New Medicine Assessment

Lidocaine (Versatis®▼)

For the treatment of localised neuropathic pain with predominance of allodynia and/or hyperalgesia and dysesthesias unresponsive to other neuropathic agents

Recommendation:

RED Specialist Medicine

Lidocaine 5% medicated plasters are recommended outside of their license of post-herpetic neuralgia (PHN) only if all of the following criteria are met;

- Patients present with localised neuropathic pain with predominance of allodynia and/or hyperalgesia and dysesthesias unresponsive to other neuropathic agents **and**
- Patients are unresponsive to or intolerant of other neuropathic pain agents recommended in NICE/LMMG guidelines **and**
- Treatment is prescribed by clinicians who specialise in the control of pain (e.g. Palliative Care consultants). The medicine should be supplied by the specialist for the duration of the treatment course. Primary care initiation or continuation of treatment is not recommended.

Patients already receiving lidocaine plasters in primary care should have the opportunity to continue with treatment until it is deemed clinically appropriate to stop.

There is limited clinical trial evidence of alleviation of non PHN neuropathic pain with a predominance of allodynia and/or hyperalgesia and dysesthesias. However, specialist clinicians have reported anecdotal evidence of efficacy in a number of patients. It is noted that clinical evidence in the group of patients in the specialist setting is difficult to obtain.

Summary of supporting evidence:

- Neuropathic pain is a debilitating condition that is notoriously difficult to treat.
- Evidence of the use of lidocaine 5% plasters outside of the licensed indication of PHN is limited, with studies often being of low quality, in small numbers of patients and/or of short duration, with a high risk of bias. For the studies included in the Cochrane review, the quality of evidence grade was reported as ‘very low’.
- Evidence assessing the effectiveness of lidocaine 5% medicated plasters in relieving the symptoms of allodynia, hyperalgesia and dysesthesias in localised neuropathic pain conditions is very limited.
- A randomised active comparator open label trial, with a cohort of patients with diabetic polyneuropathy (DPN) found that 65.3% of lidocaine plaster treated patients and 62.0% of pregabalin treated patients were classed as “responders” at week 4 (non-inferiority p=0.00656 with CI lower limit of -9.15, below the pre-defined margin of -8 percentage points). A secondary outcome measure of allodynia saw patients who rated their allodynia as “painful” or “extremely painful” decrease from 30.3% to 7.6% in the lidocaine treated patients, and from 24.4% to 6.4% in the pregabalin treated patients.

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- Although a reduction in pain or pain intensity was achieved, two of the three placebo controlled RCTs (Hashmi 2012, Cheville 2009) showed no significant difference between the lidocaine & placebo patches; this suggests that the patch itself may induce a potent placebo effect in a large number of patients. There was no outcome looking directly at improvement in allodynia or hyperalgesia in these studies; however, several self-assessment forms including the NPS, short-form MPQ, and subjects global impression of change that were collected, may give some indication, but are not specific to the neuropathic features required.
- The third placebo controlled RCT (Meier 2003) indicated ongoing pain intensity decreased significantly compared to pre-treatment levels in both lidocaine ($p<0.001$) & placebo ($p<0.05$) groups and that there were significant differences between the two groups at some, but not all, time points.
- Two open-label studies demonstrated improvements in pain measures for lidocaine plasters. Galer 2004, including patients with non-radicular lower-back pain and NPS ≥4/10 in 6/10 individual NPS descriptors, indicated that lidocaine 5% plasters significantly improved all 4 NPS composite measures at both weeks 2 and 6 compared to baseline ($p<0.001$) and similarly, results from Argoff 2004 for patients with painful diabetic neuropathy (PDN), found all four composite NPS scores significantly improved from baseline to end of week 2 ($p<0.001$).
- Three studies looking only at PHN patients reported on allodynia as a secondary outcome measure, all showed a reduction whilst using lidocaine plasters, although one study only reported in the phase when lidocaine plasters were used in conjunction with pregabalin and therefore it is unclear which medication is responsible for the reduction in that instance.
- Safety data is favourable for lidocaine medicated plasters; the active comparator trial (Baron 2009) had far fewer adverse events (AEs) for lidocaine patients compared to pregabalin, (48 in 29 patients 18.7% for lidocaine compared to 194 in 71 patients 46.4% for pregabalin) the majority of which were skin reactions. In total, 4 (2.6%) of lidocaine patients discontinued the study due to a drug related adverse event (DRAE) compared to 36 (23.5%) pregabalin patients. Cochrane reported that AEs were mostly local skin reactions that were of mild or moderate intensity, transitory and did not differ between placebo and lidocaine groups.
- For patients unwilling or unable to use systemic treatments, NICE has recommended the topical treatment of capsaicin cream be considered. Capsaicin cream is licensed for use in PHN and in painful diabetic neuropathy, the patch formulation is not recommended for initiation in non-specialist settings except on the advice of a specialist.
- A full year's therapy with lidocaine 5% medicated plasters is likely to cost in the range of £881-2,643 per patient. This compares to other NICE recommended options that are substantially less, with pregabalin costing £840 per person per year and all others averaging at £500 per person per year or less.

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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, non-hairy (remove hair with a pair of scissors, not shaved), dry, non-irritated skin[2] to cover painful area; plasters may be cut into smaller sizes.
BNF therapeutic class / mode of action Local anaesthesia (chapter 15.2) > lidocaine for surface analgesia[2]
Licensed indication(s): Lidocaine 5% plasters are 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 (Amber) for the treatment of localised neuropathic pain with predominance of allodynia and/or hyperalgesia and dysesthesias that is unresponsive to other neuropathic pain agents (NICE guidelines) or in people who are intolerant of/or cannot take oral neuropathic agents because of medical conditions and/or disability. Treatment will be reviewed in the secondary care setting to confirm effectiveness.
Course and cost: Lidocaine 5% medicated plasters; 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 with continued use).
Current standard of care/comparator therapies: Capsaicin cream. amitriptyline, gabapentin, duloxetine and pregabalin.[4]
Relevant NICE guidance: NICE CG173 Neuropathic pain - pharmacological management: The pharmacological management of neuropathic pain in adults in non-specialist settings.[4]

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Background and context

Neuropathic pain is thought to come about due to a lesion or disease affecting the somatosensory system.[5] Central neuropathic pain is defined as 'pain caused by a lesion or disease of the central somatosensory nervous system', and peripheral neuropathic pain is defined as 'pain caused by a lesion or disease of the peripheral somatosensory nervous system'. [5] It can have a huge impact on a patient's quality of life and can be extremely challenging to treat.

Neuropathic pain can be constant or intermittent, spontaneous or provoked[4] and can include a wide variety of symptoms and sensations. Patients may experience allodynia (pain caused by something that wouldn't normally elicit a painful response – e.g. a light touch, heat, cold, wind etc.) or hyperalgesia (severe pain from a normally mildly painful/not painful stimulus). Patients may also experience dysesthesias; an unpleasant abnormal sense of touch. It is estimated that neuropathic pain affects up-to 7-8% of the general population within Europe.[5] Neuropathic pain is associated with a number of conditions, 6-26% of patients with diabetes suffer from painful diabetic neuropathy, 8% of herpes zoster patients will experience PHN at 3 months post rash appearance and anywhere from 10-50% of patients will experience chronic pain following surgery.[6]

Neuropathic pain is often measured using the Neuropathic Pain Scale (NPS); this consists of 10 descriptors of which patients can rate from 0-10. The descriptors include asking the patient to rate how intense, sharp, hot, dull, cold, sensitive, itchy, and unpleasant their pain is; in addition they are asked to rate the intensity of their deep and surface pain as well as choosing statements that most closely reflect the time quality of their pain.[7]

Common conditions that show symptoms of peripheral neuropathic pain include; post-herpetic neuralgia (PHN), painful diabetic neuropathy (PDN), trigeminal neuralgia, post-surgical and chemotherapy induced neuropathy.[4] Management of chronic neuropathic pain can be difficult due to the wide variety of symptoms and underlying mechanisms, and the uncertainty often found around the exact location of a lesion or associated health condition.[4] Response to drug treatment is often inadequate, and it is estimated that no more than 40–60% of people obtain partial pain relief.[6]

Current NICE guidance for neuropathic pain recommends offering a choice of amitriptyline, duloxetine, pregabalin or gabapentin as initial treatment for neuropathic pain (except trigeminal neuralgia)[4] it goes on to suggest switching between these if they are found to be ineffective or are not tolerated. Tramadol is recommended as a consideration only if acute therapy is required. Capsaicin cream is recommended as an option for localised neuropathic pain if a patient wishes to avoid or cannot tolerate an oral medication.[4] Lidocaine 5% plasters, the subject of this review, are not mentioned as an option; but neither are they listed amongst the treatments that should not be used. Lidocaine 5% medicated plasters have a license and indication for use in neuropathic pain associated with previous herpes zoster infection (PHN);[1] their use in that condition is the subject of a separate review. This review looks at the evidence for using lidocaine 5% medicated plasters off-label to treat localised neuropathic pain with a predominance of allodynia and/or hyperalgesia and dysesthesias.

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Summary of evidence

Summary of efficacy data in proposed use:

Evidence for the use of lidocaine 5% medicated plasters in conditions other than the licensed use in PHN is limited. There is one active comparator trial, some small RCTs and some small open label studies and these cover a variety of conditions. A Cochrane review of the use of topical lidocaine in neuropathic pain in adults[8] concludes that limited information from single studies, mainly in postherpetic neuralgia, 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. However, the assessment includes lidocaine gel, cream and spray in addition to the plasters and covers all causes of NP including the licensed indication of PHN. The conclusion in the "recommendations for research" is that 'clinical practice indicates that lidocaine plasters can be helpful to carefully chosen patients with neuropathic pain limited to a defined area of superficial allodynia or hyperalgesia. For patients like this a study protocol could be generated to evaluate lidocaine plasters in individual patients. It would need to be designed carefully, with specified measurements, outcomes, and timing, and be part of a nationwide or regional assessment.'

In 2009, Baron et al.[9] published a two-stage adaptive, randomised, open-label, multi-centre, non-inferiority trial of lidocaine 5% medicated plaster against pregabalin. Whilst this study included a cohort of patients with PHN (30-40% of trial subjects) the remainder of patients were sufferers of diabetic polyneuropathy (DPN, 60-70%). Patients had to have an average pain intensity of >4 on the 11-point numerical rating scale (NRS) during the last 3 days (NRS-3). After a two-week washout phase, patients were randomised 1:1 to four weeks therapy with either lidocaine 5% medicated plasters (up to four applied for a maximum of 12 hours in a 24 hour period for those with DPN) or pregabalin monotherapy titrated to effect according to the pregabalin SPC[10]. The trial continued into an eight week combination therapy phase and a four week pregabalin sub-study where the pregabalin dose was tapered down; these were discussed in a separate paper and are not relevant to this review. The inclusion and exclusion criteria can be found in table 1; overall the baseline characteristics between the lidocaine and pregabalin groups were well balanced. 193 of the 281 patients in the per protocol set (PPS) had a diagnosis of DPN; of these 99 received lidocaine 5% medicated plasters and 94 received pregabalin. The primary endpoint of this trial was the response rate defined as a reduction of at least 2 points or an absolute value of ≤4 on the NRS-3 scale (see Table 1) after 4 weeks of treatment in the PPS. The overall result showed 94/144 (65.3%) of lidocaine and 85/137 (62.0%) pregabalin treated patients were responders at week 4. Non-inferiority p=0.00656 was demonstrated, with CI lower limit of -9.15 (which is below the predefined margin of -8 percentage points). The published paper doesn't give the actual numbers of patients responding by neuropathic pain condition; however it does give the percentages and so these can be determined. For DPN in the PPS, 66.7% (66 of 99) lidocaine 5% medicated plaster patients and 69.1% (65 of 94) pregabalin patients were classed as responders. There were several secondary outcomes, which are listed in Table 1. One of these secondary outcomes was the change in allodynia severity rating. This was measured as the response to innocuous stimuli using a 26 g von Frey hair. The area with the maximum pain was indicated by the patient and three stimulations were applied with interval of 1 second. The patient was 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). The study found that for the PPS the number of patients with painful DPN who experienced “painful” and “extremely painful” allodynia decreased from 30/99 (30.3%) to 7/92 (7.6%) for those treated with lidocaine patches and for those treated with pregabalin the number decreased from 23/94 (24.4%) to 5/78 (6.4%) (Statistical significance not reported). The paper notes that more PHN patients suffered from “painful” and “extremely painful” allodynia than DPN patients at baseline.[9]

There were three placebo-controlled RCTs in a small number of patients identified as being relevant to this review; Hashmi 2012[11], Cheville 2009[12] and Meier 2003[13].

Hashmi[11] was a double-blind, randomised placebo-controlled longitudinal study; it included 30 chronic back pain (CBP) sufferers, n=15 in each of lidocaine and placebo groups. There were also a further 15 patients who were recruited whose pain was measured at intervals similar to patch treated groups, however brain imaging data was not collected in this group. Patients had to have been diagnosed with CBP for >1 year and had a pain score of >4/10 on the Visual Analogue Scale (VAS) at the baseline visit. They were excluded if they suffered from co-morbidities, major psychiatric conditions or other medical conditions. The treatment period lasted 2 weeks, during which two acetaminophen (paracetamol in UK) 325 mg tablets could be taken daily if needed. All 30 patients in the brain imaging and treatment groups had to refrain from taking analgesic medications for 72 hours prior to the brain imaging session the two patch groups underwent. They were given specific instructions to self-administer the patch twice daily at 12 hourly intervals for a period of two weeks. The 15 patients in the observational group were not given any instructions or administered any treatments; they were told to manage their pain by any means they deemed necessary. All patch treated patients participated in three sessions, at baseline, 6 hours after first patch application and after 2 weeks of using patches, this included brain imaging. At baseline, questionnaires were filled out including the McGill pain questionnaire (MPQ), neuropathic pain scale (NPS) Beck depression inventory (BDI) and Beck anxiety inventory (BAI). Observation only patients completed the MPQ at baseline and 2 weeks. These could give some indication as to allodynia and hyperalgesia but are not broken down sufficiently in the paper to provide this information. The study found no significant difference between the placebo and lidocaine patch treated groups in terms of pain intensity, sensory and affective MPQ scores (Sensory $p>0.5$; affective $p>0.3$ at 6 hours and sensory $p>0.1$; affective $p>0.4$ at two weeks), or in pain related brain activation; however there was a marked reduction in pain observed in both the lidocaine and placebo treated groups. It concluded that the lidocaine patch was no more effective for treating pain than the placebo patch; that the patch itself induces a potent placebo effect in a significant proportion of CBP patients.

Cheville[12] was a double-blind, randomised, two-period crossover study with 28 cancer patients with postsurgical incisional pain. They had to be over 18 with a > 6month life expectancy and have persistent pain (≥ 1 month) rated ≥ 4/10 with neuropathic features (e.g. burning, paraesthesias, or allodynia), involving an area that could be covered by less than three patches; the pain had to be associated with a surgical procedure as part of cancer treatment. Participants were randomly assigned to either apply lidocaine patches or placebo patches on waking for up to 18 hours a day for four weeks; they then crossed over to the alternative therapy for a further four weeks: there was no washout period. Although 21 patients (75%) finished at least the first 4-week phase, only 18 patients (64%) finished both phases. The primary outcome measure of pain

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intensity, measured weekly, was not significantly reduced when patients used the lidocaine patch compared to placebo (4.1 vs 3.8, p=0.36). Although the inclusion criteria specifically stated neuropathic features (e.g. burning, paraesthesias, or allodynia) there was no outcome looking directly at improvement in these features; several self-assessment forms including the NPS, short-form MPQ, and subjects global impression of change may give some indication but are not specific to the neuropathic features required.

Meier[13] was a double-blind, randomised, placebo-controlled study of 58 patients with a variety of neuropathic pain conditions. 32 patients (55.2%) had PHN which is covered in the LMMG New Medicines Assessment of Lidocaine 5% Medicated Plasters in Post Herpetic Neuralgia; the remaining 26 patients had 12 differing NP conditions, of these conditions postsurgical neuralgia had the largest cohort of 10 patients, followed by neuropathy of sural nerve with 4 patients. Neuropathy of genitofemoral nerve and meralgia paresthetica each had two patients, the remaining 8 conditions (neuropathy of peroneal nerve, stump neuralgia, intercostal neuralgia, diabetic polyneuropathy, neuropathic pain first and second digit, Ilioinguinalis neuropathy, neurinoma plexus cervicalis and PNP (breast) of unclear origin) each had only one patient suffering included in the study. The study consisted of 7 days treatment with either lidocaine or placebo patches, followed by at least a 7 day wash-out period, once pain intensity had returned to pre-treatment values, the patient continued with 7 days therapy with the alternative treatment. The study showed a statistically significant ongoing pain intensity reduction compared with pre-treatment levels in both lidocaine ($p<0.001$) and placebo groups ($p<0.05$) and there were significant differences between the groups in terms of this at hours 2 ($p=0.003$) 4 ($p=0.004$) and days 4 ($p=0.03$), 5 ($p=0.02$) and 7 ($p=0.002$); however the results weren't broken down to the type of neuropathic pain and previously stated the largest cohort of patients suffered from PHN which is the focus of an alternative review.

Other efficacy data:

In addition, there were two open-label studies: Galer 2004[14] and Argoff 2004,[15] as well as some studies covering only PHN where allodynia was assessed.[16-18]

Galer[14] was a 6-week parallel-group study where patients applied up to four lidocaine 5% plasters alongside any pre-existing analgesic regimes with no dose alterations or treatment additions for first two weeks. From day 14, investigators could taper other analgesic treatment doses by 25% every 5 days until discontinued if patients achieved at least moderate pain relief.[14] Participants were adults (n=71) who all had a diagnosis of non-radicular low back pain with an NPS score ≥ 4/10 for at least 6/10 individual NPS descriptors at baseline, despite prn use of NSAIDs, COX-2 inhibitors, gabapentin, tramadol or opioids. Several of these descriptors could be used to give an indication of severity of allodynia, hyperalgesia and dysesthesias.

Patients were stratified based on duration of lower back pain (n=11 acute/sub-acute, n=17 short-term chronic, n=43 long-term chronic.)[14] Effectiveness was measured by mean change from baseline to week 6 in four NPS composite measures; NPS-10, which includes the sum of all 10 NPS pain descriptors on a scale of 0-100, NPS-4, which is the average score of the sum of 4 common neuropathic descriptor scores (sharp, hot, dull and deep), NPS-8 (total descriptor score), which is a standardised average score the sum of all the descriptors other than 'intensity' and

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'unpleasantness' and NPS-NA, which is a standardised average score the sum of descriptors that do not assess allodynia or hyperalgesia (all other than 'skin sensitivity' and 'surface pain'. Lidocaine 5% plaster significantly improved all these NPS composite measures at both 2 and 6 weeks of treatment ($p<0.001$) vs. baseline.[14] Although severity of allodynia and hyperalgesia were not specifically measured as an outcome, improvements in the NPS composite scores could give some indication that these symptoms were improved.

Argoff was a 2-week prospective pilot study;[15] it included adult patients with PHN (n=10), painful diabetic neuropathy (PDN) (n=41) or chronic lower back pain (LBP) (n=29) who had had a partial response to analgesic regimens, which included ≥14 days of stable doses of gabapentin. Up to four lidocaine 5% plasters were applied to the area of maximal pain and changed every 24 hours. Patients were maintained on their other analgesic regimen with no dose adjustment or additions allowed.

Effectiveness was measured by change from baseline to week two in four NPS composite scores (NPS-10, NPS-4, NPS-8 and NPS-NA) which were obtained at baseline, week one and end of week two; all composite measures for PDN were significantly improved ($p<0.001$ vs. baseline)[15] actual figures not provided, but an estimate from figure 3 shows NPS-10, NPS-4 and NPS-NA composite scores dropping from approximately 60 to 40, NPS-8 appears to fall from approximately 55 to 35 at 2 weeks.[15] Again, whilst not specifically measuring allodynia/hyperalgesia and not powered to statistical significance, it does give some indication of improvement in these pain qualities.

Although both these open-label studies show lidocaine 5% medicated plasters have a significant effect on NPS composite measures, they are not against a placebo, which, in the RCTs discussed above, confirm that a placebo also has a significant improvement in neuropathic pain, to a similar level as the lidocaine plasters.

The request specifically referred to use of lidocaine 5% medicated plasters in patients with localised neuropathic pain with predominance of allodynia and/or hyperalgesia and dysesthesias. There is very little evidence looking at the effect lidocaine plasters have on allodynic patients outside of the licensed indication, only being looked at as a secondary outcome as discussed in Baron et al[9] above. As discussed in more detail in a separate review for the licensed indication, there are three papers assessing lidocaine plasters in PHN patients which include allodynia severity as a secondary outcome which are briefly discussed below.[16-18]

Hans 2009[16] was a phase III, open-label study included 247 adults with PHN (newly recruited (n=97) and recruited from a previous study (n=152). 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. One of the secondary outcomes related to allodynia severity. This was assessed during the first 12 months using a standardised brush used by the investigator to stroke the painful PHN-affected area in patients. Five brush stroke stimuli were applied to a region of skin 2cm long with an interval of at least 5 seconds and the severity of allodynia was rated by the investigator, according to patient responses, using the 4-point categorical scale. (0=no pain or discomfort to touch, 1=uncomfortable, but tolerable to touch, 2=painful, 3=extremely painful,

patient cannot tolerate touching).[16] Painful and extremely painful allodynia (severity rating of ≥2 on a scale of 0-3) was markedly reduced in newly recruited patients at 12 months compared with baseline (n=42 (43.3%) rated 2 and n=9 (9.3%) rated 3 at baseline, compared to n=14 (15.2%) rated 2 and n=3 (3.3%) rated 3 at 12 months).[16] The percentage of newly recruited patients reporting no pain (severity rating 0) increased from 6.2% (n=6) at baseline to 21.4% (n=51) at 12 months.[16] The study reported that pre-treated patients were found to have comparable benefit in terms of allodynia relief with 5% lidocaine medicated plaster treatment at baseline, which was sustained during the study.[16]

Binder 2009[17] was an enriched enrolment, randomised withdrawal study in patients with PHN ≥ 3/12 after rash healing and mean pain intensity of ≥ 4 on an 11 point NRS. After an 8-week open-label run-in phase where all patients (n=263) received the 5% lidocaine medicated plasters. Responding patients (n=71) were either continued with the lidocaine plaster (n=36) or were switched to placebo (n=35), which was double blinded.[17] Allodynia severity was assessed as a secondary outcome and was measured in the same way as for Hans (discussed above).[16] Of the 71 randomised responders, 54.9% rated their allodynia as "painful" at enrolment, at withdrawal this reduced to 12.7%. Those who rated their allodynia as "extremely painful" reduced from 15.5% at baseline to 2.8% at withdrawal. For non-randomised responders (n=66) who reported "painful" allodynia the proportion decreased from 37.9% to 15.4%, those who reported "extremely painful" allodynia, the percentage of patients reduced from baseline to week 8 of run in from 13.6% to 6.2%. The percentage of non-randomised non-responders (n=128) who had "painful" allodynia reduced from 43.7% to 38.2%, and those with "extremely painful" allodynia reduced from 23.8% at baseline to 14.6% at the end of week 8 of run-in.[17] It should be noted that at randomisation, there were imbalances observed between the two treatment groups in the proportions of patients reporting allodynia in each severity category. In the per protocol population, there was significant between-group differences for the proportion of patients without allodynia (p=0.0450).[17] In the double-blind phase, worsening in some secondary endpoints took place for those switched to placebo, but allodynia was not listed among them.[17]

Rehm 2010[18] was an extension study of the Baron 2009 paper discussed above[9] It was a phase III open-label, randomised study; the extension study includes only the study population with the indication PHN. Inclusion and exclusion criteria are the same as for Baron[9] and are listed under that study in table 1. Patients received monotherapy of either lidocaine plasters or pregabalin for 4 weeks. Those sufficiently treated at week 4 (NRS-3 ≤ 4) continued monotherapy throughout the following 8-week combination phase; those insufficiently treated (NRS-3>4) received a combination of both medications. Allodynia severity was assessed in the same way as for Baron[9] and fewer patients rated their allodynia as 'painful' or 'extremely painful' (severity ratings 2 and 3) after receiving combination treatment however this was in the combination phase of the study and it is unknown whether the reduction is due to the effect of lidocaine, pregabalin or the combination. The study also claimed that patients who had been sufficiently treated during the first 4 weeks and continued with monotherapy also showed further improvements in allodynia severity ratings, however when looking at the table provided in the paper, 1 patient out of 22 rated ≥2 at baseline and 0 at the end of the 8 week extension.

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Summary of safety data:

Overall the safety data provided in trials seems favourable for lidocaine 5% plasters. In the 2009 active comparator trial[9] the lidocaine plasters were better tolerated than the pregabalin; with 48 adverse events (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 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 Cheville 2009 study 10 out of 28 discontinued treatment;, 9 of these did so while using lidocaine versus placebo patches (p=0.02). Two of those who discontinued did so due to AEs, of which further details are not provided. One patient was switched to alternative treatment but seven were discontinued for unknown reasons.[12]

Meier 2003[13] reported 41 AEs in 29 of the 58 participants, none were serious and no difference in frequency was reported between the lidocaine and placebo groups. It was stated that 35 of these events were treatment related. The most frequently reported symptoms were mild skin irritations at the site of patch application, such as reddening or sensation of warming, burning and itching at the site of patch application, which disappeared immediately or within a few hours of patch removal. Only one reaction (eczematous folliculitis) led to withdrawal from the study; that patient was in the lidocaine treatment phase rather than the placebo treatment phase.[13]

Galer 2004[14] reported a total of 11 AEs, these included; dizziness (n=3), nausea (n=2), dermatitis (n=2), dermatitis (n=2), papules (n=2), pruritis (n=2).[14] Well defined erythema developed in 3 patients. Applications site papules were mild and developed in 3 patients. Skin sensitivity to light touch and pinprick were maintained in all patients for whom sensitivity data were available at baseline and week 6/end of treatment. 6 patients discontinued the study due to treatment related AEs.

Argoff 2004[15] found the most commonly reported treatment-related AEs included application site vesicles, papules, and rash (n=3, 3.6%). Systemic treatment related AEs were experienced by 4 patients, these included a case of headache, elevated aspartate aminotransferase levels, increased blood pressure, burning and tingling sensations and muscle spasms. During 2 weeks of treatment with the lidocaine patch 2 patients developed slight oedema at the application site and 5 patients developed well defined erythema. Application site vesicles and papules occurred in 1 patient. Patients who had normal light touch and pinprick sensations continued to do so after 2 weeks of lidocaine treatment. 3 patients discontinued the patch due to treatment related AEs.

Cochrane[8] reported that adverse events were mostly of mild or moderate intensity, transitory and did not differ between placebo and Lidocaine groups; for patches it described them as mostly local skin reactions, erythema, application site reactions, rash, pruritus, and skin reddening.[8]

The lidocaine medicated plaster SPC[1] states that approximately 16% of patients can be expected to experience an adverse reaction, but that they were predominantly of mild or moderate intensity and less than 5% would lead to product discontinuation. Administration site reactions are listed as being very common. Other observed reactions were classed as uncommon (skin injury or skin lesion) or very rare (open wound, anaphylactic reaction/hypersensitivity).[1]

Strengths and limitations of the evidence:

Strengths:

- The population groups covered by some of the studies were appropriate, adult patients with a variety of neuropathic pain conditions relevant to this review, however the numbers of patients were extremely small.
- There are randomised placebo-controlled trials available, but are not powered to show statistical significance to demonstrate the efficacy of lidocaine 5% medicated plasters in comparison to the placebo plasters
- There is one active comparator study, allowing lidocaine plasters to be assessed against another standard recommended neuropathic pain medication.

Weaknesses:

- There is a lack of available studies assessing the efficacy of lidocaine plasters in patients with symptoms of allodynia, hyperalgesia and dysesthesias.
- The studies recruited very small numbers of patients and therefore are not powered to show statistical significance, so the results cannot determine whether the outcomes seen are due to chance.
- The active comparator non-inferiority study was open-label and not blinded and therefore there is a risk of bias. It is recognised there is improvement in pain measures through the placebo affect
- There is a lack of direct head to head studies, with only information for lidocaine plasters compared to pregabalin, not to other potential neuropathic pain therapies, available.
- There were open label studies which didn't have a comparison either to placebo or an active agent which could lead to bias.
- Most of the studies were only of relatively short duration. It is anticipated by the applicant that patients would continue this treatment for 3 months.
- The quality of the studies varied, and generally was not high.
- Several of the studies had differing dosing schedules to that seen in the licensed indication (plasters applied for up to 12 hours in 24 with a 12 hour plaster free period). They were not all consistent with each other; there was twice daily application at 12 hour intervals and apply on waking for up to 18 hours among others, making it difficult to draw conclusions across all the trials.
- Cheville 2009 was closed early due to recruitment problems, and had a high dropout rate which wasn't sufficiently explained.

Summary of evidence on cost effectiveness:

There are no cost effectiveness studies on the use of lidocaine medicated plasters outside of the licensed indication of relief of neuropathic pain associated with previous herpes zoster infection (PHN).

Prescribing and risk management issues:

Lidocaine 5% medicated plasters are only licensed for use in neuropathic pain associated with previous PHN. For use outside of this follow GMC good practice guidance on "unlicensed medicines": prescribers should be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy[19]. They should also ensure that decisions are made in collaboration with the patient (or carers) by discussing the options with them and providing sufficient information about the medicine to allow them to make an informed decision; where prescribing unlicensed medicines is supported by authoritative clinical guidance, it may be sufficient to describe to the patient in general terms, why the medicine is not licensed for the proposed use.[19]

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 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 (£220-661 for 3 months)**
Pregabalin (licensed for peripheral and central neuropathic pain)	300-600 mg daily in divided doses	150 mg & 300 mg caps are both 56=£64.40	£840 BD dosing

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Gabapentin (licensed for neuropathic pain)	300 mg tds (up to max 3.6 g daily in divided doses)	300 mg cap, 100 = £3.80. 600 mg tab 100=£10.86	£42-£238
Amitriptyline (unlicensed indication, licensed indications included depression and nocturnal enuresis)	10 mg at night (increased up to 75 mg daily, higher doses under specialist supervision)[20]	10 mg, 28 = 95p. 25 mg, 28 = 98p. 50 mg, 28=£1.18	£13 to £28
Duloxetine (licensed for diabetic neuropathy)	60 mg once daily, (maximum 120 mg daily in divided doses.)	60 mg capsules, 28 =£26.65	£347-£695
Capsaicin Cream (licensed for PHN and for painful diabetic neuropathy under expert supervision)	Apply 3-4 times a day, sparingly.	45 g =£14.58	Assuming 2 fingertip units per application, would require 3 tubes per month, this equates to £525 per year.
Costs based on MIMS list prices December 2015.[3] This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

No available discounts known.

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 for PHN and possibly also for other neuropathic pain conditions. It 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. It may reduce pressure on pain clinic services by allowing prescribing to be continued in primary care rather than continued in the specialist secondary care service. Alternatively, in areas where it is not currently in use, due to the requirement that it be initiated in secondary care, it could 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 therapy.

Anticipated patient numbers and net budget impact:

There is no accurate estimate available for the population prevalence of neuropathic pain.[4] The request suggested around 4 patients a month per CCG would require treatment with lidocaine 5% medicated plaster; this would be almost 400 patients per year. An annual cost for these 400 patients at £2642.60 per patient per year would be £1,057,040. However the request also suggested that most patients would use for three months, if this were the case the cost reduces to £264,260. In addition, the request didn't differentiate, in terms of numbers of patients, between those being treated for licensed and unlicensed indications, so it is likely that some of these patients would be PHN sufferers covered under the licensed use of lidocaine 5% medicated plasters review.

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 cost of £743,528.61; however it is impossible to know whether these were for use in the licensed indication of PHN or for other forms of neuropathic pain.

Innovation, need, equity:

The NICE neuropathic pain guidance lists capsaicin cream as an alternative to oral treatments, it is licensed for PHN, and for painful diabetic neuropathy under expert supervision. lidocaine 5% medicated plasters are not currently listed by NICE as a possible alternative due to lack of available evidence, however it is listed as a research recommendation to further investigate its use for localised peripheral pain as it is recognised as a potential alternative treatment for people who do not wish to, or are unable to, take oral medications. ; however, Whereas the capsaicin patches are listed by NICE as a treatment not to be started to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so: lidocaine plasters are not, leaving them available as an innovative product for those that cannot make use of the oral treatment options.

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Table 1: Summary of key Lidocaine 5% medicated plaster studies relevant to use in neuropathic pain

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	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	• 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 (193 with DPN) • 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 4 plasters if DPN. • Creatinine clearance above 60 mL/min • DPN patients required to have controlled, treated, type 1 or 2 diabetes mellitus with glycosylated haemoglobin (HbA_{1c}) ≤11%.	281 patients in PPS; 193 with DPN. 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 DPN patients lidocaine=-2.5 (SD 1.99), pregabalin=-2.5 (SD 1.79) 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%). DPN patients: lidocaine = 59 (59.6%) pregabalin = 53 (56.4%) ≥50% reduction PPS: all patients: lidocaine=56 (38.9%) pregabalin= 44 (32.1%). DPN patients: lidocaine = 40 (40.4%) pregabalin = 35 (37.2%) Changes in allodynia severity rating from baseline in painful and extremely painful on allodynia severity rating scale, PPS: all patients: lidocaine	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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	least one dose of the investigational medicinal products and for whom at least one 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	• DPN patients also had to suffer from painful, distal, symmetrical sensorimotor polyneuropathy of the lower extremities for ≥ 3 months with at least two of: burning sensation, tingling or prickling, paraesthesias, painful heat or cold sensation. • 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 • No palpable pulse of the arteria dorsalis pedis in one or both feet. • Clinical signs of venous insufficiency and/or post-thrombotic syndrome stage III/IV, or ulcers on the lower extremities. • 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			38.9 to 12.9%, pregabalin 36.5 to 17%. DPN patients: lidocaine 30.3 to 7.6%, pregabalin 24.4 to 6.4% 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), DPN patients: lidocaine 0.13 (SD 0.245) pregabalin 0.06 (SD 0.211) Patients Global impression of change (PGIC) and Clinical Global Impression of Change (CGIC). PGIC “very much or much improved” in DPN patients, lidocaine = 49.5%, pregabalin 50%. CGIC “very much or much improved” in DPN patients, lidocaine=43.4% pregabalin=52.1% 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?’) DPN patients rating very good or excellent: lidocaine 24.2%, pregabalin 33.0% Safety evaluations: 48 AE in 29 (18.7%) lidocaine patients vs. 194 AE in 71 (46.4%)	

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		gabapentin within last 6 months • Concomitant use of adjuvant drugs for neuropathic pain or local anaesthetics, use of capsaicin 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.			pregabalin patients. 16 DRAEs in 9 (5.8%) lidocaine patients (9 mild, 6 moderate, 1 severe) compared with 161 DRAEs in 63 (41.2%) pregabalin patients. (60 mild, 73 moderate, 28 severe).	

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

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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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