New Medicine Assessment

Lidocaine 5% medicated plasters (Versatis®▼)
in Post-Herpetic Neuralgia (PHN)

Recommendation: Green

Lidocaine 5% medicated plasters are recommended as an option for the treatment of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia) in adults.

Initiation should only be after first line topical and systemic therapies have either failed or led to intolerable side effects, as per the LMMG Neuropathic Pain Guidance. An assessment of the tolerance and efficacy should be made after 2 – 4 weeks of treatment initiation, before continuation.

After three months of treatment there should be an assessment as to whether the number of patches can be reduced or the patch free interval can be extended.

Summary of supporting evidence:

- SMC restricts the use of lidocaine 5% medicated plasters in NHS Scotland for the treatment of neuropathic pain associated with previous herpes zoster infection (PHN) and acknowledges the limited availability of comparative data and that the comparative clinical effectiveness remains unclear. However, there have been subsequent active comparator trials published (discussed within the assessment).
- A Cochrane review assessing topical lidocaine in neuropathic pain, published in July 2014, concluded that there is limited information from single studies, mainly in PHN, and indicates that topical lidocaine 5% plasters may be effective in treating neuropathic pain in a small number of patients, and is well tolerated in the short-term.
- There are several systematic reviews and meta-analyses assessing the efficacy of treatments for PHN. They mostly draw their conclusions from the same trials and note the studies are small numbers of patients, limited size and quality. The conclusions are broadly similar and recommend that lidocaine 5% plasters are an option for those in whom first line therapies are not tolerated or efficacious.
- A systematic review and network meta-analysis [Wolff] concludes that lidocaine plasters were associated with similar or greater effects on pain compared to other relevant comparators.
- Most of the trials referenced in the systematic reviews and meta-analyses, although of poor quality, risk of bias and small numbers of patients, found that there was a statistically significant improvement in pain relief and pain intensity for lidocaine plasters compared to placebo.
- One paper [Binder 2009] did not meet the primary outcome of median time to exit from the double blind phase due to lack of efficacy (≥ 2 point decrease on the 6-point VRS on 2 consecutive days of plaster application compared to the mean score in the open label treatment phase) in the intention to treat population.
- The active comparator trial vs. pregabalin found a similar improvement in pain intensity; 66.4% of lidocaine treated and 61.5% of pregabalin treated patients met the pre-defined responder criteria, which was a reduction ≥ 2 points or absolute value ≤ 4 on the NRS-3

Produced October 2015

scale after 4 weeks of treatment.

- Overall the safety data seems favourable for lidocaine 5% plasters. Cochrane stated that although in the small studies there was no difference between lidocaine and placebo for the incidence of AEs and withdrawals, the studies were underpowered to show such an effect.
- The DRAEs reported in the trials were related to application site reactions and included; pruritus, skin reaction or irritation, erythema and dermatitis. It is reported that only small numbers of patients discontinued therapy due to DRAEs, however, for the longer term trials the percentage of patients who continued long term was small. This could be due to resolution of symptoms, lack of efficacy, DRAEs, or other reasons.
- A 2010 cost effectiveness study concluded that lidocaine patches were a cost effective therapy for PHN in comparison to pregabalin. It is estimated that 40 – 60 % of patients treated with first line therapies for neuropathic pain will only obtain partial pain relief. Using this estimate and that approximately 420 patients across Lancashire will suffer from PHN annually it is thought that the annual expenditure on lidocaine 5% plasters will be £147,986 to £665,935. Last 12 months prescribing data shows a spend of £743,529 across Lancashire on lidocaine 5% plasters.

Details of Review

Name of medicine (generic & brand name)**:**

Lidocaine (Versatis®)

Strength(s) and form(s):

5% medicated plaster

Dose and administration: Apply up to three plasters once daily for up to 12 hours; follow with minimum 12 hour plaster-free interval.[1] Discontinue treatment after 2—4 weeks if no response.[1] Apply to intact, dry, non-irritated skin[2] to cover painful area; plasters may be cut into smaller sizes. Hairs on the affected area must be cut off with a pair of scissors (not shaved).

BNF therapeutic class / mode of action:

Local anaesthesia (chapter 15.2) > lidocaine for surface analgesia[2]

Licensed indication(s): Versatis® is indicated for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN) in adults.[1]

Proposed use (if different from, or in addition to, licensed indication above):

For use in primary care following recommendation or initiation by a secondary care physician (Amber0) for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN) in adults over 18 years as per licensed indication, after standard neuropathic agents (as per NICE Neuropathic Pain Guidance CG173) have either failed or led to intolerable side effects.

Course and cost:

Lidocaine 5% (700 mg/medicated plaster) 30 plasters = £72.40.[3] Annual cost per patient who continues treatment ranges from £881 to £2643 dependent upon how many plasters used daily (the number of plasters used is expected to decline on usage). Patients should be reviewed at 2-4 weeks and discontinued if proving to be ineffective[1].

Current standard of care/comparator therapies:

Amitriptyline, duloxetine, gabapentin, pregabalin, capsaicin cream. NICE CG173 refers to a number of other therapies which would be for initiation in a specialist setting, most of which are unlicensed and not all are approved for use across Lancashire.[4]

Relevant NICE guidance:

NICE CG173 Neuropathic pain - pharmacological management: The pharmacological management of neuropathic pain in adults in non-specialist settings.[4]

Produced October 2015

Background and context

Post-herpetic neuralgia (PHN) is when the pain associated with shingles has become chronic; it may include symptoms of constant or intermittent pain which may be described as stabbing, aching, throbbing or burning. It can also include allodynia (pain induced by a usually non-painful stimulus, e.g. heat, cold, wind, draft), hyperalgesia (severe pain from a normally mildly painful stimulus) or intense itching.[5] It is the most common complication of shingles in adults and it is estimated that approximately 20% of people with shingles older than 50 years will develop PHN, despite antiviral treatment beginning within 72 hours of shingles rash onset.[5] It is uncommon in children. It is estimated that in the UK primary care the incidence of PHN is 28 per 100 000 person-years. The risk of a patient experiencing PHN following shingles increases with age, presence and severity of prodromal pain, and severity of acute zoster pain.[5] The pain of PHN can result in fatigue, sleep problems, and depression, and can interfere with daily activities (such as dressing, bathing, housework, driving, and shopping), especially in older people.

A person suffering with PHN may be initially offered paracetamol either alone or with codeine and practical solutions, such as wearing loose fitting cotton clothing, using protective dressings or using cool packs assuming these don't aggravate the allodynia.[5]

NICE neuropathic pain guidance does not list lidocaine 5% medicated plasters as a treatment option for neuropathic pain, and doesn't mention their use in PHN.[4] NICE advocates the use of amitriptyline, duloxetine, gabapentin or pregabalin for the management of neuropathic pain (NP).[4] The topical capsaicin 0.075% cream (Axsain®) is listed as a possibility to consider for patients who have localised neuropathic pain and cannot tolerate or wish to avoid oral treatment.[4] European neurology guidance recommends first line use of TCAs or gabapentin/pregabalin, but also first-line use of topical lidocaine to be considered in the elderly, the guidelines recommend topical lidocaine, topical capsaicin and tramadol second line in all other patients.[6]

Lidocaine 5% medicated plasters are licensed for symptomatic relief of PHN in adults. They have been accepted by the Scottish Medicines Consortium (SMC) for restricted use within NHS Scotland for the treatment of NP associated with previous herpes zoster infection (PHN). SMC notes that 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.'[7] Some of the local CCGs also have a position for use of this medication for PHN as either Amber or Red, however, there is currently no LMMG recommendation. This review looks at the evidence to support the use of lidocaine 5% medicated plasters in the treatment of PHN and makes a recommendation based upon that evidence.

Produced October 2015

Summary of evidence

Summary of efficacy data in proposed use:

There have been several systematic reviews and meta-analyses carried out assessing the pharmacological treatments for PHN and neuropathic pain, with some looking specifically at topical lidocaine therapy. In terms of the evidence for use of lidocaine plasters, the majority of these reviews draw from the same selection of trials, most of which are cross-over design, generally poor quality, short duration and very small numbers of patients. Cochrane stated that none of the studies provided data that met pre-defined criteria for first or second tier analysis. The individual trials are discussed following the summary of the reviews in which they are covered.

An earlier **Cochrane** review of topical lidocaine for PHN has been withdrawn because it is considered out of date since the standards now used to assess evidence in chronic pain trials have changed and more studies have been published. The review included three studies [Rowbotham 1995, Rowbotham 1996, Galer 2002], two of which are included in the subsequent Cochrane review, published in 2014, which assesses topical lidocaine for neuropathic pain in adults[8] The previous Cochrane review excluded Galer 1999 because it had enriched enrolment & Meier 2003 because it was not limited to PHN; both were included in 2014 review of lidocaine in neuropathic pain. This more recent 2014 Cochrane review concluded that there is limited information from single studies, mainly in PHN, and indicates that topical lidocaine 5% plasters may be effective in treating neuropathic pain in a small number of patients, and is well tolerated at least in the short term.

The review found 12 studies enrolling 508 participants with chronic neuropathic pain; six of these (208 participants) had PHN [Binder 2009, Galer 1999, Galer 2002, Kanai 2009a, Rowbotham 1995, Rowbotham 1996]. Some of these [Rowbotham 1995, Kanai 2009a] assessed alternative topical lidocaine preparations to the plaster and so are not discussed further. The Cochrane review did not include or exclude the open label active comparator trials against pregabalin [Baron 2009[9], Rehm 2010[10]] which have been discussed later in this assessment.

The following sections discuss the trials included in the Cochrane review which assessed lidocaine 5% plasters in PHN and were classed as third tier evidence. The tier allocated was according to outcome and freedom from known source of bias. Third tier relates to data from fewer than 200 patients, or where there were expected to be significant problems because, for example, of very short duration studies (<4 weeks), where there were major heterogeneity between studies, or where there were major shortcomings in allocation concealment, attrition, or incomplete outcome data. For third tier, no data synthesis is reasonable and may be misleading but an indication of beneficial effects may be possible.

Galer 1999[11], was an enriched enrolment randomised double-blind placebo controlled cross-over study.[11] It consisted of 32 patients with PHN, who for at least a month in a prior open-label trial, had used lidocaine 5% medicated plasters and benefited with at least 'moderate' relief, as well as experiencing pain prior to each new patch application. In phase A of the study, patients were assigned lidocaine 5% medicated plaster or placebo plasters to be applied daily over a 12 hour period for 14 days. They then entered phase B which involved switching therapy from placebo to lidocaine 5% plasters or vice versa for a further 14 days. The primary outcome was median time-

Produced October 2015

to-exit due to lack of efficacy (which was defined as a reduction of at least 2-points on a 6-point categorical verbal rating scale (VRS) of pain relief, with 5 being "complete relief" and 0 being "worse" compared to the pre-study pain relief score). The median time to exit was longer with lidocaine plasters compared to placebo (>14 days vs 3.8 days ($p<0.001$))[11] 78.1% of patients preferred the lidocaine treatment phase compared to 9.4% of patients preferring the placebo treatment phase (statistical significance not reported). Further information can be found in Table 1.

Rowbotham 1996[12], was a vehicle-controlled, 4 session cross-over study in 35 participants.[12] The trial consisted of four sessions, randomised in order and with a minimum of 72 hours between each; they included 2 x applications of up to three lidocaine 5% medicated plasters for 12 hours, 1 x application of up to three placebo/vehicle only plasters for 12 hours and 1 session of observation only. Change in pain intensity on a 100 mm visual analogue scale (VAS) and pain relief on a 6-point VRS were measured at time points prior to application and during application/observation. It was found that lidocaine had a mean reduction in VAS of 10.3 mm at all measured time points. The specific results for the other treatment groups are not reported but represented in a graph. The paper states that lidocaine was superior to observation only at all time points for both pain intensity and pain relief. Compared to vehicle patch (placebo) lidocaine was superior at time points 4, 6, 9 and 12 hours for both pain intensity and relief[12]. Further information can be found in Table 1.

Binder 2009[13] was an enriched enrolment, randomised withdrawal study. It had an 8-week open-label run-in phase where all patients (FAS=263) received the 5% lidocaine medicated plasters. This was followed by a double blind phase, where (n=71) responding patients either continued with the lidocaine plaster (n=36) or were switched to placebo (n=35). The primary end-point was time to exit from double-blind phase due to lack of efficacy, defined as ≥2 point decrease on 6-point VRS on 2 consecutive days of plaster application, compared with the mean in last week of open-label treatment. Median times-to-exit were 13.5 days (range 2-14 days) for lidocaine and 9.0 days (range 1-14 days) for placebo group (p=0.1510) for the ITT (FAS) population. For the per protocol population (excluded those with protocol infringements) the result was 14.0 days (range 3 – 14 days) vs. 6 days (range 1 to 14 days) for lidocaine vs. placebo respectively (p=0.0398). 25 of 36 patients (69.4%) in lidocaine and 14 of 35 patients (40.0%) in placebo group completed the 14 day double-blind phase. Patients who switched from lidocaine to placebo plasters for the double-blind phase experienced significant worsening in several secondary endpoints compared to the measurements taken at randomisation following the 8-week active treatment run in. Full details can be found in table 1.

Galer 2002[14] was a three week parallel, randomized, double-blind, vehicle controlled efficacy study in PHN patients (n=150). Of whom 96 met the NPS (neuropathic pain scale) inclusion criteria and thus were included in the analysis and those who had missing baseline or final visit NPS scores were excluded. Composite NPS score reductions were consistently greater in the lidocaine group than the placebo group (for example, change in NPS 10: lidocaine 15.3 (SD 17.9), placebo 7.7 (SD 14.2)).

A 2015 systematic review and meta-analysis **[Finnerup]**[15] of pharmacotherapy for neuropathic pain, although not specific to PHN or lidocaine, did gave a weak recommendation for second-line use of lidocaine patches, with the possibility of a first-line usage where there are side-effects or safety concerns, particularly in frail or elderly patients. The weak GRADE recommendation was

Produced October 2015

based on low quality of evidence, low effect size but high values or preferences and tolerability or safety. The conclusion was taken from a 2010 paper assessing the evidence for pharmacological treatment of neuropathic pain by the same author [Finnerup].[15] This included four lidocaine references, one using a cream, another didn't include PHN patients and the remaining two are discussed above and below. [Baron 2009[9], Galer 2002[14]].

Baron 2009[9] was an open-label, randomised, active comparator, non-inferiority trial in patients with PHN or diabetic polyneuropathy (DPN). Participants used either 5% lidocaine medicated plasters (up to 3 for PHN for up to 12 hours a day with 12 hour plaster free period) or pregabalin titrated up according to SPC[16] for 4 weeks, this was followed by 8 weeks where patients could receive both treatments, if required and then a 4 week phased withdrawal of pregabalin. The full analysis set (FAS) consisted of 300 patients, full inclusion and exclusion criteria can be found in Table 1. 101 of 152 (66.4%) lidocaine patients and 91 of 148 (61.5%) pregabalin patients, met the pre-defined responder criteria (defined as reduction ≥ 2 points or absolute value ≤ 4 on the NRS-3 scale after 4 weeks of treatment in the PPS) (non-inferiority p=0.00229, lower limit of CI=-7.03). There was no significant difference between 5% lidocaine and pregabalin in terms of not achieving the NRS-3 response in the intention to treat population; RR 0.69 (95% CI 0.44-1.09) in patients with PHN. In the per protocol population the lower limit of the 95% confidence interval was -9.15, which was below the predefined margin of -8 percentage points. All secondary endpoint results were similar between lidocaine and pregabalin, statistical significance not reported (see Table 1).

A 2014 meta-analysis **[Snedecor][17]** found a total of 28 articles which looked at 21 pharmacological treatments (including placebo) in PHN, across 4317 patients. The meta-analysis drew from only two lidocaine studies, [Baron 2009[9] and Rehm 2010[10]] which are discussed above and below. The paper concluded that lidocaine 5% plasters (n=88) and pregabalin (range n=173-366) were found to be the most effective at providing ≥ 30% and 50% pain relief.

Rehm 2010[10] was the subgroup analysis of patients with PHN (n=98) from the Baron 2009[9] paper. It was found that for those with the PHN the median time of onset of a response was 2 days (interquartile range 1-11) vs. 16 days (interquartile range 1-28 days) for lidocaine patch vs. pregabalin respectively. The pain intensity (measured by SF-MPQ on VAS) improved by -25.9 $\pm$ 23.14 with lidocaine patch compared to -17.2 $\pm$ 25.57 for pregabalin (statistical significance not reported). See table 1 for further information.

A 2013 systematic review **[Khadem][18]** assessed the therapeutic options for PHN, which included lidocaine 5% patches. It drew from the same trials discussed previously [Galer 1999[11], Baron 2009[9], Binder 2009[13], Rehm 2010[10] Galer 2002[14]]. The review concluded that Lidocaine 5% transdermal patch is an option when local, topical therapy is preferred.

A systematic review and network meta-analysis published in 2011 **[Wolff][19]** assessed the efficacy of lidocaine plasters in PHN compared to active comparators and placebo. The paper concluded that lidocaine plasters were associated with similar or greater effects on pain compared to other relevant comparators. However, the paper also noted that small numbers and limited size in addition to quality of included studies should be taken into account. It recommended further research was required due to the lack of direct comparison with other PHN treatments. A limited network meta-analyses was conducted, which included the following trials for lidocaine patches; Baron 2009, Rowbotham 1996, Galer 2002, Rehm 2010, in addition to other papers for capsaicin,

gabapentin and pregabalin, with the aim to assess their effect on pain intensity and pain relief. It was found for the change in pain from baseline that only lidocaine and gabapentin were effective in comparison to placebo. Lidocaine vs. placebo change in mean pain from baseline was -15.50 (95% CI -18.85 to -12.16 (p<0.001). Lidocaine was also more effective than capsaicin -16.45 (-95% CI [20.04 to -12.86] (p<0.001)), gabapentin -7.95 (95% CI [-13.29 to -2.61] (p=0.004)) and pregabalin -13.45 (95% CI [-19.19 to -7.71] (p<0.001)). The analysis also found that gabapentin and lidocaine 5% plasters were more effective than placebo for mean pain relief. Lidocaine vs. placebo was 26.77 (95% CI [9.11 to 44.43] (p=0.003)), vs. gabapentin -6.00 (95% CI [-25.32 to 13.32] (p=0.542). This systematic review and meta-analysis specifically excluded two reviews that were included in both Cochrane and SMC [Galer 1999[11] and Rowbotham 1996,[12]] because no results after the first phase of the cross-over were reported.

The following trials are referred to in the 2015 review **[Navez]** [20] which assesses the safety and tolerability of lidocaine plasters in PHN and is referred to in the safety section of this review.

Hans 2009[21] a phase III, open-label study included 247 (FAS) (Safety set =249) adults with PHN. Patients were either newly recruited (n=97) or recruited from a previous study (n=152) (where they had previously used lidocaine patches). Details of inclusion and exclusion criteria are available in table 1. Patients applied up to three 5% lidocaine medicated plasters to the painful area up to 12 hours a day with a plaster-free interval of at least 12 hours per day. Reported outcome measures included the change in pain intensity (using 11-pt NRS) and pain relief (using 6-pt VRS) from baseline to week 12 and week 52 (recalled from the week prior to visit). In newly recruited patients the pain intensity had reduced from a baseline of 5.9 ± 1.4 to 3.9 ± 2.3 at 52 weeks (3.9 ±1.9 at baseline to 3.4 ± 2.0 at final visit for pre-treated patients). Mean average recalled pain relief score for pre-treated patients was 4.3 ± 0.9, for the newly recruited a score of 3.4 ± 1.1 was achieved after 1 week of treatment and a level corresponding to “moderate” pain relief (4.0 ± 1.0) by 12 weeks. See Table 1 for further information.

Sabatowski 2012[22] is an extension of Hans 2009. It was a prospective evaluation of the long-term efficacy and safety of lidocaine 5% medicated plaster use. 143 patients completed the first 12 months of treatment as covered in the previous study and 102 continued for longer than a year and were included in this study. 76 of these discontinued treatment prior to study termination, many patients participated only until lidocaine plasters became commercially available in their countries. There were no primary endpoints planned for this study. The pain relief obtained in the previous study was maintained in the extension period, although represented graphically it is estimated to be 4.4 (± 2.2) at final visit. Clinicians’ global impression of change was reported as “good” or “very good” in 88% of patients. The patients global impression of change was reported as “very much” or “much” improved ranged from 71% (46/69) to 93% (40/43) at 24 months and 36 months. However, only those who are gaining benefit will have continued treatment. Further details can be found in table 1.

Summary of safety data:

Overall the safety data provided in trials seems favourable for lidocaine 5% plasters. Cochrane stated that although in the small studies there was no difference between lidocaine and placebo for the incidence of adverse events (AEs) and withdrawals, the studies were underpowered to show such an effect.

In the two enriched studies, participants who could not tolerate lidocaine plasters were not included in the randomised phase. In the Baron 2009 active comparator trial[9] lidocaine plasters were better tolerated than the pregabalin; with 48 AEs in 29 (18.7%) lidocaine treated patients compared with 194 AEs in 71 (46.4%) pregabalin treated patients (statistical significance not stated). In terms of drug related adverse events (DRAEs) there were 16 reported in 9 lidocaine treated patients (5.8%: 9 mild, 6 moderate, 1 severe) and 161 in 63 pregabalin treated patients (41.2%: 60 mild, 73 moderate, 28 severe). The most common DRAEs in lidocaine treated patients were application-site irritation and headaches; both reported by two patients. The lidocaine serious DRAE was a mental disorder due to a general medical condition. 9 of 155 (5.8%) of lidocaine treated patients experienced an AE leading to study discontinuation, compared to 39 of 153 (25.5%) pregabalin treated patients. Of these, 4 (2.6%) lidocaine patients and 36 (23.5%) pregabalin patients discontinued due to DRAEs.[9]

The Binder 2009 study reported DRAEs related to lidocaine plasters which occurred in 13.6% patients; of these, 4.5% (12 patients) had DRAEs that led to discontinuation from the study, the majority (10 of 12) being skin reactions.[13]. Hans 2009 found that over its 12 month duration, 118 of 249 (47.4%) patients experienced 323 AEs; 31 of 249 (12.4%) patients experienced 48 DRAEs, the study stated that these DRAEs were mainly administration site disorders, including pruritus, skin reaction or irritation, erythema and dermatitis. The majority of AEs reported were of mild to moderate severity, with no serious AEs reported to be related to study medication during the first 12 months of the extension phase.[21]

Some of the systematic reviews discuss the incidence of AEs. A 2015 review [**Navez** [20]] assessing the clinical safety and tolerability of lidocaine plasters in treating PHN, concluded that 5% lidocaine plasters demonstrated good short and long term tolerability with minimal risk of systemic ADRs. It found that lidocaine plasters are better tolerated than pregabalin in one trial. The paper found that the most frequent ADRs are application site reactions. The review, made reference to the trials discussed above [Galer 1999[11], Rowbotham 1996[12,] Binder 2009[13], Baron 2009[9], Rehm 2010[10], Katz 2002[23], Hans 2009[21] and its extension Sabatowski 2012[22]]. The paper noted that of 394 patients included in the analysis, 78 (19.8%) experienced 131 ADRs, none of which were considered in the paper to be serious. In 65 of 78 (83%) of patients, the ADRs were related to the skin, with application site erythema and application site pruritus the most frequently reported. Wolff 2011,[19] reported the equal numbers of DRAEs for placebo and lidocaine plaster treated groups. It also found the number of discontinuations due to DRAEs was equal for both treatment groups.[19]

Strengths and limitations of the evidence:

Strengths:

- The population groups covered by some of the trials were appropriate, adult patients, having suffered with PHN for a minimum timescale of 3 months and with a significant level of pain.
- There are double-blind, randomised placebo controlled studies available, providing information on the efficacy of the lidocaine plasters.
- There is an active comparator study, so that lidocaine plasters could be assessed against other recognised PHN treatments.

Weaknesses:

- Some of the studies used an enriched enrolment, i.e. only those patients who had responded to therapy were included in the study and analysis; however useful information could be gathered from the run-in phase.
- The active comparator non-inferiority study was open-label and not blinded.
- Many of the individual studies were only of relatively short duration.
- The quality of the studies varied, and generally was not high.
- Because of the wide differences between the studies and their outcome measures, systematic reviews could not generally provide reliable meta-analyses of the data.
- The Wolff 2011 review conducted a network meta-analysis; however these are more prone to error than a standard meta-analysis.
- For those included in Cochrane[8] [Binder 2009[13], Galer 1999[11] & 2002[14], Rowbotham 1996[12]], all were at high risk of bias due to their size, and at unclear risk of bias for allocation concealment. Three studies [Galer 1999[11] & 2002[14], Rowbotham 1996[12]] were at unclear risk of bias for random sequence generation, with Galer 2002[14] also being at unclear risk of bias for both blinding of participants and personnel and blinding of outcome assessment.

Summary of evidence on cost effectiveness:

A 2010 cost effectiveness study comparing lidocaine 5% plaster with pregabalin for PHN, concluded that 'the analysis showed that the lidocaine 5% medicated plaster is a cost-effective method for obtaining sustained relief of localized neuropathic pain associated with PHN compared with pregabalin in a UK setting, in terms of both the cost per QALY gained and the cost per additional month without symptoms, when used for patients who do not experience sufficient pain relief from standard analgesics.'[24] The Wolff 2011[19] review indicated that gabapentin and lidocaine are both similarly effective in comparison to placebo; it gave some information on how much both treatments and others available cost. However, the figures given are not the same as given by Mims, probably due to the review dating back to 2011.

Prescribing and risk management issues:

The painful area should be covered with the plaster once daily for up to 12 hours within a 24 hours period. Only the number of plasters that are needed for an effective treatment should be used. When needed, the plasters may be cut into smaller sizes with scissors prior to removal of

Produced October 2015

the release liner. In total, not more than three plasters should be used at the same time. Each plaster must be worn no longer than 12 hours. The subsequent plaster-free interval must be at least 12 hours.[1]

The plaster must not be applied to inflamed or injured skin, such as active herpes zoster lesions, atopic dermatitis or wounds. The plaster should not be applied to mucous membranes. Eye contact with the plaster should be avoided. The plaster contains propylene glycol which may cause skin irritation. It also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).[1]

The plaster must be applied to the skin immediately after removal from the sachet and following removal of the release liner from the gel surface. Hairs in the affected area must be cut off with a pair of scissors (not shaved).[1]

Treatment outcome should be re-evaluated after 2-4 weeks. If there has been no response to the lidocaine plaster after this period (during the wearing time and/or during the plaster-free interval), treatment must be discontinued as potential risks may outweigh benefits in this context. Treatment should be reassessed at regular intervals to decide whether the amount of plasters needed to cover the painful area can be reduced, or if the plaster-free period can be extended.[1]

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Lidocaine 5% Medicated plasters	**1 - 3 plasters per day**	**30 = £72.40**	**£881 - £2643**
Pregabalin	300-600 mg daily in divided doses	150 mg & 300 mg caps are both 56=£64.40	£840 *BD dosing*
Gabapentin	300 mg tds (up to max 3.6 g daily in divided doses)	300 mg cap, 100 = £4.36. 600 mg tab 100 = £11.56	£48 - £253
Amitriptyline (unlicensed indication)	10 mg at night (increased up to 75 mg daily, higher doses under specialist supervision)	10 mg, 28 = 96p. 25 mg, 28 = 99p. 50 mg, 28 = £1.16	£13 to £28
Costs based on MIMS list prices September 2015.[3] This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

No available discounts known.

Produced October 2015

Productivity, service delivery, implementation:

It is unclear what impact the use of this medication would have on service delivery. It is already being used in some areas, and would not be used first line but only after standard neuropathic agents initiated in primary care have either failed or led to intolerable side effects; in this case it may reduce pressure on services by allowing prescribing to be continued in primary care rather than continued by secondary care. Alternatively, in areas where it is not currently in use, due to the requirement that it be initiated in secondary care, it could have the opposite effect and actually increase pressure. Because of this, the effort and resource required to implement is also unclear. It is worth noting that the request stated that on average patients only receive 3 months follow up, therefore there could be an impact due to the recommended 2-4 week follow up.

Anticipated patient numbers and net budget impact:

In UK primary care, the incidence of post-herpetic neuralgia is estimated to be 28 per 100,000 person-years.[5] With a Lancashire population of 1.5 million, this equates to potentially 420 patients annually. The request is only for use after standard neuropathic agents have either failed or led to intolerable side effects, therefore it is unclear how many of these patients would fail on standard therapy and be initiated on lidocaine patches. The NICE Clinical Knowledge Summary (CKS) around neuropathic pain states that 'response to drug treatment is often inadequate, with no more than 40–60% of people obtaining partial pain relief'.[25] Although not specifically for PHN, if used as a guide then 40-60% people could require second line treatment with the lidocaine 5% plasters. Of 420 patients, this would mean 168-252 potential patients at an annual cost of £147,986 to £665,935. The request stated that the average duration of treatment for a patient using lidocaine 5% patches is 3 months; therefore using these figures a three month treatment would cost £36,996 to £166,484.
Currently in some areas across Lancashire, lidocaine plasters for PHN are already in use. Prescribing information for the whole of Lancashire indicates that in the 12 months August 2014 to July 2015, 11,410 prescriptions for lidocaine plasters were dispensed in primary care, with a quantity x items of 330,045 and a total cost of £743,529. It is interesting that this figure is higher than the estimated maximum potential usage; however some of these prescriptions will be for unlicensed indications.

Innovation, need, equity:

There are limited topical agents available and licensed for the symptomatic relief of PHN; as such the lidocaine 5% medicated plaster could be an option for those that cannot make use of the oral treatment options. However, NICE does recommend considering capsaicin cream for those with localised neuropathic pain who cannot tolerate or wish to avoid oral treatments.

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Table 1: Summary of key Lidocaine 5% medicated plasters RCTs relevant to use in Post-Herpetic Neuralgia

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
Baron 2009[9]	Two-stage adaptive (including one planned interim analysis) randomised, open-label, multi-centre, non-inferiority trial. Study duration; drug washout phase; 2 weeks, randomised 1:1 to 5% lidocaine plaster or pregabalin treatment ; 4 weeks, then combination phase; 8 weeks (discussed in another paper), then 4 week sub-study where pregabalin tapered down (discussed in another paper). Number of patients required was calculated as 300 for FAS (Full assessment set; all randomised patients who received at least one dose of the	• n=311 randomised. (3 not treated so safety population =308). No post-baseline assessment in 8 patients so excluded from FAS FAS=300 patients. 19 patients excluded due to violations of study protocol so PPS = 281 patients • 18 years or older with PHN (pre-defined range - 30-40%) or painful DPN (pre-defined range 60-70%). • Experiencing average pain intensity of >4 on NRS-3 • Most painful area can be covered by up to 3 plasters if PHN. • Creatinine clearance above 60 mL/min • PHN pain present for ≥3 months after healing of herpes zoster skin rash	281 patients in PPS; 144 administered 5% lidocaine plaster monotherapy (45 with PHN, 99 with DPN) (maximum of 12 hours per 24 hour period) Applied average 2.47 plasters to cover painful area (PHN: 1.71, DPN: 2.83, Safety set) 137 received pregabalin monotherapy (43 with PHN, 94 with DPN) titrated to effect according to pregabalin SPC. (All receiving 150 mg/day in week 1 & 300 mg/day in week 2). Those with insufficient analgesic efficacy at end week 2 (NRS-3 ≥4) increased stepwise to 600 mg/day – 86 patients required this higher dose.	Response rate; defined as a reduction ≥2 points or absolute value ≤4 on the NRS-3 scale after 4 weeks of treatment in the PPS. Withdrawals rated as non-responders In PPS 94/144 lidocaine (65.3%) and 85/137 (62.0%) pregabalin responders at week 4. Non-inferiority p = 0.00656 with CI lower limit of -9.15 (below the predefined margin of -8 percentage points) In the FAS 101/152 (66.4%) lidocaine 5% plaster and 91/148 (61.5%) pregabalin met the pre-defined responder criteria at week 4. Non-inferiority p=0.00229, lower limit of CI = -7.03	NRS-3 pain intensity score and changes from baseline. Mean change in PPS in; all patients lidocaine=-2.5 (SD 2.01) pregabalin =-2.3 (SD1.95) & in PHN patients lidocaine=-2.4 (SD 2.07), pregabalin=-2.0 (SD 2.24) Proportion of patients with 30% and 50% reductions from baseline in NRS-3 pain intensity score. ≥30% reduction: PPS; all patients: lidocaine=85 (59%) pregabalin =74 (54%). PHN patients: lidocaine = 26 (57.8%) pregabalin = 21 (48.8%) ≥50% reduction PPS: all patients: lidocaine=56 (38.9%) pregabalin= 44 (32.1%). PHN patients: lidocaine = 16 (35.6%) pregabalin = 9 (20.9%) Changes in allodynia severity rating from baseline in painful and extremely painful on allodynia severity rating scale, PPS: all patients: lidocaine 38.9 to 12.9%, pregabalin 36.5 to 17%. PHN only patients: lidocaine 57.8	Patient-oriented outcome measure?: Yes Allocation concealment?: yes Blinded if possible?: No Intention to treat analysis?: No Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes Level 2 evidence based on patient orientated outcomes without blinding. Risk of bias: High based on lack of blinding

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	investigational medicinal products and for whom at least on post-baseline NRS-3 was available) and 240 for PPS (Per protocol set; all randomised patients who adhered to the study protocol). Based on a non-inferiority margin of 8%, a one-sided significance level for the primary endpoint of 2.5% and a power of 80%. Null hypotheses rejected if combined p-value less than 0.0038	• Inclusion criteria for the pick-up arm were a CrCl of ≥30 mL/min and ≤60 mL/min at enrolment or occurrence of intolerable adverse events during pregabalin treatment in the comparative phase. Exclusion criteria • Active herpes zoster lesions • Dermatitis at affected site • Neurological block or neurosurgical intervention for pain control • Severe renal impairment (CrCl < 30 mL/min) • Evidence of another cause for pain potentially confounding trial results • Any former treatment with topical lidocaine for neuropathic pain, pregabalin or gabapentin within last 6 months • Concomitant use of adjuvant drugs for neuropathic pain or local anaesthetics, use of capsaicin			to 25%, pregabalin 62.8 to 41.1% EroQol-5 dimension quality of life index (EQ-5D). Mean change from baseline (PPS): all patients: lidocaine 0.12 (SD 0.240) pregabalin 0.04 (SD 0.235), PHN patients: lidocaine 0.12 (SD 0.231) pregabalin 0.00 (SD 0.276) Patients Global impression of change (PGIC) and Clinical Global Impression of Change (CGIC). PGIC “very much or much improved” in PHN patients, lidocaine = 51.2%, pregabalin 41.9%. CGIC “very much or much improved” in PHN patients, lidocaine=53.3% pregabalin=32.6% Patient satisfaction with treatment measured on a 5 point rating scale (0=poor to 4=excellent in response to ‘how would you rate the trial medication you received for your pain?’) PHN patients rating very good or excellent: lidocaine 44.5%, pregabalin 23.3% Safety evaluations: 48 AE in 29 (18.7%) lidocaine patients vs. 194 AE in 71 (46.4%) pregabalin patients. 16 DRAEs in 9 (5.8%) lidocaine patients (9 mild, 6 moderate, 1 severe) compared with 161	

		within the month prior to enrolment , concomitant use of TENS, • Contraindications to any of the study drugs • Co-existing condition or illness that could preclude participation in study or interfere with study results. Baseline characteristics overall were well balanced, however when broken down to condition, PHN patients showed a large variation in mean duration of pain between the lidocaine (29.3 ± 36.0 months) and pregabalin (43.9 ± 73.5 months) groups			DRAEs in 63 (41.2%) pregabalin patients. (60 mild, 73 moderate, 28 severe)_	
Rehm 2010[10]	Extension study of the Baron 2009 paper discussed above[9] Phase III open-label, randomised study. This extension study includes only the study population with the indication PHN.	• 148 PHN Caucasian patients screened. 98 randomised. n=50 lidocaine, n=48 pregabalin. • Patients with PHN present for ≥3 months after healing of herpes zoster skin rash. • NRS-3 score ≥4 • After the 4 week comparator,	Following the 4 week comparator phase discussed in reference [9], patients sufficiently treated at week 4 (NRS-3 ≤4) continued monotherapy for the duration of the 8-week combination phase (n=14 pregabalin, n=25 lidocaine). Those insufficiently treated (NRS-3 ≥4) received combination of both drugs (n=18 pregabalin added to lidocaine, n=17 lidocaine added to pregabalin)	Response rate in PPS ≥2 point reduction from baseline in NRS-3 or overall score of ≤4 after 4 weeks of treatment. Results not included in this paper, covered in Baron 2009	Of those responding at week 4; 82.1% lidocaine patients (23/28) were already responders at week 2 vs 65.0% pregabalin patients (13/20) Mean daily number of paracetamol tablets taken during the last 3 days prior to each visit. Lidocaine; 2.02 ± 1.52 at baseline to 0.93 ± 1.26 at week 4. Pregabalin; 1.70±1.60 at baseline to	Patient-oriented outcome measure?: Yes Allocation concealment?: No Blinded if possible?: No Intention to treat analysis?: Yes Adequate power/size?: No – not for the subgroup

		responders continue into an extension of monotherapy and those who haven't responded are able to enter a combination phase. Exclusion criteria as under reference [9]	During the pregabalin down-titration subtrial, pregabalin down-titrated in steps of 150 mg per week over 4 weeks, not discussed in this paper Paracetamol (up to 2 g per day) allowed as rescue medication during entire trial.		1.79±1.56 at week 4. Median time to onset of response; Lidocaine = 2 days (interquartile range 1, 11). For Pregabalin = 16 days (1,28) Pain intensity on SF-MPQ on VAS improved by -25.9 ± 23.14 with lidocaine plaster and by -17.2 ± 25.57 with pregabalin. Mean change in total SF-MPQ score -7.6 ± 6.66 with lidocaine vs -5.3 ± 7.93 for pregabalin. NPSI total score reduction from baseline -1.6 ± 1.73 for lidocaine vs -1.4 ± 1.87 for pregabalin	Adequate follow-up (>80%)?: Yes Level 2 evidence based on patient orientated outcome but not blinded Risk of bias: High based on lack of blinding
Binder 2009[13]	Multicentre, enriched enrolment, randomised withdrawal study. 8 week open-label phase followed by randomisation of responders to 2-week, double-blinded, placebo plaster controlled phase Planned sample size of study was 70 responders in randomised phase (35 per treatment group) for an α=5%	• n=265 enrolled patients. Open label FAS=263 patients who entered the run-in phase and received study medication. N=71 went on to double-blind phase. • Aged ≥ 50 years (mean 72.5 ± 8.5 years) • PHN ≥ 3 months after rash healing • Mean pain intensity ≥4 on 11-point NRS. • 42.6% male Exclusion criteria	8 week open-label run-in phase: up to 3 lidocaine 5% medicated plasters (to cover affected area) applied for up to 12 hours per day (minimum 12 hour plaster free period). At end of 8-week run in phase; 137 (51.7%) enrolled patients were classified as treatment responders in week prior to randomisation. Double-blind phase: either, lidocaine 5% medicated plaster (n=36) or placebo plaster (n=35) up to 3 plasters applied for up to 12 hours per day (minimum 12 hour plaster free period). Patients were asked to apply plasters after their pain had returned or increased.	Time to exit from double-blind phase due to lack of efficacy in ITT group, (time to exit defined as number of days after randomisation where there was ≥ 2 point decrease in pain relief on VRS on 2 consecutive days of plaster application compared with mean in last week of open-label treatment, before randomisation). Median times-to-exit were 13.5 days (range 2-14 days) for the lidocaine group, vs 9.0	Significant worsening in these secondary endpoints when patients switched from lidocaine to placebo in the double blind phase: • daily pain intensity prior to plaster removal (p=0.0289) • Daily pain relief (p=0.0040) • Daily pain reduction (p=0.0007) • Mean pain relief in last week (p=0.0012) • SF-MPQ total score (p=0.0254) • SF-MPQ sensory sub-score (p=0.0180) Open label phase 39.5% FAS	Patient-oriented outcome measure?: Yes Allocation concealment?: No Blinded if possible?: Yes Intention to treat analysis?:Yes Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes Level 2 evidence based on patient orientated but short duration.

Produced October 2015
Midlands and Lancashire CSU, 2015

	(two-sided) and 90% power (β=0.1) to detect a difference between the lidocaine and placebo plasters in primary efficacy endpoint.	• Hypersensitivity to lidocaine or amide local anaesthetics • Active herpes zoster lesion or dermatitis at site of PHN • History neurological ablation by nerve block or surgical intervention to control post-zoster pain • Use of topical analgesics to PHN area • Other severe pain conditions and/or hepatic or renal disorders • Use of immunosuppressant or treatments for HIV or Cancer. Randomisation criteria for double-blind phase: • Responders (mean pain relief of "moderate" or more measured at the randomization visit on the 6-pt VRS, recalled for the previous week. • Regular plaster use during 4 weeks prior to randomisation (≥ every second day)	Concomitant stable analgesic therapy allowed, except topical analgesics or additional lidocaine therapy for PHN or other pain conditions.	days (range 1-14 days) for the placebo group. (p=0.1510) in ITT (FAS) population. In PPS 14.0 days (range 3-14 days) and 6.0 days (range 1-14 days) for active and placebo treated patients respectively (p=0.0398) 25/36 (69.4%) in lidocaine group and 14/35 (40.0%) in placebo group completed double-blind phase. Lidocaine group: patients withdrew because of at least one of; lack of efficacy (9/36 – 25%), protocol violation (3/36 – 8.3%) or no information (1/36 – 2.8%) From the placebo group these figures were; lack of efficacy (16/35 – 45.7%) protocol violation (1/35 – 2.9%) withdrawal of informed consent (1/35 – 2.9%) AE – elevation in liver enzymes (1/35 – 2.9%) other (3/35 – 8.6%) no information 1/35 (2.9%)	reported ≥30% and 25.9% FAS reported ≥50% reduction in mean pain intensity. In the double blind phase, in the per protocol population, there was significant worsening in: daily pain intensity before plaster removal (p=0.0186), daily pain relief (p=0.0050), daily pain reduction (p=0.0018) mean pain intensity in the last week (p=0.0275), least pain intensity in the last week (p=0.0457) and mean pain relief in the last week (p=0.0043) AEs: In the 8-week run in phase, at least 1 AE was experienced by 30.6% (81/265) patients. Of these 12.8% (34/265) were DRAE, with the majority (6.5%, 17/265 patients) having skin and subcutaneous tissue reactions; mostly of mild or moderate intensity and resolved upon removal of the plaster. During the double-blind phase, 4.2% (3/71 patients) experienced at least 1 AE. Of these, 2.8% (2/71 patients) were considered DRAE, one patient in each treatment group. The placebo patient reported three DRAE which were elevations in liver enzymes. The lidocaine	Risk of bias: low / based on blinded of adequate size and follow-up

		• Mean daily pain intensity ≤7 on 11-point NRS when using plaster, with increase in pain when plaster not worn.			patient experienced two DRAEs, erythema and pruritus. Overall DRAE related to lidocaine plaster occurred in 13.6% of patients. In 12 patients (4.5%) AE related to lidocaine plaster warranted premature discontinuation of their participation in the study. In 10 patients (3.8%) these events were skin reactions. One patient from the double-blind phase withdrew because of DRAEs; they were in the placebo group. No reported effects of 5% lidocaine medicated plaster on laboratory parameters or vital signs in the study population.	
Galer 1999[11]	Double-blind, balanced-random assignment, placebo-controlled, two period cross-over trial of 28 days maximum duration.	• PHN patients either participants in previous lidocaine trials who had requested open-label use or refractory patients with approved compassionate use, who had been using lidocaine patches for ≥ 1 month. • Current pain relief from plasters rated as ≥ moderate on 6 point VRS • Experienced PHN pain prior to	Phase A: Lidocaine 5% medicated plaster, up to 3 plasters applied onto painful area. Or placebo plaster, up to 3 plasters applied onto painful area. Phase B: Reverse of above. Concomitant analgesic medication was allowed. Patients received a daily telephone call to obtain: time of patch application and removal, verbal pain relief scale, analgesic medication use and description of any AEs.	Time-to-exit from double-blind treatment phase due to lack of efficacy (≥ 2-point decrease in verbal pain relief on the 6 point VRS on 2 consecutive days of plaster application compared with pre-study open-label treatment. Median time to exit for lidocaine patch treatment period was >14 days vs 3.8 days for the vehicle patch (p<0.001)	Subjects assessment of treatment phase that provided best pain relief (A vs.B): 25/32 (78.1%) preferred lidocaine treatment phase, 3/32 (9.4%) preferred placebo treatment phase (p<0.001). 4/32 (12.5%) had no preference. Daily reports of pain relief: 29/32 reported “moderate” or greater pain relief for at least 5 out of 14 days treatment with lidocaine patches. 7 patients used concomitant rescue medication during	Patient-oriented outcome measure?: yes Allocation concealment?: unclear Blinded if possible?: yes Intention to treat analysis?: yes Adequate power/size?: no Adequate follow-up (>80%)?: yes Level 2 evidence based on patient orientated

Produced October 2015

		applying new patch • Increase in pain during plaster-free periods. • n=32, • Male=14, female=18. Mean age 77.4 years. Duration of pain > 8 months. • Mean duration of lidocaine patch use 3.3 years			treatment; 3 during lidocaine use, 4 during placebo use. AEs: No serious adverse events were reported that were deemed possible or probably related to the study medication. All reported adverse events were deemed mild or moderate in severity. No significant difference was observed between the lidocaine and placebo patches for adverse events that were reported by at least 5% of subjects in either treatment group (p≥0.492) Application site reaction reported by 9 (28%) in lidocaine phase and 11 (34%) in placebo phase.	outcome, randomised, blinded but small sample size. Risk of bias: unclear based on unclear allocation concealment
Rowbotham 1996[12]	Four session, random order, double-blind, vehicle-controlled study.	• PHN present >1 months after healing of skin rash. • Well defined area of painfully sensitive (allodynic) skin on torso or limbs. • Stable health, without contraindications to topical local anaesthetic application • Without neurolytic or neurosurgical therapy for PHN.	Randomised to session order, stratified by gender. 4 sessions, up to 3 plasters applied to painful area for 12 hours. 2 x sessions with lidocaine 5% plaster, 1 x placebo plaster, 1 x session with observation only. Minimum 72 hours between applications Sessions were at least 72 hours apart and typically 1 week apart. If subjects experienced prolonged pain relief from one session the next session was delayed until pain returned to at	Pain intensity on a 100 mm VAS prior to application (2 to 3 times over 45 minutes) and at 0.5, 1,2,4,9 and 12 hours after application. Mean pre-application VAS; lidocaine session 49.3 mm, vehicle patch session 48.4 mm & observation session 47.2 mm. Lidocaine session treatment greatest reduction in VAS 12.3 mm at 4 hour time point, average reduction across all time points 10.3 mm.		Patient-oriented outcome measure?: Yes Allocation concealment?: Unclear Blinded if possible?: Yes Intention to treat analysis?: Yes Adequate power/size?: No Adequate follow-up (>80%)?: Yes Level 2 evidence based

Produced October 2015

		• n=40 recruited n=35 completed • Men = 20 women = 15 • Age range 50-90, mean 75 years. • Mean duration of PHN 48 months • Any topical pain treatment stopped ≥2 weeks before study. Established oral medications continued unchanged. • Subjects kept daily pain diary throughout study which recorded medications taken and overall pain level that day	least 75% of average pain level prior to entering study. If skin irritation noted further test sessions were delayed until resolved.	Lidocaine superior to observation only at all time points (individual time points p=0.0001 to p=0.021). Compared to vehicle patch superior at 4,6,9 and 12 hours (individual time points p<0.001 top=0.038) Pain relief on 6 point VRS at same time points as for pain intensity. Pre-application the rating was assumed to be 1 (no relief of pain). For observation session the scale was modified to indicate worsening or improvement relative to beginning of observation session. Highest for lidocaine patch application at all time points. Average relief fell between slight and moderate. Lidocaine superior to both observation only (p<0.001) and vehicle patch (p=0.033). vehicle also superior to observation only (p=0.001)		on patient orientated outcome, vehicle-controlled and blinded, but small sample size Risk of bias: unclear based on unclear allocation concealment and inadequate power/size.
Hans 2009[21]	Open-label, multi-centre, phase III study	• SAF n=249 • FAS=247, 143 completed treatment • 56.2% female • ≥50 years (mean age 72.4 ± 8.6	Applied up to three 5% lidocaine medicated plasters on painful area at any time of day for up to 12 hours with a plaster-free interval of at least 12 hours per day. (number of plasters dependent on painful	Pain intensity recalled during week prior to visit using 11-pt NRS. Newly recruited patients had mean of 5.9 ± 1.4 at baseline, decreased to 3.9 ± 1.6 at week 12 and	Severity of allodynia: Newly recruited patients; 6.2% of patients scored 0 (no pain or discomfort) at baseline which increased to 18.5% of patients at 12 months. Pre-treated patients; 14.8% of	Patient-oriented outcome measure?: Yes Allocation concealment?: No Blinded if possible?:No

Produced October 2015

		years) • PHN persisting ≥ 3 months after healing of herpes zoster skin rash. • Either recruited from previous study (pre-treated with lidocaine plasters) (n=152) or newly recruited (n=97) • If newly recruited baseline pain of ≥4 on NRS recalled from previous week before baseline visit. Excluded based on: • Known hypersensitivity to lidocaine or amide local anaesthetics • Active herpes zoster lesion or dermatitis at PHN pain site • Previous neurological ablation by nerve block or surgical intervention to control post-zoster pain. • Current use of topical analgesics on PHN area. • Presence of other severe pain conditions • Presence of hepatic or renal	area) Visits were at week 1, 6, 12, 18, 26, 34, 42 and 52 Other medication for PHN including analgesics, with exception of topical analgesics or additional lidocaine therapy for PHN permitted.	remained stable until final visit week 52 (3.9 ± 2.3). Pre-treated patients decreased further from baseline 3.9 ± 1.9 to final visit 3.4 ± 2.0 Pain relief recalled during week prior to visit using 6-pt VRS. Newly recruited patients; mean average pain relief score of 3.4 ± 1.1 achieved after 1 week of treatment, reaching level corresponding to moderate pain relief (4.0 ± 1.0) at 12 weeks. Recruited from previous lidocaine study: mean average recalled pain relief score of 4.3 ± 0.9 at 12 weeks. Pain relief levels were maintained throughout initial 12 month study period (exact figures not quoted)	patients reported score 0 at baseline which increased to 23.3% of patients at 12 months. Statistical significance not reported. SF-MPQ total: Newly recruited patients; 17.3 ± 8.3 at baseline to 12.6 ± 8.5 at 12 months. Pre-treated patients; 13.3 ± 7.6 baseline for pre-treated to 11.2 ± 8.6 at 12 months. CGIC: improvement rated as very much (21.1%) much (36.0%) or minimally (20.2%) compared to study entry for FAS patients after 12 months treatment. DRAE and SAE: In 12 month study period 118 of 249 patients experienced 323 AEs, 12.4% experienced 48 DRAEs (related to lidocaine plaster). DRAEs; administration site disorders, including; pruritus, skin reaction or irritation, erythema and dermatitis. 11 of 249 patients discontinued the study drug due to DRAEs. No serious AEs were reported to be related to the study medication. Most common AEs; bronchitis and nasopharyngitis.	Intention to treat analysis?: Yes Adequate power/size?: No Adequate follow-up (>80%)?: Yes Level 3 evidence based on open label Risk of bias: High based on open label design.

		disorders • Current use of immunosuppressants or treatment for HIV or Cancer.				
Sabatowski 2012[22]	Extension of Hans 2009 Open-label, multicentre phase III extension study Prospective evaluation of long-term efficacy and safety. Extension phase of 1 year study of up to 3 years.	• As above. n=143 completed first 12 months treatment of study (discussed in reference [13]). n=102 were satisfied with treatment and continued treatment for > one year were included in this extension study (up to 3 years). • n=90 qualified for inclusion into the FAS (had ≥ 1 pain relief assessment in extension period) • 76 of the 102 discontinued treatment prior to study termination. Reasons included; (n=10) lack of efficacy, (n=9) AEs, (n=27) other reasons including the lidocaine plaster becoming commercially available in their country. • 63.5% female • Mean age 71.3 ± 9.2 years	Applied up to three 5% lidocaine medicated plasters on painful area at any time of day for up to 12 hours with a plaster-free interval of at least 12 hours per day. Other medication for PHN including analgesics, with exception of topical analgesics or additional lidocaine therapy, for PHN were permitted. 6 monthly visits conducted.	No primary endpoint planned for this study.	Pain relief (6-pt VRS): mean pain relief of 4.3 (± 0.9) achieved in main period of study was maintained in extension phase – exact outcomes not reported, estimated at final visit to be 4.4 (+ 2.2). CGIC at final visit rated as "good" or "very good" in 88% (67/76) of patients. PGIC (only recorded during extension phase) those rating "very much" or "much" improved ranged from 71% (46/69) at 24 months to 93% (40/43) at 36 months. . Safety: During 5 years of treatment 79/102 patients experienced 384 AEs, most common included; back pain (n=9), hypertension (n=8), bronchitis (n=7), dizziness (n=7), headache (n=7), nasopharyngitis (n=7), UTI, application site hypersensitivity, diarrhoea, influenza like illness, MI, pneumonia, sciatica, T2DM.30 of 384 events in 19/102 patients were reported by the investigators as probably/likely (n=13) or possibly (n=17) related to the	Patient-oriented outcome measure?: No Allocation concealment?:No Blinded if possible?:No Intention to treat analysis?: Yes Adequate power/size?: no Adequate follow-up (>80%)?: Yes Level 3evidence based on no patient orientated primary outcome Risk of bias: High based on open label, inadequate size.

					use of 5% lidocaine medicated plaster. DRAEs mainly administration site reactions, including pruritus, skin reaction or irritation, erythema and dermatitis. After removal of plaster skin reactions resolved without further treatment in all patients. Dysgeusia, myalgia, decreased blood glucose, unilateral deafness, tinnitus and tachycardia reported as possibly DRAEs by investigators. 3 of 102 patients terminated study due to DRAEs all of which were application site hypersensitivities.	

Footnotes**: FAS**= full assessment set. **PPS**=per protocol set**. SAF**= Safety set PHN=Post-herpetic Neuralgia. **DPN**=Diabetic polyneuropathy. **CI**= Confidence Interval **SD**=Standard Deviation **AE** = Adverse Event **DRAE**= Drug Related Adverse Event. **SAE**= Serious Adverse Event **VAS**=Visual Analogue Scale

NRS-3= an average of the previous 3 days daily scores on the numerical rating scale of pain intensity (an 11 point scale where 0= no pain to 10=pain as bad as you can imagine).

Allodynia severity response to innocuous stimuli using a 26g von Frey hair, three stimulations applied with interval of 1 second, patient immediately asked to rate on 4-point categorical scale (where 0=no pain or discomfort to touch, 1=uncomfortable, but tolerable to touch, 2= painful, 3=extremely painful, patient cannot tolerate touching)

EQ-5D generic health-related quality of life instrument. Patients select from 3 statements (no problem, some problem, extreme problem) that best describe their health status for each of the five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). These are then expressed in a score using the values set which ranges from 1 for full health with no problem in any dimension to -0.111 for severe problems in all five dimensions. Small differences can be clinically meaningful; an increase of 0.01 compared to baseline means a 10% improvement in quality of life.[9]

PGIC and CGIC= patients global impression of change and clinical global impression of change. Both 7 point scales measuring overall impression of change 1= very much improved to 7=very much worse.

W-NRS=daily assessment in evening of worst pain experienced in the last 24 h using an 11 point scale as in NRS-3.

Time to onset of response in Rehm 2010 the time between comparative phase baseline and the first day of a 3-day period with decreased average pain intensity during the last 24 f by ≥2 points or scores ≤4 on all 3 days – time to onset for non-responders was counted as 28 days.

SF-MPQ=Short Form McGill Pain Questionnaire, measure of sensory and affective domains of pain. Rated over previous 7 days on a 4-point categorical scale of none, mild, moderate or severe. Provides a 15-item score - sensory sub-score (sum of first 11 items) and affective sub-score (sum of last 4 items). Pain intensity assessed on a continuous visual analogue scale ranging from 0=no pain to 100=worst possible pain.

NPSI=Neuropathic Pain Symptom Inventory. Combined interview and examination questionnaire with 11-point NRS scales. Total score calculated as sum of 10 single items divided by 10.

SF-36=short form-36 health survey most widely used patient-based health status survey in the world. Measures health status and outcomes from the patient's point of view. 8 items rated on a scale ranging from 0 to 100 with higher values indicating a better outcome.

Responders (as in Binder 2009[13]) A clinically relevant response to treatment defined as: a mean pain relief of 'moderate' or more measured at the randomization visit on the 6-item

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Midlands and Lancashire CSU, 2015

VRS recalled for the previous week.
VRS= verbal rating scale, 1=worse, 2=no pain relief 3=slight 4=moderate 5=a lot 6=complete pain relief

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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