Original article

Safety and efficacy outcomes of long-term treatment up to 4 years with 5% lidocaine medicated plaster in patients with post-herpetic neuralgia

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5% lidocaine medicated plaster – Drug therapy – Follow-up study – Lidocaine/therapeutic use/adverse effects – Long-term treatment – Neuralgia – Post-herpetic

Abstract

Objective:
Prospective evaluation of the long-term efficacy and safety of the 5% lidocaine medicated plaster in patients with post-herpetic neuralgia (PHN).

Research design and methods:
Patients with persisting pain for ≥ 3 months after acute herpes zoster and a baseline pain intensity of at least 4 on an 11-point numerical rating scale (NRS 0–10) were treated with 5% lidocaine medicated plasters for up to 5 years and monitored in regular intervals. Efficacy parameters are presented for the first 4 years and include patients’ recall of pain relief (6-point verbal rating scale (VRS), clinical global impression of change (CGIC), patients’ global impression of change (PGIC), and the global evaluations of study medication. Safety parameters (clinical examination, skin evaluation, laboratory) and adverse events (AEs) were assessed at regular visits.

Clinical trial registration:
KF10004/02.

Results:
A total of 102 patients continuing from a 1 year main study period were included in an extension phase of up to 3 years. Ten patients (9.8%) dropped out due to lack of efficacy and 9 patients (8.8%) due to treatment-related AEs; 56 patients (54.9%) left the study for non-treatment-related reasons. Twenty-seven patients (26.4%) were still under treatment after a total treatment period of 4 years. On average, a pain relief of at least 4.3 (between moderate and a lot) was achieved throughout the study. At all visits the CGIC and the PGIC were much or very much improved in about 80% of patients. At the final visit, study medication was rated at least to be good by 91% of physicians and 89% of patients. Drug-related adverse events (DRAEs) were reported in 19 of 102 patients, mainly mild to moderate localized skin reactions. There were no hints for a reduced analgesic effect or an increase of DRAEs with long-term treatment.

Conclusions:
This study demonstrates that long-term treatment of ≥12 months with the 5% lidocaine medicated plaster is effective and well tolerated in PHN patients. These findings support the recommendations to use the 5% lidocaine medicated plaster as baseline therapy for localized neuropathic pain after herpes zoster infection (PHN).

Introduction

The limited effectiveness of available treatment options, the occurrence in an elderly, multi-morbid population, and the chronicity of PHN are posing a
substantial challenge for the treating physician. PHN can persist for many years and may even be a life-long problem with serious impairment of patient’s quality of life1–4.

The 5% lidocaine medicated plaster for treatment of PHN has been available in the USA since 1999 and has been introduced into most European Union countries. It consists of a 10 × 14 cm² hydrogel matrix carrying 700 mg of lidocaine of which only 3 ± 2% is systemically absorbed when applied for 12 hours to undamaged skin. In several clinical studies5–12 the 5% lidocaine medicated plaster was found to provide clinically relevant pain relief in 51.7%6 to 65.3%5 of patients with PHN. Relevant differences regarding gender or ethnicity are not reported. Pain relief seems to be induced by an isolated but only partial block of Aβ- and C-fibers. Aβ function, however, seems not to be affected13. Drug-related adverse events were generally infrequent, predominantly comprising reversible, local skin reactions14. Specific advantages of the 5% lidocaine medicated plaster include the pharmacological action being limited to the site of application, a reduced risk of systemic toxicity, and a reduced potential of drug–drug interactions with the opportunity to combine this topical treatment option with systemic treatments without the need for dose adjustments. Today several European and USA guidelines recommend it as first line therapy for PHN15–17.

The long-term safety and efficacy of the 5% lidocaine medicated plaster was investigated in an open-label multicenter phase III study. In this ‘main study’ more than 200 patients suffering from PHN received the treatment for up to 1 year. The results of the main study have been published elsewhere7. In this manuscript we report on the long-term outcomes of a subset of 102 patients who needed continued treatment and agreed to participate in an extension phase following the 1 year main study period.

This is the first prospective, systematic study with a significant number of PHN patients observed over a prolonged and clinically meaningful treatment period. The objectives were to monitor the long-term safety, the persistence of efficacy, and the general satisfaction of clinicians and patients with the 5% lidocaine medicated plaster for PHN.

Patients and methods

Study design

The study was an open-label, multicenter, phase III study including main study and extension period. It was conducted in 12 European countries (Austria, Croatia, France, The Netherlands, Poland, Spain, UK, Belgium, Germany, Portugal, Italy and Russia).

Patients were recruited for the main study between July 2003 and July 2005 and received the treatment for 12 months7. Patients who were satisfied with the treatment but still needed continued application after 12 months could participate in the open-ended extension phase. For many patients this was an opportunity to bridge the time gap until the 5% lidocaine medicated plaster became commercially available and reimbursed in their countries. The extension phase was officially closed by the sponsor in February 2009. This manuscript presents efficacy data of all patients who had participated in the main study and received further extended treatment of up to 3 years i.e. had a continuous treatment with 5% lidocaine medicated plaster of up to 4 years. Due to the small group sample size no efficacy data is presented for the study population of more than 4 years’ treatment. Safety data is included.

During the first 12 months of the main study, visits were performed at week 1, 6, 12, 18 then every 8 weeks (week 26, 34, 42) and finally at week 52. In the extension phase regular visits were conducted in 6 month intervals as long as treatment was continued. For practical reasons, during the extension phase subjects attended their visits up to 2 weeks before or after the initially scheduled visit dates. When patients dropped out a final visit with full efficacy and safety assessments was performed.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before participating in the study and before entering the extension phase.

Patients

To be eligible for enrolment, patients were required to be at least 50 years old and to suffer from PHN, defined as neuropathic pain persisting for ≥3 months after healing of a herpes zoster skin rash. Eligible patients had an average baseline pain intensity of at least 4 on an 11-point NRS (0 = no pain to 10 = worst pain imaginable), recalled from the previous week before the enrolment visit.

Patients were excluded from the study if they met one of the following criteria: known hypersensitivity to lidocaine or amide local anesthetics; active herpes zoster lesion or dermatitis at the PHN pain site; a previous neurological ablation by nerve block or surgical intervention to control post-zoster pain; current usage of topical analgesics on the area affected by PHN; presence of other severe pain conditions, presence of severe hepatic or renal disorders; current use of immunosuppressants; or treatment for HIV or cancer.

Initially, 259 patients were enrolled in the study and 143 completed the first 12 months of treatment according to the study protocol7. A total of 102 patients continued treatment for longer than 1 year and were included in the present study.
Patient disposition

Of the 259 patients who were initially enrolled in the study, 102 patients continued in the extension period, i.e., were treated for longer than 12 months and included into the SAF. Of these, 90 patients had at least one pain relief assessment in the extension period and qualified for inclusion into the full analysis set (FAS; Figure 1). Twenty-six patients were still participating in the study at the time it was officially terminated by the sponsor. The longest duration between first (main study) and last visit reported in one patient was 5.44 years. The number of patients who were assessed at each regular visit during the extension period is given in Table 1.

A total of 76 of the included 102 patients discontinued the topical treatment before the study termination; the reasons for discontinuations are listed in Table 2. Of these 76 discontinuations, 10 patients (9.8%) dropped out due to lack of efficacy, 9 patients due to adverse events, and 27 patients for other reasons including when the 5% lidocaine medicated plaster became commercially available in their countries.

Twenty-seven (27/102) patients had a treatment duration of at least 4 years, sixteen of 4.5 years, two of 5 years, and one of 5.44 years. A final visit could be conducted in 84 patients who terminated the trial.

Demographic and clinical characteristics of patients

Of the 102 patients participating in the extension phase, 65 (63.5%) were female and 37 (36.3%) were male. The mean age (±SD) was 71.3 ± 9.2 years. With the exception of one patient with Latin-American ethnicity, all patients were Caucasian Europeans. Demographic parameters at baseline are summarized in Table 3.

The duration of PHN before enrolment into the study showed a wide range starting from 0 months to about 20 years. On average (±SD) the patients included in the study had been suffering from PHN for 31.4 months (±36.1) and the mean onset of herpes zoster was 34.6 (±37.0) months before screening (range 3–243 months).

Table 2. Reasons for discontinuations during the extension phase.

<table>
<thead>
<tr>
<th>Reason</th>
<th>N</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>102</td>
<td>100</td>
</tr>
<tr>
<td>Total withdrawalsa</td>
<td>76</td>
<td>74.5</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>10</td>
<td>9.8</td>
</tr>
<tr>
<td>Withdrawal of informed consent</td>
<td>24</td>
<td>23.5</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td>Adverse events</td>
<td>9</td>
<td>8.8</td>
</tr>
<tr>
<td>Death</td>
<td>8</td>
<td>7.8</td>
</tr>
<tr>
<td>Other reasonsb</td>
<td>27</td>
<td>26.5</td>
</tr>
</tbody>
</table>

aPatients could have more than one reason for discontinuation.
bOther reasons include but are not limited to: subject moved away, lost to follow-up, subject felt too old for the trial, prescription of 5% lidocaine medicated plaster, compassionate use program, unable to use plasters because of stoma, non-compliance, PHN resolved.

Table 3. Demographic parameters at baseline and data sets for statistical analysis.

<table>
<thead>
<tr>
<th></th>
<th>Safety set (n = 102)</th>
<th>Full analysis set (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female N (%)</td>
<td>65.0 (63.7)</td>
<td>58 (64.4)</td>
</tr>
<tr>
<td>Male N (%)</td>
<td>37 (36.3)</td>
<td>32 (35.6)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>71.3 (9.2)</td>
<td>70.9 (9.3)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>26.6 (4.4)</td>
<td>26.9 (4.3)</td>
</tr>
</tbody>
</table>

BMI = body mass index; SD = standard deviation.
Nearly all patients (93.8%) experienced allodynia at baseline, which is representative of a patient population with PHN.

Concomitant diseases and medication

The most common concomitant disease was hypertension in 60 of 102 patients (58.8%). Other common diseases at baseline were type 2 diabetes mellitus (in 15 patients [14.7%]), coronary artery disease and myocardial ischemia (in 12 patients [11.8%] each), hypercholesterolemia and osteoporosis (in 11 patients [10.8%] each), and osteoarthritis (in 10 patients [9.8%]). Eight of the 102 patients (7.8%) had a myocardial infarction in their medical history. Fifty-one patients (50.0%) had undergone surgical and interventional procedures.

Sixty of 102 patients (58.8%) were taking at least one concomitant medication for PHN. The most common types of medications used were antiepileptic drugs, taken by 38/102 patients (37.3%), anti-inflammatory and antipyretic drugs (paracetamol, metamizol) taken by 35 patients (34.3%) and antidepressants taken by 12 patients (11.8%).

During the whole trial period, the numbers of patients taking concomitant medication for their PHN differed between 43 (42.2%) at trial enrolment, 60 (58.8%) at any time during the treatment period, and 56 (54.9%) at the final assessment. This increase was mainly due to the increase in the prescriptions of analgesics, anti-inflammatory drugs, and antipyretics. The changes in concomitant medication should not have affected the assessment of 5% lidocaine medicated plaster as the medications were only taken during a limited period of time (e.g. local anesthetics for dental treatments) and/or were considered not to influence the severity of neuropathic pain (e.g. paracetamol for treatment of fever, low dose acetylsalicylic acid for cardiac ischemia).

Treatment

Patients applied up to three 5% lidocaine medicated plasters on the painful skin area for up to 12 hours per day, with a plaster-free interval of at least 12 hours per day to ensure the skin was rested between applications. The number of plasters used by each individual patient was dependent on the size of the painful area. Patients were allowed to continue taking other medication for the treatment of PHN, including analgesics and co-analgesics, with the exception of topical analgesics or any additional lidocaine therapy for PHN.

Exposure to treatment

On average patients applied 1.8 ± 0.6 (SD) plasters per day. There was a tendency towards the application of a lower number of plasters per day in the later study phase (Figure 2).

Efficacy and safety assessments

No primary endpoint was planned for this study. A descriptive analysis for all trial variables was performed. The following assessments were regularly performed.
Allodynia severity rating

Allodynia was rated only at the first visit of the main study by the investigator using the following categorical scale: 0 = no pain or discomfort to touch; 1 = uncomfortable, but tolerable to touch; 2 = painful; 3 = extremely painful, patient can not stand touching. To test allodynia intensity a standardized brush (N12) was used, delivered by the sponsor. Five stimuli were to be applied with an interval of at least 5 seconds and to a region of skin 2 cm long.

Pain relief

Pain relief was measured according to the patient’s recall of pain relief experienced during the previous week before each visit using a 6-point VRS (1 = worse pain, 2 = no pain relief, 3 = slight relief, 4 = moderate relief, 5 = a lot of relief, 6 = complete relief).

Global Impression of Change (CGIC and PGIC)

Global change was assessed by the investigator using the clinical global impression of change (CGIC) questionnaire. The patient’s global impression of change (PGIC) was assessed only during the extension phase.

CATEGORIES FOR BOTH QUESTIONNAIRES WERE: VERY MUCH IMPROVED, MUCH IMPROVED, MINIMALLY IMPROVED, NO CHANGE, MINIMALLY WORSE, MUCH WORSE AND VERY MUCH WORSE.

Global evaluation of the lidocaine 5% plaster by clinicians and patients

At each visit, investigator and patient were asked how they rated the study medication. Rating categories were poor, fair, good, very good, and excellent.

Safety parameters

Safety evaluations comprising brief physical examinations (including a brief neurological examinations at the final/withdrawal visit), skin examination, and vital signs (in supine position after 5 minutes rest: blood pressure systolic/diastolic, heart rate) were performed at each visit. Clinical laboratory examinations were performed at the first and final visit of the extension phase and included hematology (hemoglobin, hematocrit, white blood cell count, red blood cell count, platelet count), biochemistry (total bilirubin, ALT, AST, gamma-glutamyltransferase, creatinine, total protein, glucose, sodium, potassium, calcium, blood urea nitrogen, creatine kinase, lactate dehydrogenase, and uric acid), and urinalysis (specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, leukocytes, nitrite). A microscopic examination was performed at central lab if a urine dipstick test was abnormal.

Adverse events

Adverse events (AEs) were continually monitored for, or asked about, at each visit. Every AE or abnormal laboratory result considered clinically significant was followed up until it resolved, became stable, or could be explained due to other known causes (i.e., concurrent condition or medication) and clinical judgment indicated that further evaluation was not warranted.

AEs and serious adverse events (SAEs) were classified according to GCP standards. The causal relationship of an AE to the 5% lidocaine medicated plaster was classified by the investigator using the criteria published by Edwards and Birrell. Drug-related adverse events (DRAEs) were defined when the causal relationship was at least possibly related. Discontinuations due to AEs were also reported.

Drug accountability

For each patient, the number of plasters dispensed and returned at the following visit was documented in the first 12 months of the trial. For the extension period, the number of boxes dispensed at each visit was documented along with the number of complete boxes returned at the final visit. The number of single unused plasters not returned/returned was calculated.

Data management and statistical analyses

Specific patient questionnaires were filled in by patients independently. Clinical examination and study procedures were performed by the treating physician.

Efficacy and safety data were summarized using descriptive statistics. All analyses were generated using the SAS Version 8.2 program.

Data were analyzed for different analysis populations: safety data analyses were performed on the safety analysis set (SAF), which included patients receiving any amount of 5% lidocaine medicated plaster in the extension period. Efficacy data presented are based on the analysis using the full analysis set (FAS), which comprised a subset of patients with at least one pain relief assessment in the extension period.

Results of efficacy variables were presented for the first 4 years of treatment only, because the number of patients continuing for longer than 4 years was considered to be too small (n = 2) for a reasonable evaluation. The analysis of safety variables was performed for the full treatment duration.
Results

Efficacy results

This manuscript presents efficacy data of all patients who had a continuous treatment with 5% lidocaine medicated plaster of up to 4 years. Due to the small sample size no efficacy data is presented for the study population of more than 4 years treatment. Safety data is included.

Pain relief

A mean pain relief (±SD) of 4.3 (±0.9) had been achieved already after 6 weeks of treatment in the main period of this trial, which translates into a pain relief between 'moderate' and 'a lot'. This level of pain relief was maintained throughout the 1 year main study and the subsequent extension phase (Figure 3).

CGIC and PGIC

The evaluation of the global clinical impression of change by the investigators was positive throughout the study (Figure 4). At each visit, the investigators rated the change in patient’s condition as ‘very much improved’ or ‘much improved’ in about 80% of patients. The patients’ corresponding global impression of change (PGIC), which was evaluated only during the extension period, was

![Figure 3. Average pain relief scores (±SD) during the 48 months of treatment and at the final visit.](image)

![Figure 4. Clinical Global Impression of Change. Evolution over time.](image)
similarly positive (Figure 5). At each visit the proportion of patients reporting ‘very much’ or ‘much’ improvement ranged between 71% (49/69 at 24 months) and 93% (40/43 at 36 months).

Global evaluation of the 5% lidocaine medicated plaster

At the final visit, 91% (67/74) of the investigators and 88% (67/76) of the patients rated the 5% lidocaine medicated plaster as excellent, very good, or good (Figure 6). This positive evaluation pattern remained similar at all assessments.

Safety results

No effects on vital signs or safety laboratory parameters were attributed to treatment during the study.

During the complete treatment duration of more than 5 years (main study and extension phase), 79 out of 102 patients (77.5%; SAF) experienced 384 AEs. The most frequently reported AEs were back pain (n = 9); hypertension (n = 8); bronchitis, dizziness, headache, and nasopharyngitis which occurred in 7 patients each; followed by urinary tract infection in 5 patients; and application site hypersensitivity, diarrhea, influenza-like illness, myocardial infarction, pneumonia, sciatica, and Type II diabetes mellitus in 4 patients each. All other AEs occurred in ≤3 patients each. The majority of AEs were of mild (113 of 384, 29.4%) or moderate intensity (194 of 384, 50.5%), while 77 of the 384 AEs (20.1%) were severe.

Thirty of 384 events (7.8%) in 19 of 102 patients (18.6%) were reported by the investigators as probably/likely related (n = 13) or possibly related (n = 17) to the use of 5% lidocaine medicated plaster. All DRAEs are listed in Table 4. There was no increased frequency of DRAEs in the 36 month extension period compared to the first 12 months of treatment.

DRAEs were mainly administration site reactions, including pruritus, skin reaction or irritation, erythema and dermatitis. After removal of the plaster, skin reactions resolved without further treatment in all patients. In addition dyseusia, myalgia, decreased blood glucose, unilateral deafness, tinnitus, and tachycardia were reported as possibly drug-related by the investigators. However, this relationship was considered unlikely by the sponsor, because the systemic availability of topical lidocaine is known to be very low (see Discussion) and the concomitant diseases and/or related treatments could explain the respective AEs in these patients.

In general, the spectrum of SAEs was representative for that of a multi-morbid elderly population. Twenty-eight of
102 patients (27.5%) experienced 54 SAEs during the combined treatment period (main study and extension period). Of these, 10 SAEs (myocardial infarction [n = 2], glioblastoma, pancytopenia, pneumonia, respiratory failure and cardiovascular insufficiency [cardiopulmonary failure], death due to an unknown cause, or after metastatic neoplasm and multi-organ failure [n = 1 each]) had a fatal outcome in eight patients (7.8%). None of the SAEs was causally related to the study medication.

Only three of 102 patients terminated the study due to DRAEs, all of which were application site hypersensitivities.

### Discussion

In this prospective study the 5% lidocaine medicated plaster proved to be a safe and effective long-term treatment for patients with PHN.

During the 4.5 years of the extension period, only three patients discontinued the treatment for DRAEs (one patient had a DRAE and lack of efficacy).

Already in the first weeks of the main study patients gained a mean pain relief score of at least 4.3 points, meaning moderate (4) to a lot of (5) pain relief. This favorable result was maintained throughout the 1 year main study and also during the extension phase. At the final visit clinicians and patients rated the global evaluation of the treatment to be good, very good or excellent in about 90% of cases (Figure 6). The ratings of patients’ and clinician’s global impression of change were correspondingly positive. No hints of the development of tolerance to the analgesic effect were observed.

The proportion of patients with an initial treatment response to topical lidocaine may be due to their primary sensory profile and to a lesser extent to the underlying neuropathic pain syndrome (e.g. PHN, diabetic polyneuropathy)\(^1\). In our study no quantitative sensory testing was performed; however, the high initial presence of mechanical allodynia in our patient population may help to understand the positive treatment response.

The safety profile of the 5% lidocaine medicated plaster was favorable. During the long treatment period no treatment-related SAEs were reported. DRAEs emerged in only 19 of 102 patients (18.6%) 14 of which were application site reactions. The other DRAEs such as hypoglycemia, deafness, dysgeusia, myalgia, tachycardia, and urticaria were classified by investigators as possibly drug-related, probably because these are known side effects of lidocaine when administered systemically. However, a causal relationship with the study medication is unlikely, because the systemic availability of lidocaine resulting from the 5% lidocaine medicated plaster was found to be very low in previous studies. In particular, a population kinetics analysis of the clinical efficacy studies in patients suffering from PHN revealed a mean maximum lidocaine plasma concentration of 45 ng/ml after application of the

<table>
<thead>
<tr>
<th>Combined study period</th>
<th>Main study phase</th>
<th>Extension phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of patients</strong></td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>Patients with DRAE</td>
<td>19</td>
<td>18.6</td>
</tr>
<tr>
<td>Application site reactions (total)</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>4</td>
<td>3.9</td>
</tr>
<tr>
<td>Erythema</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>Irritation</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>2.9</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Blood glucose decreased</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Deafness unilateral</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>1.0</td>
</tr>
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</table>

Combined study period: DRAEs during the combined main and extension phase (4 years of treatment); main study phase: DRAEs occurring during the first 12 months of treatment; extension phase: DRAEs occurring during the 3 year extension period.
three plasters simultaneously for 12 hours per day for up to 1 year. In comparison, the therapeutic plasma concentration for tinnitus suppression (>1.5μg/ml) is more than 20 times higher and plasma levels lower than 5μg/ml are considered non-toxic.

In this elderly, multi-morbid, multi-medicated patient group, the local topical plaster application turned out to be an important advantage regarding the low risk of systemic adverse reactions and the negligible risk of drug interactions with concomitant medication. The combination of the 5% lidocaine medicated plaster with oral medication for PHN such as anticonvulsants was shown to further improve the patients’ condition, achieving a meaningful pain relief without inducing adverse drug–drug interactions. This advantage allows using the 5% lidocaine medicated plaster as a baseline medication which can be combined with additional first line treatments if necessary. The medication was recommended as first line treatment for localized neuropathic pain in recently issued treatment guideline.

The results of this study are generally in line with previous clinical studies and the long-term observations of individual patients published by Garnock-Jones and Keating (2009), Gailer and Gammaitoni (2003) and Wilhelm et al. (2011). The authors reported treatment with the 5% lidocaine medicated plaster in PHN patients of up to 7 and 5 years, respectively. Their conclusion was that the plaster provides long-term benefit for PHN patients with a high degree of patient satisfaction, minimum side effects and without the development of analgesic tolerance.

Limitations of this study result from the necessary methodological compromises to facilitate the long-term participation of patients in this study. To reduce the burden of filled in various questionnaires, the efficacy parameters assessed in the extension period were restricted to easy and simple scores, and no detailed assessments of quality of life or sleep were performed. The contribution of concomitant medication to the overall pain relief is uncertain. The inclusion criteria of the main study accepted a wide range of concomitant drugs and no subgroup analysis for patients with concomitant medication was performed.

The overall frequencies of concomitant medication at the first visit, after 12 months and at the final visit of the extension period do not indicate significant changes of concomitant drugs over time but a rather stable treatment situation.

Conclusions

The 5% lidocaine medicated plaster provided substantial pain relief for patients suffering from PHN with a low incidence of DRAEs, mainly reactions at the application site. The favorable benefit/risk ratio was sustained for 4 years of treatment. The 5% lidocaine medicated plaster is of specific benefit in elderly, multi-morbid patients with an elevated risk of DRAEs and drug–drug interactions. The results of this study support the recommendations available in the literature to use 5% lidocaine medicated plaster as baseline therapy for patients with localized neuropathic pain after herpes zoster infection.

Transparency

Declarations of funding

This study was initiated for regulatory purposes and funded by Grünenthal GmbH, Aachen.

Declaration of financial/other relationships

R.S. has disclosed that he has received grants from Grünenthal, Astell and Allergan, and is on the Speakers’ Bureaus of MSD and Janssen-Cilag. G.H. has disclosed that he has received sponsorship from Grünenthal. I.T., S.K., and B.B. have disclosed they are employees of Grünenthal. R.B. has disclosed that he has received honoraria from Allergan, Schwarz, Pfizer, Grünenthal, Medtronic, Mundipharma, Eisai, Sanofi-Pasteur and Genzyme and received research funding from Pfizer, Grünenthal and Genzyme.

CMRO peer reviewers have received honoraria for their review work on this manuscript, and have disclosed that they have no other relevant financial relationships.

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