

# Medicines Management Programme

## Lidocaine 700 mg medicated plaster (Versatis®)

### Prescribing and Cost Guidance



<b>Approved by:</b>	Prof. Michael Barry, Clinical Lead, Medicines Management Programme (MMP).
<b>Date approved:</b>	21/04/2021
<b>Version:</b>	1.1 (Evidence Update)
<b>Previous versions</b>	1.0

## Table of contents

1. Background .....	1
2. Purpose .....	1
3. Definitions.....	2
4. Mode of action.....	2
5. Posology and administration .....	2
6. Special warnings and precautions for use .....	3
7. Undesirable effects .....	3
8. Clinical evidence for lidocaine 700 mg medicated plaster (Versatis®) .....	4
8.1 Clinical evidence for the use of lidocaine 700 mg medicated plaster in PHN .....	4
8.2 Clinical evidence for the use of lidocaine 700 mg medicated plaster in neuropathic pain.....	6
9. Clinical Guidelines .....	7
9.1 National Guidelines .....	7
9.1.1 National Clinical Effectiveness Committee: Pharmacological management of cancer pain in adults national clinical guideline no. 9 (2015) .....	7
9.2 International Guidelines .....	7
9.2.1 NICE (NG 193): Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (April 2021) .....	7
9.2.2 NICE (CG 177): Osteoarthritis: care and management (2014, updated Dec 2020) .....	8
9.2.3 NICE (NG 59): Low back pain and sciatica in over 16s: assessment and management (2016, updated Sep 2020) .....	8
9.2.4 NICE (CG 173): Neuropathic pain in adults: pharmacological management in non-specialist settings (2013, updated Sep 2020) .....	8
9.2.5 Canadian Pain Society: Pharmacological management of chronic neuropathic pain: revised consensus statement (2014).....	8
9.2.6 European Federation of Neurological Societies (EFNS): Guidelines on the pharmacological treatment of neuropathic pain (2010 revision) .....	9
10. Recommendations for prescribing.....	10
11. Expenditure on lidocaine 700 mg medicated plaster .....	11
12. Pharmacoeconomic evaluation of lidocaine 700 mg medicated plaster.....	12
12.1 National Centre for Pharmacoeconomics (NCPE) evaluation of lidocaine 700 mg medicated plaster .....	12
12.2 Health Technology Assessments in other jurisdictions .....	13
12.2.1 National Institute of Health and Care Excellence (NICE) .....	13
12.2.2 Scottish Medicines Consortium (SMC) .....	13

12.2.3 Pharmaceutical Benefits Advisory Committee (PBAC) .....	13
13. Alternative topical treatment options and associated costs .....	13
13.1 Topical treatment options for the treatment of post-herpetic neuralgia .....	13
13.2 Topical treatment options for the treatment of muscular/rheumatic pain .....	14
13.3 Cochrane review on ‘Topical NSAIDs for acute musculoskeletal pain in adults’ .....	15
13.4 Cochrane review on ‘Topical NSAIDs for chronic musculoskeletal pain in adults’ .....	16
14. Health Technology Management.....	16
15. Conclusion.....	17
16. References .....	19

## List of Tables

Table 1: Adverse drug reactions associated with lidocaine 700 mg medicated plaster .....	4
Table 2: Clinical evidence for the use of lidocaine 700 mg medicated plaster in PHN.....	4
Table 3: Overview of the utilisation of lidocaine 700 mg medicated plaster .....	11
Table 4: Topical products and price comparison of treatments for PHN .....	14
Table 5: Topical products and price comparisons of treatments for non-PHN indications.....	15

## List of Figures

Figure 1: Monthly expenditure for lidocaine 700 mg medicated plaster (Versatis®) under the Community Drug Schemes from January 2012 to August 2017. ....	11
--	----

## List of abbreviations

BNF	British National Formulary
CDS	Community Drug Schemes
DPN	Diabetic polyneuropathy
GRADE	Grading of recommendations assessment, development and evaluation
HSE	Health Service Executive
HSE-CPU	Health Service Executive-Corporate Pharmaceutical Unit
HTA	Health technology assessment
HTM	Health technology management
ICER	Incremental cost effectiveness ratio
MMP	Medicines Management Programme
N	Number of participants
NCPE	National Centre for Pharmacoeconomics
NICE	National Institute of Health and Care Excellence
NNT	Number needed to treat
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
PBAC	Pharmaceutical Benefits Advisory Committee
PCRS	Primary Care Reimbursement Service
PHN	Post-herpetic neuralgia
QALY	Quality adjusted life year
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics

## 1. Background

Lidocaine 700 mg medicated plaster (Versatis®) is licensed for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection known as post-herpetic neuralgia (PHN) in adults.<sup>1</sup> This plaster has been reimbursed under the Community Drug Schemes (CDS) in Ireland since 2010.<sup>2</sup> Total annual expenditure (including pharmacy fees and VAT) on the CDS was increasing in a sustained manner, with a total expenditure of approximately €20.17 million in 2014, €27.93 million in 2015 and €31.1 million in 2016. In the first eight months of 2017, total expenditure was approximately €22.95 million.<sup>3</sup>

The Medicines Management Programme (MMP) in its remit to promote safe, effective and cost-effective prescribing of medicines in Ireland identified large increases in the utilisation of lidocaine 700 mg medicated plaster from 2012 to 2015. The Health Service Executive-Corporate Pharmaceutical Unit (HSE-CPU) in accordance with the Health Act 2013, (section 18(4)), requested the National Centre for Pharmacoeconomics (NCPE) to assess the cost-effectiveness of lidocaine 700 mg medicated plaster and a health technology assessment (HTA) was undertaken in 2015. The NCPE concluded that the cost-effectiveness of lidocaine 700 mg medicated plaster had not been demonstrated. The NCPE report is explained in detail in section 12 of this document. Following the HTA report, the HSE negotiated a price reduction for lidocaine 700 mg medicated plaster from €93.96 to €77.52 in March 2016.

In March 2016, the number of patients receiving lidocaine 700 mg medicated plaster under the CDS was 19,831. This number continued to increase reaching a total of 25,337 patients in August 2017.<sup>3</sup> Due to these sustained increases, the utilisation of and expenditure on lidocaine 700 mg medicated plaster was identified as a priority for the MMP.

## 2. Purpose

This document outlines the available evidence, current guidelines, cost and practice tips for the prescribing and reviewing of lidocaine 700 mg medicated plaster in adults. Recommendations are also provided on suitable alternative topical preparations where lidocaine 700 mg medicated plaster has been shown to be ineffective or prescribed for unlicensed indications.

In January 2021, a further review was conducted to update clinical evidence relevant to the use of lidocaine 700 mg medicated plasters. In addition a clinical guideline section was added to this document taking into account recommendations for pain management of both PHN and non-PHN indications.

**Prescribers should be aware that lidocaine 700 mg medicated plaster is licensed ONLY in the treatment of neuropathic pain associated with post-herpetic neuralgia (PHN) and should be prescribed ONLY for this indication.**

### **3. Definitions**

For the purpose of this report the associated cost refers to the reimbursed cost of the preparation as listed on the HSE Primary Care Reimbursement Service (PCRS) website ([www.pcrs.ie](http://www.pcrs.ie)).<sup>4</sup>

Only licensed, reimbursable products are included in this review. Versatis® is the only licensed reimbursed topical lidocaine medicated plaster in Ireland. Where alternative therapies are discussed in this review only topical, local-acting agents are considered. Systemic preparations in the treatment of PHN and other forms of neuropathic pain are outside the scope of this document.

This review should be used in conjunction with clinical judgement and decision-making appropriate to the individual patient. Prescribers should refer to sources such as the summary of product characteristics (SmPC) for Versatis® and the British National Formulary (BNF) to inform decisions made with individual patients.

The brand name has been updated to reflect the change in the name of this medicinal product from Versatis® 5% medicated plaster to Versatis® 700 mg medicated plaster.<sup>5</sup>

Costs are correct as of January 2021.

### **4. Mode of action**

Lidocaine 700 mg medicated plaster exerts its effect by stabilising the neuronal membranes and causing down-regulation of neuronal sodium channels. As a result, this impairs the conduction of signals associated with the perception of pain.<sup>6</sup> The medicated plaster consists of a white hydrogel adhesive material which is applied to a non-woven polyethylene terephthalate backing containing lidocaine 700 mg and covered with a polyethylene terephthalate film release-liner.<sup>1</sup> Lidocaine 700 mg medicated plaster has a dual mode of action. Firstly, the lidocaine diffuses continuously into the skin providing a local analgesic effect and secondly it exerts a mechanical effect on the pain due to the hydrogel layer contained within the plaster.<sup>1</sup>

### **5. Posology and administration**

The painful area should be covered with the lidocaine 700 mg medicated plaster once daily for up to 12 hours within a 24 hour period.<sup>1</sup> Plasters may be applied day or night with a subsequent plaster-free interval of at least 12 hours.<sup>1</sup> The minimum number of plasters that demonstrate a therapeutic benefit should be used and not more than three plasters should be used at the one time.<sup>1</sup> The plaster

can be cut into smaller sizes prior to removal of the release liner.<sup>1,7</sup> After first opening, the sachet (containing 5 plasters) should be tightly sealed and the plasters should be used within 14 days.<sup>1</sup>

The plaster must be applied to intact, dry, non-irritated skin after the healing of shingles. The plaster must not be applied to inflamed or injured skin, such as active herpes zoster lesions, atopic dermatitis or wounds.<sup>1</sup>

Treatment outcome should be evaluated after 2-4 weeks. If there has been no response to lidocaine 700 mg medicated 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.<sup>1</sup>

**Lidocaine plasters must be applied to intact, dry, non-irritated skin after healing of the shingles rash/lesions.**

## **6. Special warnings and precautions for use**

Lidocaine 700 mg medicated plaster should be used with caution in severe cardiac, renal and hepatic impairment.<sup>1</sup> The plaster contains propylene glycol which may cause skin irritation. It also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions and these effects may be delayed.<sup>1</sup> One of the metabolites of lidocaine, 2,6 xylidine, has been shown to be genotoxic and carcinogenic in rats. Also, secondary metabolites have been shown to be mutagenic. The clinical significance of this is unknown and therefore the long-term treatment with lidocaine 700 mg medicated plaster is only warranted if there is a therapeutic benefit for the patient.<sup>1</sup>

## **7. Undesirable effects**

Approximately 16% of patients can be expected to experience an adverse reaction.<sup>1</sup> These reactions are generally localised due to the nature of the product. The most commonly seen adverse reactions are related to administration site reactions e.g. burning, dermatitis, erythema, pruritus, rash and skin irritation.<sup>1</sup>

Table 1 lists adverse drug reactions that have been reported in studies of patients with PHN receiving lidocaine 700 mg medicated plaster.<sup>1</sup> The adverse-effects are listed by body system and frequency; very common ( $\geq 1/10$ ) and uncommon ( $\geq 1/1,000$  to  $1 < 100$ ).

**Table 1: Adverse drug reactions associated with lidocaine 700 mg medicated plaster**

Body system	Adverse Drug Reaction	Frequency
General disorders and administration site conditions	Administration site reactions	Very common
Skin and subcutaneous tissues disorders	Skin lesion	Uncommon
Injury, poisoning and procedural complications	Skin injury	Uncommon

## 8. Clinical evidence for lidocaine 700 mg medicated plaster (Versatis®)

### 8.1 Clinical evidence for the use of lidocaine 700 mg medicated plaster in PHN

Table 2 describes the main Phase III studies supporting the use of lidocaine 700 mg medicated plaster in clinical practice for the treatment of PHN and painful diabetic polyneuropathy (DPN).

**Table 2: Clinical evidence for the use of lidocaine 700 mg medicated plaster in PHN**

Study	Design	Population	N	Time	Primary endpoint	Comparator	Conclusion
KF 10004/H32 <sup>8</sup>	Double-blind, randomised, crossover study.	PHN patients identified as lidocaine plaster responders	32	14 days	Time to exit	Lidocaine plaster vs. placebo	The median time to exit was 14 days for lidocaine and 3.8 days for placebo (p<0.001).
KF 10004/01 <sup>9</sup>	Double-blind randomised, parallel group, withdrawal design	PHN patients identified as lidocaine plaster responders	71	2-14 days	Lack of efficacy for two consecutive application days leading to treatment withdrawal*	Lidocaine plaster vs. placebo	9/36 on lidocaine withdrew and 16/35 on placebo withdrew due to lack of efficacy.
Baron et al 2009 <sup>10</sup>	Open-label, two-stage adaptive, non-inferiority	PHN (n = 96) and DPN (n = 204) patients	96 <sup>†</sup>	4 weeks	Response rate at four weeks	Lidocaine plaster vs. pregabalin	Lidocaine 700 mg plaster was numerically better than pregabalin 62.2% vs. 46.5% in the PHN subgroup.

N = Number of participants PHN = Post-herpetic neuralgia DPN = Diabetic polyneuropathy † PHN subgroup

\* SmPC Versatis® 700mg medicated plaster

The first study (KF10004/H32) was a randomised, double-blind, placebo-controlled, two-period crossover trial consisting of 32 patients with PHN.<sup>8</sup> Patients who were recruited were regular users of lidocaine 700 mg medicated plaster from open-label extension studies. Patients were assigned to receive 14 days of lidocaine 700 mg medicated plaster followed by 14 days of placebo or vice versa with no washout period.<sup>8</sup> The primary end-point was the “time to exit” where patients withdrew because their pain relief was two points lower than their normal response on a six-point categorical verbal rating scale of pain relief (worse, no pain relief, slight relief, moderate relief, a lot of relief and complete relief). The median time to exit was 14 days for lidocaine 700 mg medicated plaster and 3.8 days for placebo ( $p < 0.001$ ).<sup>8</sup> The secondary endpoint was the patient’s preference between treatments. Three patients (9.4%) preferred the placebo plaster compared with 25 (78.1%) patients who preferred the lidocaine 700 mg medicated plaster.<sup>8</sup>

The second study (KF10004/01) was a double-blind, randomised, parallel group, withdrawal design which examined a subgroup of patients with PHN who were known to respond to the lidocaine 700 mg medicated plaster and aimed to measure the effect of treatment cessation.<sup>9</sup> Patients initially received an eight week open-label lidocaine 700 mg medicated plaster treatment and only those with a positive response to treatment after this time were entered into the randomised withdrawal treatment phase. Of the 265 patients who entered the eight week open-label phase, 137 (52%) were classified as responders with at least moderate relief with lidocaine 700 mg medicated plaster treatment.<sup>9</sup> A total of 71 patients were randomised to either receive lidocaine 700 mg medicated plaster (36 patients) or placebo (35 patients) for 2-14 days.<sup>9</sup> The primary end-point was lack of efficacy on two consecutive days after which patients were to withdraw from the study.<sup>1,9</sup> Lack of efficacy was defined as pain relief two points lower than the normal response on a six point scale.<sup>1</sup> Nine out of the 36 patients on lidocaine 700 mg medicated plaster and 16 out of the 35 on placebo withdrew due to lack of efficacy.<sup>9</sup>

A European Mutual Recognition Procedure Public Assessment Report published in January 2019 reviewed the clinical evidence from studies KF10004/H32 and KF10004/01.<sup>9</sup> The report noted that, while there is some evidence of small clinical benefit for the use of lidocaine 700mg medicated plaster in the treatment of PHN, it is likely there may also be an additional placebo effect in this condition.<sup>9</sup> The report concluded that there did not appear to be an important safety concern associated with this product, that risk-benefit appeared positive and that marketing authorisation could be granted.<sup>9</sup>

The third study was a two-stage adaptive, open-label, multicentre, non-inferiority study of lidocaine 700 mg medicated plaster versus pregabalin.<sup>10</sup> This non-inferiority study aimed to compare the efficacy of lidocaine 700 mg medicated plaster to pregabalin in patients with PHN and DPN, an

unlicensed indication in Ireland. Patients were included if the neuropathic pain was present for  $\geq 3$  months after healing of the herpes zoster skin rash. There were two phases to this study. The first phase of the trial lasted four weeks in which adults with PHN or painful DPN received either lidocaine 700 mg medicated plaster or twice daily pregabalin capsules titrated according to the SmPC. The response was compared in terms of efficacy, quality of life, safety and tolerability. The primary endpoint of the comparative phase was response rate at 4 weeks, defined as reduction averaged over the last three days from baseline of  $\geq 2$  points or an absolute value of  $\leq 4$  points on the 11-point Numerical Rating Scale (NRS-3).<sup>10</sup> Secondary endpoints included pain intensity scores, changes from baseline, allodynia severity rating and quality of life parameters. In the second phase, patients with adequate responses to monotherapy continued their previous therapy while those with insufficient response received combination therapy, i.e. the lidocaine 700 mg medicated plaster with pregabalin. Alternatively, patients received pregabalin and were titrated again according to the SmPC. There were 96 patients who were treated for PHN and 204 patients with painful DPN. The results showed that lidocaine 700 mg medicated plaster was found to be numerically better than pregabalin for PHN in terms of response rate (62.2% lidocaine 700 mg medicated plaster vs. 46.5% pregabalin).<sup>10</sup> In patients with DPN the response rate was comparable (66.7% lidocaine 700 mg medicated plaster vs. 69.1% pregabalin). In the overall mixed population of patients with PHN or DPN included in this study, lidocaine 700 mg medicated plaster was found to be non-inferior to pregabalin in the full analysis set (PHN and DPN), but not in the per protocol group following statistical testing.<sup>10</sup>

## **8.2 Clinical evidence for the use of lidocaine 700 mg medicated plaster in neuropathic pain**

The Cochrane Library performed a review (July 2014) on 'Topical lidocaine for neuropathic pain in adults' to assess the analgesic efficacy of topical lidocaine 700 mg medicated plaster for chronic neuropathic pain in adults and to assess the associated side-effects. This review involved 12 small studies with 508 participants in total that tested topical lidocaine 700 mg medicated plaster against topical placebo for a number of weeks. The limited information from single studies mainly in PHN indicated that topical lidocaine 700 mg medicated plaster may be effective in treating neuropathic pain in a small number of patients and is well tolerated, at least in the short-term. There was no clear evidence of an effect on the incidence of adverse effects or withdrawals. However, the reviewers noted that the studies included 'very low quality evidence' and all had a 'high risk of bias' due to small size and incomplete outcome data.<sup>11</sup>

## **9. Clinical Guidelines**

The reimbursement of lidocaine 700 mg medicated plaster on the CDS is approved for the licensed indication of PHN as outlined in section 14. However, reimbursement may also be considered for other indications in exceptional circumstances of unmet clinical need. The following clinical guidelines were reviewed for recommendations in relation to the use of lidocaine 700 mg medicated plaster for both PHN and non-PHN indications, where there is evidence that prescribing is occurring.

### **9.1 National Guidelines**

National clinical guidelines for pain management in Ireland were reviewed. The National Clinical Effectiveness Committee (NCEC) have published one National Guideline relating to pain management: Pharmacological Management of Cancer Pain in Adults. Ireland specific guidelines for the management of neuropathic pain, osteoarthritis and other forms of chronic non-cancer pain were not identified.

#### **9.1.1 National Clinical Effectiveness Committee: Pharmacological management of cancer pain in adults national clinical guideline no. 9 (2015)**

Recommendation 36.2 in this guideline states that there is limited evidence to support the use of topical lidocaine medicated plaster in cancer pain (grade D).<sup>12</sup> Grade D recommendations are based on inconsistent or inconclusive studies or expert committee/clinical experience. Two studies were identified that examined topical lidocaine use in the cancer care setting.<sup>13,14</sup> The study methodologies used limit the interpretation of findings and preclude evidence level grading.<sup>12,15</sup>

### **9.2 International Guidelines**

A range of guidelines relating to pain management from other jurisdictions were identified and evaluated as part of this review.

#### **9.2.1 NICE (NG 193): Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (April 2021)**

This guideline states that local anaesthetics (topical or intravenous), should not be initiated in people aged 16 years and over to manage chronic primary pain, unless as part of a clinical trial for complex regional pain syndrome.<sup>16</sup>

### **9.2.2 NICE (CG 177): Osteoarthritis: care and management (2014, updated Dec 2020)**

This guideline does not contain a recommendation for the use of lidocaine 700 mg medicated plaster in the pharmacological management of osteoarthritis. It advises consideration of topical NSAIDs or topical capsaicin as an adjunct to core treatments for knee or hand osteoarthritis.<sup>17</sup> Capsaicin 0.025% cream is licensed for the symptomatic relief of pain associated with osteoarthritis.<sup>18</sup>

### **9.2.3 NICE (NG 59): Low back pain and sciatica in over 16s: assessment and management (2016, updated Sep 2020)**

This guideline does not contain a recommendation for the use of lidocaine 700 mg medicated plaster in the treatment of low back pain and sciatica in patients over sixteen years of age.<sup>19</sup>

### **9.2.4 NICE (CG 173): Neuropathic pain in adults: pharmacological management in non-specialist settings (2013, updated Sep 2020)**

This guideline does not contain a recommendation for the use of lidocaine 700 mg medicated plaster in the pharmacological management of neuropathic pain in non-specialist settings. It advises consideration of capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.<sup>20</sup> Capsaicin cream 0.075% is licensed for the symptomatic relief of PHN and painful diabetic peripheral polyneuropathy.<sup>21</sup>

This guidance reflects a change in recommendations compared with previous NICE guidance, Clinical Guideline 96 Neuropathic pain in adults: pharmacological management in non-specialist settings (March 2010). Clinical Guideline 96 had suggested that topical lidocaine could be considered as a third line therapy for localised neuropathic pain (unlicensed use if not post-herpetic neuralgia) for those unable to take oral medication because of medical conditions and/or disability, while they wait for a referral to specialist services.<sup>22</sup>

### **9.2.5 Canadian Pain Society: Pharmacological management of chronic neuropathic pain: revised consensus statement (2014)**

In this document, the Canadian Pain Society, provide a stepwise approach to the pharmacological management of neuropathic pain by ranking analgesic agents into first- to fourth–line therapies.<sup>23</sup> Topical lidocaine 5% (cream, gel or patch) is classified as a fourth line agent having been downgraded from second-line in the original 2007 consensus statement.<sup>23,24</sup> It was downgraded due to conflicting evidence of efficacy, with the exception of PHN management, for which it remains a second-line option.<sup>23</sup>

### **9.2.6 European Federation of Neurological Societies (EFNS): Guidelines on the pharmacological treatment of neuropathic pain (2010 revision)**

The EFNS task force reviewed the existing evidence for the pharmacological treatment of neuropathic pain. They made recommendations for drug treatment in the following commonly studied neuropathic pain conditions; diabetic neuropathic pain, PHN, trigeminal neuralgia and central pain. The sole recommendation for lidocaine 700 mg medicated plaster treatment was as a first-line treatment option for PHN in the elderly, especially if there are concerns regarding central nervous system side effects of oral medications.<sup>25</sup>

Evidence was reviewed and classified but no formal recommendations were made for drug treatments in less commonly studied neuropathic pain conditions; HIV neuropathy, post-traumatic or post-surgical neuropathic pain, chronic radiculopathy, cancer neuropathic pain, phantom pain and multi-aetiology neuropathic pain. Lidocaine medicated plaster did not have a level A or B rating for efficacy for any of the listed conditions.<sup>25</sup> There were, however, level A/B ratings for inefficacy/poor efficacy or discrepant results for the use of lidocaine medicated plasters in the treatment of HIV neuropathy and multi-aetiology neuropathic pain.<sup>25</sup>

**National and international pain management guidelines reviewed outlined the following:**

- **For the treatment of PHN, the Canadian Pain Society and EFNS guidelines recommend the use of lidocaine plaster as second line therapy and first line therapy (in the elderly) respectively.**
- **NICE (CG 173) considers the treatment of neuropathic pain including PHN and does not recommend the use of lidocaine plaster.**
- **For the treatment of non-PHN pain, the guidelines reviewed do not recommend the use of lidocaine plaster, with the exception of the Canadian Pain Society, who classify this therapy as a fourth line neuropathic pain agent.**
- **The recommendation for the use of lidocaine plaster in neuropathic pain was downgraded by the Canadian Pain Society and removed by NICE (CG 173) in their updated evidence reviews.**

## 10. Recommendations for prescribing

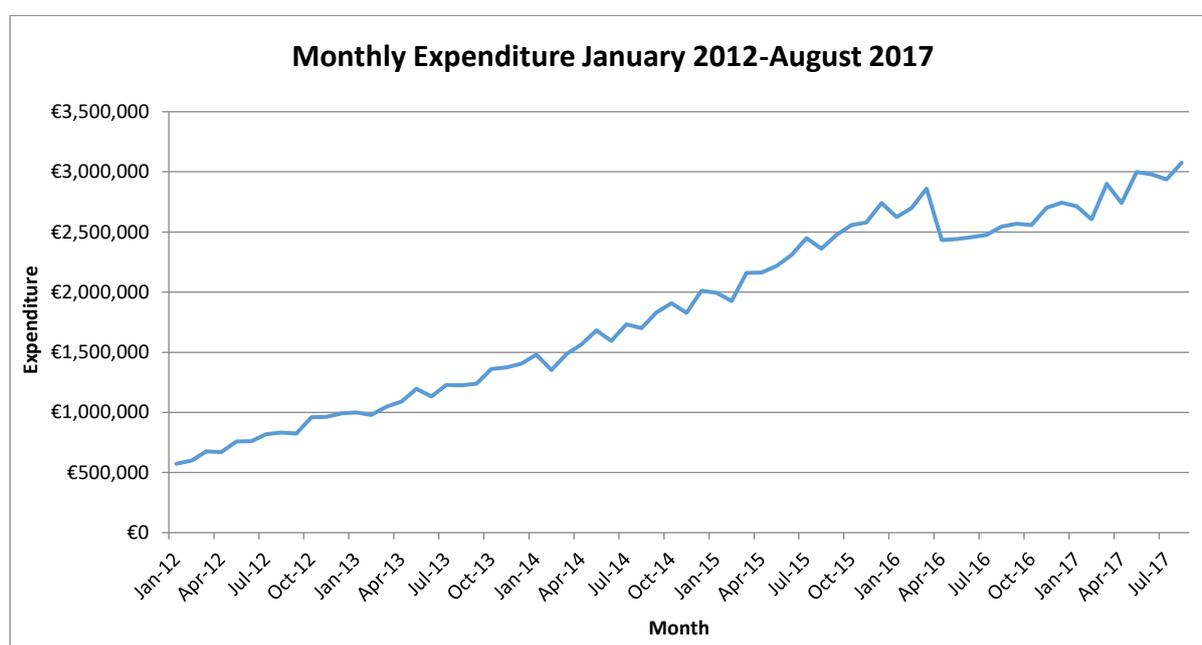
### MMP recommendations for the prescribing of lidocaine 700 mg medicated plaster

- ✓ Prescribing of lidocaine 700 mg medicated plaster should be restricted to patients with post-herpetic neuralgia (PHN) ONLY.
- ✓ Treatment should be reviewed after 2-4 weeks and stopped if ineffective or if the relieving effect is solely due to protection of the area by the plaster.
- ✓ Prescribers should ensure all patients are using the patch correctly.
- ✓ Patients on long-term therapy should be assessed for continued need and aim to have treatment discontinued or alternatively, try to have a longer plaster-free period between treatments.<sup>23</sup>

## 11. Expenditure on lidocaine 700 mg medicated plaster

Figure 1 illustrates the monthly expenditure on lidocaine 700 mg medicated plasters under the CDS from January 2012 to August 2017. Expenditure on lidocaine 700 mg medicated plasters under the CDS in August 2017 was €3.075 million with 25,337 patients receiving treatment.<sup>3</sup>

While the price reduction agreed in March 2016 led to a short term decrease in expenditure, the continued increase in the number of patients initiating treatment resulted in further expenditure increases. This resulted in a total expenditure in 2016 exceeding that of 2015 despite the reduced reimbursement price (table 3).



**Figure 1: Monthly expenditure for lidocaine 700 mg medicated plaster (Versatis®) under the Community Drug Schemes from January 2012 to August 2017.**

**Table 3: Overview of the utilisation of lidocaine 700 mg medicated plaster**

Reimbursement price per pack (30 plasters)	€77.52*
Total expenditure under Community Drug Schemes 2015 <sup>3</sup>	€27.93 million
Total expenditure under Community Drug Schemes 2016 <sup>3</sup>	€31.1 million
Total expenditure under Community Drug Schemes January-August 2017 <sup>3</sup>	€22.95 million
Total number of patients receiving treatment as of December 2016 <sup>3</sup>	22,847
Total number of patients receiving treatment as of August 2017 <sup>3</sup>	25,337

\*€93.96 prior to March 2016

## **12. Pharmacoeconomic evaluation of lidocaine 700 mg medicated plaster**

As previously outlined in section 1, in accordance with the Health Act 2013, the HSE-CPU requested the NCPE to evaluate the cost-effectiveness of lidocaine 700 mg medicated plaster in 2015.

### **12.1 National Centre for Pharmacoeconomics (NCPE) evaluation of lidocaine 700 mg medicated plaster**

The NCPE completed the HTA in September 2015 and concluded that the cost-effectiveness of lidocaine 700 mg medicated plaster was not demonstrated for the following reasons:<sup>26</sup>

- The vast majority of prescribing of lidocaine 700 mg medicated plaster under the state schemes was for indications other than PHN. The company did not submit a cost-effectiveness evaluation for other potential indications due to lack of relevant clinical evidence.
- As the cost-effectiveness analysis relates only to the indication of PHN it only represents a small percentage of overall use and does not give a clear indication of real world utilisation.
- The information submitted for HTA had limitations regarding the quality of the clinical efficacy data presented. This resulted in significant uncertainty with the reported outcomes associated with lidocaine 700 mg medicated plaster.
- In the economic model submitted, the base case incremental cost-effectiveness ratios (ICERs) which are represented in quality adjusted life years (QALYs) were €9,871/QALY for lidocaine 700 mg medicated plaster compared to pregabalin, €7,771/QALY for lidocaine 700 mg compared to gabapentin and €6,216/QALY for lidocaine 700 mg compared to amitriptyline. However, the NCPE did not consider these estimates to be robust and, as mentioned above, no ICERs were presented for non-PHN indications.
- In the budget impact analysis, the number of patients receiving the product and the duration of treatment differed substantially from the figures submitted by the company and the figures obtained by the NCPE from the national reimbursement database for 2014. The NCPE estimated that 5-10% of patients receive the product for its licensed indication of PHN.

Following the HTA assessment, the HSE agreed a price reduction in March 2016 reducing the price per 30 plasters from €93.96 to €77.52. In line with this development, the MMP issued guidance on the use of Versatis® by means of prescribing tips and tools to highlight appropriate use and the prescribing of Versatis® off-license. The prescribing tips and tools are available on [www.hse.ie/yourmedicines](http://www.hse.ie/yourmedicines).

## **12.2 Health Technology Assessments in other jurisdictions**

### **12.2.1 National Institute of Health and Care Excellence (NICE)**

As outlined in section 9.2.4 above, NICE Clinical Guideline 173 for 'Pharmacological treatment of neuropathic pain in adults in non-specialist setting' does not recommend the use of lidocaine 700 mg medicated plaster as a treatment option for neuropathic pain due to limited clinical evidence to support its use.<sup>20</sup>

### **12.2.2 Scottish Medicines Consortium (SMC)**

Lidocaine 700 mg medicated plaster is accepted for restricted use within the NHS Scotland for the treatment of neuropathic pain associated with previous herpes zoster infection, PHN. The SMC state that there is only limited comparative data available for lidocaine 700 mg medicated plasters and the comparative clinical effectiveness remains unclear.<sup>6</sup> It is restricted to use in patients who are intolerant to first-line systemic therapies for PHN or where other therapies have been ineffective.<sup>6</sup>

### **12.2.3 Pharmaceutical Benefits Advisory Committee (PBAC)**

The PBAC of Australia rejected the request to list lidocaine 700 mg medicated plaster for the treatment of patients with PHN on the basis of uncertain cost-effectiveness compared with pregabalin. The PBAC considered that there was a mismatch between the restriction, the clinical treatment algorithm, the model, and the clinical trial data.<sup>27</sup>

## **13. Alternative topical treatment options and associated costs**

### **13.1 Topical treatment options for the treatment of post-herpetic neuralgia**

As previously discussed in section 8.1 above, there is limited clinical evidence to support the use of topical lidocaine 700 mg medicated plaster for PHN. There is also a lack of evidence comparing other topical therapies with lidocaine 700 mg medicated plaster. For patients receiving treatment for PHN and who are unable to tolerate or wish to avoid oral medication, NICE (CG 173) recommends the use of topical capsaicin 0.075% cream as a suitable alternative.<sup>20</sup> Capsaicin 0.075% cream is licensed for the symptomatic relief of neuralgia associated with and following herpes zoster infections i.e. PHN, after the open skin lesions have healed and also for the management of painful diabetic peripheral polyneuropathy under the supervision of a hospital specialist.<sup>21</sup> Table 4 below details the cost of lidocaine 700 mg medicated plaster versus capsaicin 0.075% cream for topical treatment of PHN.

**Table 4: Topical products and price comparison of treatments for PHN**

Product	Cost* per 30 days	Directions	Licensed indications
Lidocaine 700 mg medicated plaster (Versatis®) <sup>1</sup>	€77.52 - €232.56	Apply one to three plasters for 12 hours in a 24 hour period.	Licensed for post-herpetic neuralgia only.
Capsaicin cream 0.075% (Axsain®) 45g <sup>21</sup>	€17.52	Apply sparingly 3-4 times daily.	Licensed for PHN & painful diabetic peripheral polyneuropathy under specialist supervision.

\*Cost = reimbursed price as listed on [www.PCRS.ie](http://www.PCRS.ie). Costs are correct as of January 2021.

PHN= Post-herpetic neuralgia

Similar to lidocaine 700 mg medicated plaster, capsaicin 0.075% cream should be used after open skin lesions have healed. Both also have a similar safety and adverse-effect profile. It is important to be aware that transient burning may occur on application of capsaicin 0.075% cream. This burning is observed more frequently when applications greater than four times daily are used and hands should be washed immediately after application. Patients and carers should avoid inhalation of the vapours of the cream as transient irritation of the mucous membranes of the eyes and the respiratory tract may occur.<sup>21</sup>

### 13.2 Topical treatment options for the treatment of muscular/rheumatic pain

Topical analgesics are commonly used for the treatment of muscular and rheumatic pain e.g. non-steroidal anti-inflammatory (NSAID) gels. While lidocaine 700 mg medicated plaster is not licensed for these types of pain, there is evidence that prescribing is occurring for other forms of pain. As previously discussed, the evidence has failed to demonstrate efficacy in forms of pain other than PHN and so the treatment of lidocaine 700 mg medicated plaster in these patients should be reviewed and therapy discontinued. Table 5 below, outlines the different costs associated with licensed topical therapies for muscular and rheumatic pain compared to the cost of lidocaine 700 mg medicated plaster if used in this patient cohort. The list is not exhaustive. A full list of topical NSAID preparations and associated reimbursed cost can be found on [www.PCRS.ie](http://www.PCRS.ie)<sup>4</sup> The recommendations of this report should be applied in conjunction with clinical judgement and decision-making appropriate to the individual patient. Prescribers should refer to the drug's SmPC and the BNF to inform decisions made with individual patients.

**Table 5: Topical products and price comparisons of treatments for non-PHN indications**

Product	Cost* per original pack	Directions for use	Licensed indications
Difene® Gel 1% 50g (Diclofenac) <sup>28</sup>	€1.18	Apply 2-4 times daily for a recommended 14 days. Treatment should not exceed 6 weeks.	Licensed for trauma of the tendons, ligaments, muscles and joints & localised forms of soft tissue rheumatism.
Phorpain 5% Gel 100g (Ibuprofen) <sup>29</sup>	€4.07	Apply a thin layer up to 3 times daily. Review after 2 weeks.	Licensed as a topical analgesic and anti-inflammatory for backache, rheumatic and muscular pain, sprains, strains and neuralgia.
Fastum Gel 2.5% 100g (Ketoprofen) <sup>30</sup>	€6.69	Apply 2-3 times daily. Maximum duration should not exceed 10 days.	Licensed for local relief of pain and inflammation associated with rheumatic, muscular disorders and soft tissue injuries.
Lidocaine 700 mg medicated plasters (Versatis®) <sup>1</sup>	€77.52 - €232.56	Apply one to three plasters for 12 hours in a 24 hour period.	Licensed for post-herpetic neuralgia only.

\*Cost = reimbursed price as listed on [www.PCRS.ie](http://www.PCRS.ie). Costs are correct as of January 2021.

PHN= Post-herpetic neuralgia

### 13.3 Cochrane review on ‘Topical NSAIDs for acute musculoskeletal pain in adults’

The Cochrane Library published a review in 2010 titled “Topical NSAIDs for acute pain in adults” and this updated review in 2015 was titled “Topical NSAIDs for acute musculoskeletal pain in adults” to better reflect the content of the report.<sup>31</sup> The inclusion criteria for the 2015 review remained the same as the original analysis and consisted of randomised, double-blind trials comparing topical NSAIDs to placebo or another active treatment and outcomes close to seven days (minimum 3 days). There were 61 studies and included 8,386 participants. The results showed that gel formulations of topical diclofenac, ibuprofen, ketoprofen, piroxicam and indomethacin (not licensed in Ireland) demonstrated significantly higher rates of clinical success (more participants with at least 50% pain relief) than matching topical placebo. However, benzydamine cream did not. Three drug formulation combinations had numbers needed to treat (NNT) for clinical success below 4. For diclofenac, the Emulgel® formulation had the lowest NNT of 3.2. Ketoprofen gel had an NNT of 2.5 and Ibuprofen gel had a NNT of 3.9. All of the other drugs and formulation had a NNT above 4, indicating lower efficacy. Local skin reactions were generally mild and transient and did not differ from placebo. There were also very few systemic adverse reactions or withdrawals due to adverse effects.

In conclusion, gel formulations of diclofenac (as Emulgel®), ketoprofen and ibuprofen provided the best clinical efficacy based on NNT. Benzydamine was not significantly better than placebo (based on pooled analysis from 3 studies).<sup>31</sup>

### **13.4 Cochrane review on ‘Topical NSAIDs for chronic musculoskeletal pain in adults’**

The Cochrane Library also updated its 2012 review titled “Topical NSAIDs for chronic musculoskeletal pain in adults” in 2016.<sup>32</sup> The inclusion criteria for this review differed from that of the review of topical NSAIDs for ‘acute’ musculoskeletal pain in adults. For inclusion, studies needed to be randomised, controlled, double-blind trials comparing topical NSAIDs with placebo or other active treatment for chronic musculoskeletal pain, with at least 10 participants per treatment arm and duration of at least two weeks, but ideally 6 weeks or longer. There were 33 studies included in this review involving 10,873 participants comparing topical NSAIDs to each other, placebo, another oral NSAID or alternative topical remedy. All studies examined topical NSAIDs for use in osteoarthritis. In studies lasting 6 to 12 weeks, topical diclofenac and topical ketoprofen were significantly more effective at reducing pain. With regards to diclofenac, the NNT for clinical success based on 6 trials was 9.8. With regards to topical ketoprofen, the NNT based on 4 trials was 6.9. There was too little information for analysis of the other individual topical NSAIDs. These efficacy results were almost completely derived from patients with knee osteoarthritis. In conclusion, topical diclofenac and ketoprofen provide good levels of pain relief in osteoarthritis but there is little evidence for other chronic painful conditions.<sup>32</sup>

## **14. Health Technology Management**

In September 2017, a reimbursement application system for lidocaine 700 mg medicated plasters was introduced by the HSE.<sup>33</sup> The reimbursement of lidocaine 700 mg medicated plaster is approved for patients with PHN following the submission of an online application detailing information relating to the patient’s diagnosis and treatment. For unlicensed indications there is a requirement for prescribers to outline the exceptional circumstances of unmet clinical need for reimbursement.<sup>33</sup> The online reimbursement application system requests clinical information such as the underlying diagnosis, the location(s) of pain, the number of medicated plasters required per month, other therapies used and any extenuating factors to be taken into consideration.<sup>34</sup>

This process represents the ongoing use of health technology management (HTM) by the HSE to ensure evidence based use of a medication.<sup>35</sup> The increasing expenditure on lidocaine 700mg medicated plaster detailed in section 11 was largely related to prescribing for unlicensed indications

such as osteoarthritis, rheumatoid arthritis, deep venous thrombosis, and angina pectoris.<sup>34</sup> HTM in this case has resulted in a reduction in expenditure due to indication based reimbursement approval for PHN, and the use of a managed approach for unlicensed indications.

## **15. Conclusion**

Although licensed to treat post-herpetic neuralgia, the clinical evidence of efficacy for lidocaine 700 mg medicated plaster is extremely limited. International guidelines that consider the treatment of PHN give conflicting recommendations for the use of lidocaine 700 mg medicated plaster.

There is also limited clinical evidence for the use of lidocaine 700 mg medicated plaster outside of its licensed indication. The national and international guidelines that were reviewed, and which consider the treatment of other chronic pain types, do not support the use of lidocaine 700 mg medicated plaster.

The current reimbursement of lidocaine 700 mg medicated plasters through a HTM approach helps to ensure evidence-based and cost-effective utilisation of healthcare resources and promotes best practice prescribing.

Tips and tools to support the appropriate prescribing of lidocaine 700mg medicated plaster are available online at:

<https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/prescribing-tips-and-tools/>

## MMP recommendations on the use of lidocaine 700 mg medicated plaster

- ✓ Prescribing of lidocaine 700 mg medicated plaster should be restricted to patients diagnosed with post-herpetic neuralgia.
- ✓ Treatment should be reviewed after 2-4 weeks and stopped if ineffective or if the relieving effect is solely due to protection of the area by the plaster.
- ✓ Prescribers should ensure all patients are using the patch correctly and have at least a 12 hour free period every 24 hours.
- ✓ Patients on long-term therapy should be assessed for continued need and aim to have treatment discontinued or alternatively, try to have a longer plaster-free period between treatments.
- ✓ NICE (CG 173) does not recommend the use of topical lidocaine 700 mg medicated plaster. For patients who wish to avoid or who are unable to tolerate oral medication for PHN, capsaicin 0.075% cream is recommended.
- ✓ MMP does not recommend the use of topical lidocaine 700 mg medicated plaster for unlicensed indications due to lack of clinical evidence.

## 16. References

1. Gruenthal Pharma Ltd. Versatis® 700mg medicated plaster. Summary of product characteristics. Last revised July 2018. Available: [https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA2242-007-001\\_09022021095736.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2242-007-001_09022021095736.pdf) [Accessed 5th Feb 2021].
2. Primary Care Reimbursement Service Drug Enquiry. Data on file.
3. HSE Primary Care Reimbursement Service. PCRS Prescribing report. On file.
4. Primary Care Reimbursement Service List of reimbursable items. Available: <https://www.sspcrs.ie/druglist/pub>. [Accessed 26th Jan 2021].
5. Irish Pharmaceutical Healthcare Association. Versatis® 700mg medicated plaster summary of product characteristics document history. SPC update Feb 2018. Available: <https://www.medicines.ie/medicines/versatis-700-mg-medicated-plaster-34171/doc-history> [Accessed 26th Feb 2021].
6. Scottish Medicines Consortium (SMC). Lidocaine 5% medicated plaster 5% (Versatis®) 334/06; August 2008. Available: [https://www.scottishmedicines.org.uk/media/1934/lidocaine\\_5\\_per\\_cent\\_medicated\\_plaster\\_versatis\\_resubmission\\_final\\_july\\_2008doc\\_for\\_website.pdf](https://www.scottishmedicines.org.uk/media/1934/lidocaine_5_per_cent_medicated_plaster_versatis_resubmission_final_july_2008doc_for_website.pdf). [Accessed 19th Apr 2021].
7. Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press Available from: <https://www.medicinescomplete.com/#/content/bnf/772587537?hspl=versatis#DMD11052611000001103> [Accessed 15th Jan 2021].
8. Galer BS, Rowbotham MC, Perander J, et al. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*. 1999;80(3):533-538.
9. Bundesinstitut für Arzneimittel und Medizinprodukte. Public Assessment Report: Mutual Recognition Procedure. Versatis 5% wirkstoffhaltiges Pflaster Lidocain Grünenthal 5% wirkstoffhaltiges Pflaster (Lidocaine) 2019. Available: [https://mri.cts-mrp.eu/Human/Downloads/DE\\_H\\_5733\\_001\\_PAR.pdf](https://mri.cts-mrp.eu/Human/Downloads/DE_H_5733_001_PAR.pdf) [Accessed 18th Mar 2021].
10. Baron R, Mayoral V, Leijon G, et al. 5% lidocaine medicated plaster versus pregabalin in postherpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. *Current medical research and opinion*. 2009;25(7):1663-1676.
11. Derry S, Wiffen PJ, Moore RA, et al. Topical lidocaine for neuropathic pain in adults. *Cochrane Database of Systematic Reviews*. 2014(7).
12. Department of Health. Pharmacological Management of Cancer Pain in Adults. National Clinical Guideline No. 9. November 2015. ISSN 2009-6259. Available: <https://assets.gov.ie/11597/e701fec1048245cdb9c6f98b00a3bcb6.pdf> [Accessed 15th Jan 2021].
13. Fleming JA, O'Connor BD. Use of lidocaine patches for neuropathic pain in a comprehensive cancer centre. *Pain Research and Management*. 2009;14(5):381-388.
14. Garzón-Rodríguez C, Merchan MC, Calsina-Berna A, et al. Lidocaine 5% patches as an effective short-term co-analgesic in cancer pain. Preliminary results. *Supportive Care in Cancer*. 2013;21(11):3153-3158.
15. McGuinness J, Robinson A, Ward J. The lidocaine plaster: does it have a role in palliative care? *European Journal of Palliative Care*. 2012;19(1):10-13.
16. National Institute for Health and Care Excellence (NICE) April 2021. Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. Available: <https://www.nice.org.uk/guidance/ng193/resources/chronic-pain-primary-and-secondary-in-over-16s-assessment-of-all-chronic-pain-and-management-of-chronic-primary-pain-pdf-66142080468421> [Accessed 19th Apr 2021].

17. National Institute for Health and Care Excellence (NICE) Clinical Guideline 177. 2014, updated Dec 2020. Osteoarthritis: care and management. Available: <https://www.nice.org.uk/guidance/cg177/resources/osteoarthritis-care-and-management-pdf-35109757272517>. [Accessed 18th Jan 2021].
18. Teva B.V. Zacin 0.025% w/w cream. Summary of product characteristics. Last revised Mar 2021. Available: [https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA1986-090-001\\_18032021162702.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1986-090-001_18032021162702.pdf) [Accessed 19th Apr 2021].
19. National Institute for Health and Care Excellence (NICE) National Guideline 59. 2016, updated Sep 2020. Low back pain and sciatica in over 16s: assessment and management. Available: <https://www.nice.org.uk/guidance/ng59/resources/low-back-pain-and-sciatica-in-over-16s-assessment-and-management-pdf-1837521693637> [Accessed 18th Jan 2021].
20. National Institute for Health and Care Excellence (NICE) Clinical Guideline 173. 2013, updated Sep 2020. Neuropathic Pain in Adults: Pharmacological Management in non-specialist setting. Available: <https://www.nice.org.uk/guidance/cg173>. [Accessed 18th Jan 2021].
21. Teva B.V. Axsain 0.075% w/w cream. Summary of product characteristics. Last revised Mar 2021. Available: [https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA1986-088-001\\_19032021151124.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1986-088-001_19032021151124.pdf) [Accessed 19th Apr 2021].
22. PrescQIPP Community Interest Company. 2017. Bulletin 200: Lidocaine plasters (DROP-List) Available: <https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f1415%2fb200-lidocaine-plasters-drop-list-30.pdf> [Accessed 31st Jan 2021].
23. Moulin D, Boulanger A, Clark A, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Research and Management*. 2014;19(6):328-335.
24. Moulin D, Clark A, Gilron I, et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Research and Management*. 2007;12(1):13-21.
25. Attal N, Cruccu G, Baron Ra, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European journal of neurology*. 2010;17(9):1113-e1188.
26. National Centre for Pharmacoeconomics (NCE). Lidocaine 5% plaster Versatis®. Available: <http://www.nce.ie/drugs/lidocaine-5-plasters-versatis/>. [Accessed 27th Jul 2016].
27. Pharmaceutical Benefits Advisory Committee (PBAC). Public summary document March 2015. Available: <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/lignocaine-psd-march-2015.pdf>. [Accessed 26th Jul 2016].
28. Glenwood GmbH Difene 1% w/w gel. Summary of product characteristics. Last revised Jan 2021. Available: [https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA2256-001-005\\_26012021151059.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2256-001-005_26012021151059.pdf) [Accessed 19th Jan 2021].
29. Amdipharm Limited Phorpain 5% w/w gel. Summary of product characteristics. Last revised Feb 2021. Available: [https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA1142-026-001\\_05022021134649.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1142-026-001_05022021134649.pdf) [Accessed 26th Feb 2021].
30. A Menarini Fastum 2.5% w/w gel. Summary of product characteristics. Last revised Oct 2015. Available: [https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA1142-026-001\\_05022021134649.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1142-026-001_05022021134649.pdf) [Accessed 26th Feb 2021].
31. Derry S, Moore RA, Gaskell H, et al. Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews*. 2015(6).
32. Derry S, Conaghan P, Da Silva JA, et al. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2016;4(4):Cd007400.
33. Smith A, Doran S, Daly M, et al. Effect of an Online Reimbursement Application System on Prescribing of Lidocaine 5% Medicated Plaster in the Republic of Ireland. *Applied Health Economics and Health Policy*. 2020:1-8.

34. Smith A, Barry M. Combining health technology assessment and health technology management to deliver cost-effective prescribing and cost containment—the Irish experience. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2020;20(5):431-436.
35. Primary Care Reimbursement Service. GP Circular 032/17. Reimbursement of lidocaine 5% plasters (Versatis®) effective 1st September 2017. Available from: <https://www.hse.ie/eng/staff/pcrs/circulars/gp/032-2017-reimbursement-of-lidocaine-versatis.pdf> [Accessed 22nd Mar 2021].