.nice.org.uk)

Scottish medicines Consortium [www.scottishmedicines.org.uk](http://www.scottishmedicines.org.uk)

PrescQIPP [www.prescqipp.info](http://www.prescqipp.info)

NHS Evidence via [www.evidence.nhs.uk](http://www.evidence.nhs.uk)

Cochrane Library via [www.thecochranelibrary.com](http://www.thecochranelibrary.com)

Medicines and Healthcare Products Regulatory Agency [www.mhra.gov.uk](http://www.mhra.gov.uk)

Medline - ("NEURALGIA, POSTHERPETIC"/ AND LIDOCAINE/) [DT 2013-2017]

EMBASE - (LIDOCAINE/ AND ("NEUROPATHIC PAIN"/ AND "POSTHERPETIC NEURALGIA"/)) [DT 2013-2017]

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