Public Assessment Report

Repeat-Use Mutual Recognition Procedure

VERSATIS 5% MEDICATED PLASTER
LIDOCAINE 5% MEDICATED PLASTER

(Lidocaine)

Procedure No: UK/H/1040-1041/001/E03

UK Licence No: PL 21727/0016-0017

Grunenthal Limited
LAY SUMMARY
VERSATIS 5% MEDICATED PLASTER
LIDOCAINE 5% MEDICATED PLASTER
(lidocaine)

This is a summary of the Public Assessment Report (PAR) for Versatis/Lidocaine 5% Medicated Plaster (PL 21727/0016-0017). It explains how Versatis/Lidocaine 5% Medicated Plaster was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Versatis/Lidocaine 5% Medicated Plaster.

For practical information about using Versatis/Lidocaine 5% Medicated Plaster, patients should read the package leaflet or contact their doctor or pharmacist.

Versatis/Lidocaine 5% Medicated Plaster will be referred to as ‘Versatis/Lidocaine’ in this report.

What is Versatis/Lidocaine and what is it used for?
Versatis/Lidocaine is used to provide relief in a painful skin condition called post-herpetic neuralgia. This is generally characterised by localised symptoms such as burning, shooting pain or stabbing pain.

Versatis/Lidocaine is not recommended for use in patients under 18 years of age.

How does Versatis/Lidocaine work?
The active ingredient in Versatis/Lidocaine is lidocaine, which is a local anaesthetic. Lidocaine works by reducing pain in the skin.

How is Versatis/Lidocaine used?
Versatis/Lidocaine is available as a medicated plaster and the route of administration is application to the skin. Versatis/Lidocaine 5% Medicated Plasters should be applied to the painful area of skin.

This medicine should be used exactly as advised by the prescribing doctor. The patient should check with the doctor or pharmacist if unsure.

The usual daily dose is to use between one and three plasters of the size of the painful areas of skin. Versatis/Lidocaine may be cut into smaller pieces to fit the affected area. Not more than 3 plasters should be used at the same time. The plasters should be removed after 12 hours of use, so that the patient has a 12 hour period with no plaster.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Versatis/Lidocaine can only be obtained with a prescription.

What benefits of Versatis/Lidocaine have been shown in studies?
Grunenthal Limited provided its own data on efficacy and safety studies. These studies have shown that Versatis/Lidocaine is effective in the treatment of post-herpetic neuralgia.
What are the possible side effects of Versatis/Lidocaine?
Like all medicines, Versatis/Lidocaine can cause side effects, although not everybody gets them.

If irritation or burning sensation occurs whilst using the plaster, the plaster should be removed. The area of irritation should remain plaster-free until the irritation stops.

Very common side effects which may affect more than 1 in 10 people are listed below.

These include skin conditions at or around the site of plaster application, which may include redness, rash, itching, burning, dermatitis, and small blisters.

For the full list of all side effects reported with Versatis/Lidocaine, see section 4 of the package leaflet available on the MHRA website.

Why was Versatis/Lidocaine approved?
The MHRA decided that the benefits of Versatis/Lidocaine are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Versatis/Lidocaine?
A risk management plan has been developed to ensure that Versatis/Lidocaine is used as safely as possible. Based on this plan safety information has been included in the Summary of Product Characteristics and the package leaflet for Versatis/Lidocaine including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Versatis
National Marketing Authorisations for Versatis/Lidocaine 5% Medicated Plaster (PL 21727/0016-0017) were granted in the UK on 05 January 2007 to Grünenthal Limited.

Versatis/Lidocaine 5% Medicated Plaster (PL 21727/0016-0017) then went through a first wave Mutual Recognition Procedure (MRP; UK/H/1040-1041/001/MR) involving Belgium, Germany, France, Luxembourg, Sweden and Slovenia. The procedure was completed on 27 September 2007.

A second-wave MRP (UK/H/1040-1041/001/E01) involving the Concerned Member States Austria, Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Spain, Iceland, Lithuania, Latvia, Malta, Portugal, Romania and Slovak Republic was concluded on 23 December 2009.

Versatis/Lidocaine 5% Medicated Plaster (PL 21727/0016-0017) then went through a third-wave MRP (UK/H/1040-1041/001/E02) involving Denmark, Finland, Hungary, Ireland, Italy, Norway and Poland. This procedure was completed on 28 July 2010.

A fourth-wave MRP (UK/H/1040-1041/001/E03) involving the Netherlands as Concerned Member State was concluded on 09 December 2013.
The full PAR for Versatis/Lidocaine follows this summary.

For more information about treatment with Versatis/Lidocaine, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2015.
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I Introduction

Based on the review of the data on quality, safety and efficacy the Netherlands considered that the applications for Versatis 5% Medicated Plaster (PL 21727/0016) and Lidocaine 5% Medicated Plaster (PL 21727/0017) could be approved via the Mutual Recognition Procedure (UK/H/1040-1041/001/E03). The products are prescription-only medicines.

These are a set of parallel applications for one strength of medicated plasters (5% lidocaine), submitted as full dossier applications according to Article 8.3 of Directive 2001/83/EC.

National Marketing Authorisations for Versatis 5% Medicated Plaster (PL 21727/0016) and Lidocaine 5% Medicated Plaster (PL 21727/0017) were granted in the UK on 05 January 2007 to Grünenthal Limited.

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A fourth–wave MRP (UK/H/1040-1041/001/E03) involving the Netherlands as Concerned Member State was concluded on 09 December 2013.

The products contain the active ingredient lidocaine, a local amide-type anaesthetic that interacts with voltage-sensitive sodium channels on the cell membrane. Topically, lidocaine is used as a surface anaesthetic and is rapidly and extensively absorbed following application to mucous membranes or damaged skin. It is, however, poorly absorbed systemically through intact skin.

Versatis/Lidocaine 5% Medicated Plasters are hydrogel plasters containing 5% lidocaine and are indicated for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN) in adults.
II Quality aspects

II.1 Introduction
The finished product is comprised of an adhesive material, containing the active ingredient, which is uniformly spread on one side of a non-woven fabric (consisting of polyethylene terephthalate fiber) used as a backing and covered with a polyethylene terephthalate (PET) film used as a release-liner. The release-liner is removed prior to application of the medicated plaster to patient skin. The self-adhesive layer is composed of glycerol, liquid sorbitol (crystallising), carmellose sodium, propylene glycol (E1520), urea, heavy kaolin, tartaric acid, gelatin, polyvinyl alcohol, aluminium glycinate, disodium edetate, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), polyacrylic acid, sodium polyacrylate and purified water. The backing fabric and the release liner are composed of polyethylene terephthalate.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory.

A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

II.2. Drug Substance
Active substance
INN: Lidocaine base

Lidocaine Base (Ph Eur) is supplied as a white or almost white, crystalline powder, practically insoluble in water, very soluble in alcohol and methylene chloride, and freely soluble in ether. The melting point is between 66ºC and 70ºC, determined without previous drying.

It does not appear to exhibit polymorphism.

The applicant has provided a certificate of suitability for lidocaine base provided by the active substance manufacturer.

An appropriate active substance specification is provided for the lidocaine. The finished product manufacturer has stated which tests are performed on receipt of each batch of active substance and has provided certificates of analysis from representative batches.

Appropriate stability data have been generated supporting a shelf life of 60 months.

II.3 Medicinal Product
All excipients used comply with their respective Ph Eur monograph, with the exception of sodium polyacrylate (which complies with the Japanese Standard of Cosmetic Ingredients) and polyacrylic acid solution (which complies with an in-house specification). Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin, none of the excipients used contain materials of animal or human origin. The manufacturer of gelatin has provided a TSE certificate of suitability.
Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on the product. The results appear satisfactory.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the Product
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. An additional shelf life of 14 days has also been applied after the product is opened.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III Non-clinical aspects
Investigations in healthy human volunteers are stated to have shown that only 3% of the plaster drug contents are systemically available. From the maximum recommended use of three plasters containing 2100mg lidocaine, approximately 64mg will be systemically available per day of administration (i.e. 1mg/kg/day) as a mean value. After the application of the maximum recommended number of three lidocaine 5% medicated plasters during 12 hours/day to healthy volunteers a C_{max} of 0.084µg/mL and of 0.125µg/mL was observed. Administration of lidocaine 5% medicated plasters at the maximum recommended regimen was also performed in patients with acute herpes zoster (AHZ) and with post herpetic neuralgia (PHN). The mean maximum plasma concentrations of lidocaine were lower than in healthy volunteers (patients with PHN: 0.05±0.03µg/mL and patients with AHZ: 0.08 ± 0.04µg/mL).

The clinical safety of lidocaine as a local anaesthetic and antiarrhythmic agent is well known. Since the plasma concentrations of lidocaine obtained with the use of lidocaine 5% medicated plaster are much lower than that observed during regional anaesthesia or antiarrhythmia treatment (50ng/mL vs 1,500-5,000ng/mL), new non-clinical studies have been limited to a skin irritation test in rabbits and a skin sensitisation test in guinea pigs (modified Buehler test). In addition, plasma exposure and the toxicity of the metabolite 2,6-xylidine was evaluated following oral administration of 2,6-xylidine in rats. These studies are described below.

A nonclinical expert report has been written by a suitably qualified person and is satisfactory.

In a 1992 GLP-compliant study the skin sensitization potential of Lidoderm Patch (stated to
be the same as the lidocaine 5% medicated plaster) was assessed in male and female guinea pigs. There was no evidence of skin sensitisation.

In a 1990 GLP-compliant study the dermal irritation and absorption of different lidocaine formulations were studied in rabbits. Lidocaine 5% was applied as a poultice, as a gel or as a commercially available lot of ointment. These 3 formulations were non-irritating under the test conditions. In a few cases low serum concentrations of lidocaine were detected but only in rabbits with abraded skin.

In a 2004/5 GLP-compliant study, 2,6-xylidine was administered to rats for 10 weeks via the diet at concentrations of 300, 1000 or 3000 ppm. A control group was treated with standard diet only. There were ten animals/sex/group in the control groups and 34 animals/sex/group in the treated groups. An additional 12 animals/sex/group were used for toxicokinetics and a further 12 animals/sex/group were used to determine further metabolites. The nominal mean test compound intake (in mg/kg/day) was approximately proportional to dose but about 25% higher in females than in males being 19 and 25mg/kg/day at 300ppm, 62 and 85mg/kg/day at 1000ppm and 177 and 229mg/kg/day at 3000ppm in males and females respectively. There were no treatment related deaths or overt signs of toxicity. There was reduced food consumption in both sexes during the first week of treatment at 3000ppm and reduced food consumption in males during the first treatment week at 1000ppm. There was reduced body weight gain in males at 3000ppm during the first four treatment weeks and sporadic decreased body weights and body weight gain in females at 1000ppm and throughout treatment at 3000ppm. There were no treatment-related gross pathological findings.

Histopathology appears not to have been conducted. There were no consistent treatment related adverse effects except for an increase in relative liver weight in both sexes at the top dose. This was considered to be an adaptation rather than an adverse effect. The week-10 mean AUC₀-2₄ [h.ng/ml] values of 2,6-xylidine were 2043±560, 9943±3017 and 33501±2908 in males and 3361±711, 19793±4679 and 58849±21837 in females at 300ppm, 1000ppm and 3000ppm respectively.

Ecotoxicity/environmental risk assessment (ERA)

An Environmental Risk Assessment for Lidocaine 5% Medicated Plaster has been performed according to the “Note for Guidance on Environmental Risk Assessment of Medicinal Products for Human Use” draft SWP/4447/00 dated July 2003. In the Phase I, the exposure of the environment was evaluated. The predicted environmental concentration (PEC) in surface water was calculated as 0.01mg/L lidocaine. Because this value was above the critical value of 0.01µg/L, a Phase II environmental effect analysis was conducted. A Phase II tier A assessment was performed in which acute toxicity tests were conducted on fish, daphnia and algae in order to determine the predicted no-effect concentration (PNEC). Based on the results of these studies and the fact that the n-octanol/water partition coefficient is lower than 1000 which indicates a low potential for transfer of lidocaine from the aquatic environment to organisms and accumulation therein, the results indicate that the therapeutic use of Lidocaine 5% Medicated Plaster is unlikely to pose a risk to the aquatic environment.

Discussion on the non-clinical aspects

The non-clinical overview was based almost entirely on published literature. This is considered to be acceptable in view of the clinical experience with lidocaine as a local anaesthetic and antiarrhythmic agent. In addition, the present application concerns a dermal product where the systemic exposure to lidocaine and its metabolites is much lower than that
observed with other lidocaine usages.

The grant of Marketing Authorisations is recommended.

IV Clinical aspects

Primary Pharmacodynamics
The local anaesthetic properties of lidocaine are well known. Two Phase II proof-of-concept studies were performed (see Efficacy section below).

Secondary Pharmacodynamics
There were three Phase I studies, HP10004/H11, H12 and H13. These were conducted to assess the dermal irritancy and sensitisation potential of the product.

Pharmacokinetics
A comparative pharmacokinetic study was performed in healthy volunteers, patients with herpes zoster and patients with post herpetic neuralgia (PHN; Study H14).

In a study in healthy volunteers, no accumulation of lidocaine in plasma was observed after repeated application of the maximum recommended dose (three plasters at a time for 12 hours of application, followed by a 12 hours plaster-free interval) over 5 days. Steady state for systemic lidocaine concentrations was achieved after 3 days. Mean maximum concentrations (± standard deviation) of lidocaine on day 5 of the study were observed to be 84 ± 36ng/ml (n=20; range 41-177ng/ml). In another Phase I study, the mean maximum concentration (± standard deviation) of lidocaine on Day 3 was 125 ± 51ng/ml. These concentrations are about 10 to 20 times lower than the minimum effective plasma concentration during therapy of cardiac arrhythmias (1,500-5,000ng/ml, in individual cases >5,000ng/ml), and about 40 to 60 times lower than potentially toxic plasma levels (>5,000ng/ml). During the use of the plaster in patients suffering from post herpetic neuralgia, lower maximal plasma concentrations (± standard deviation) of 52 ± 31 ng/ml (mean ± S.D.; n=8) were measured. This result is supported by a population kinetics analysis of one of the clinical efficacy studies in patients suffering from PHN, revealing a mean maximum concentration for lidocaine of 64 ng/mL after application of three plasters simultaneously during 12 hours once a day after repeated application for up to 10 weeks.

Distribution
After intravenous administration of lidocaine to healthy volunteers, the volume of distribution was found to be 1.3 ± 0.4 l/kg. The volume of distribution is decreased in patients with congestive heart failure and increased in patients with liver disease. At plasma concentrations produced by application of the plaster, approximately 70 % of lidocaine is bound to plasma proteins. Lidocaine crosses the placental and blood-brain barriers, presumably by passive diffusion.

Biotransformation
Lidocaine is metabolised rapidly in the liver to a number of metabolites. The primary metabolic route for lidocaine is N-dealkylation to monoethylglycinexylidide (MEGX) and glycineethylidide (GX), both of which are less active than lidocaine and available in low concentrations. These are hydrolyzed to 2,6-xylidine, which is converted to conjugated 4-
hydroxy-2,6-xylidine. From *in vitro* studies it is known that hepatic cytochrome P450 enzymes CYP1A2 and CYP3A4, as well as esterases, are involved in the metabolism of lidocaine.

The minor metabolite, 2,6-xylidine, has unknown pharmacological activity, but shows carcinogenic potential in rats in a highly sensitive test system with very high doses (see nonclinical safety data in section 5.3 of the SmPC). The steady state maximum plasma concentration of 2,6-xylidine (± standard deviation) observed in healthy volunteers was about 8 ± 3 ng/ml (n=20; range 4-16 ng/ml) following multiple application of three plasters. This finding is supported by a population kinetics analysis of one of the clinical efficacy studies in patients suffering from PHN, that revealed a mean maximum concentration for 2,6-xylidine of 8 ng/ml after repeated daily applications of three plasters over 12 hours for up to 10 weeks. These concentrations are approximately 120-fold lower than those that caused tumour formation in animals. Data on lidocaine metabolism in the skin are not available.

**Elimination**

Lidocaine and its metabolites are excreted by the kidneys. More than 85 % of the dose is found in the urine in the form of metabolites or active substance. Less than 10 % of the lidocaine dose is excreted unchanged. The main metabolite in urine is a conjugate of 4-hydroxy-2,6-xylidine, accounting for about 70 to 80% of the dose excreted in the urine. 2,6-xylidine is excreted in the urine in man at a concentration of less than 1% of the dose. In a Phase 1 study, the half-life of lidocaine elimination from plasma following intravenous administration (± standard deviation) is 107 ± 22 minutes (n=15). The mean half-life of lidocaine elimination from the plasma following multiple administration of the plaster in 20 healthy volunteers is 7.6 hours (range 4.5-13 hours). The elimination half-lives of MEGX, GX and 2,6-xylidine after plaster application in healthy volunteers are 6.4 hours (range 3.6-12 hours), 13 hours (range 9.1-19 hours) and 15 hours (range 10-18 hours). The systemic clearance of lidocaine in healthy volunteers (± standard deviation) is 0.635 ± 0.175 l/min (n = 15, range 0.332 - 0.952 l/min). The excretion of lidocaine and its metabolites may be delayed in cardiac, renal or hepatic insufficiency.

**Clinical Assessor’s Comment on Pharmacokinetics and Pharmacodynamics**

Systemic absorption appears to have been adequately studied and does not raise a safety concern.

**EFFICACY**

**Medical and Statistical Assessment of Main Efficacy Studies**

There were two Phase II studies, H21 and H31, and two main Phase III studies, H32 and 01.

**Phase II - Study KF10004/H21**

A single-dose application was used in this single-centre trial to assess the efficacy of Lidocaine in patients with chronic moderate to severe PHN. It was a double-blind, randomised, placebo-controlled, four-way crossover trial of 12 hours of dosing conducted in one centre in the US. Each patient underwent four separate 12-hour sessions, at least 3 days apart. Two sessions were with Lidocaine 5% medicated plasters, one was with placebo plaster and one was with no treatment. The placebo active comparison was double-blind.

The primary efficacy endpoints were the change from baseline pain intensity using a 100mm VAS (0 representing no pain and 100 the worst imaginable pain) and pain relief which was
assessed using a six item rating scale. Both were collected over the 12-hour period when patients received treatment. Only patients who completed all four sessions were included in the primary analysis.

**Patient disposition and results:**
A total of 39 patients were randomised into this study of which 36 received two sessions of Lidocaine treatment and 35 received placebo. Thirty-five patients completed all four sessions and were included in the primary analysis.

**Change from baseline**

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine 5% medicated plaster (LID)</th>
<th>Placebo plaster (PLA)</th>
<th>Observation period (OBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain intensity</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mm</td>
<td>10#</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Number of applications</strong></td>
<td>70</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td><strong>Standard deviations</strong></td>
<td>13</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td><strong>Pain relief</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.2##</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Number of applications</strong></td>
<td>70</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td><strong>Standard deviations</strong></td>
<td>1.0</td>
<td>0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* For pain intensity-0 represents no pain and 100 the worst imaginable pain.
** For pain relief: 0-is an increase in pain, 1-is no pain relief, 2-is a slight pain relief, 3-is a moderate pain relief, 4-is a marked pain relief and 5-is complete pain relief)
#  Statistically significant from placebo (p-value=0.008) using an ANCOVA.
## Statistically significant from placebo (p-value=0.033) using an ANCOVA.

**Assessors' comment:**
There is about a 6mm difference in pain intensity in the 100mm VAS and a 0.3 unit difference in pain relief between the Lidocaine and placebo plasters. Both primary endpoints were statistically significant, although the absolute differences from placebo were small. This was only designed as a proof-of-principle study and should be considered as exploratory. A small effect from the placebo plaster cannot be excluded.

**Phase II - Study KF 10004/H31**
This Phase II study recruited patients with at least moderate PHN. It was double-blind, randomised, parallel-group, placebo-controlled, multiple-dose study conducted in two centres in the US.

The primary variables were pain intensity using the 100mm VAS, pain relief using a 6-point item rating scale (which was different than in study H21) and allodynia severity testing. The primary endpoints were the average change from baseline in pain intensity during sessions 1 and 2, in pain relief during sessions 1, 2 and 3 and in allodynia over sessions 1 and 2. The baseline value was evaluated prior to each treatment period. Only patients who were
considered evaluable for the per protocol population were included in the primary analysis.

Each patient was treated for 30 days in total, consisting of three sessions. Two of these sessions were in the clinic and used a single application of the plaster (sessions 1 and 2). Thereafter, patients were treated for 21-28 days at home (session 3), during which the patients were allowed up to three plasters per day. The third session in the clinic took place after the home period had completed and this in turn was followed by a 1-week washout period. Patients were allowed to continue treatment if they wished after the washout period in an open-label extension. Patients were randomly assigned to double blind treatment with either the Lidocaine 5% plaster, or placebo, in a 2:1 ratio. The primary efficacy criteria were assessed after the single application, the multiple other endpoints were exploratory.

**Patient disposition and results:**

A total of 167 patients were randomised into this study of which 110 were randomised to receive the Lidocaine plaster and 57 the placebo plaster. There were 10 and 7 patients who withdrew during treatment from the Lidocaine and placebo treatment groups, respectively. A total of 100 patients in the Lidocaine treatment group and 50 in the placebo treatment group were included in the per-protocol population.

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine 5% medicated plaster (n=100)</th>
<th>Placebo plaster (n=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain intensity (VAS scale mm-mean (SD))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Session 1 baseline</td>
<td>55.5 (18.9)</td>
<td>57.5 (17.0)</td>
<td>0.695</td>
</tr>
<tr>
<td>Average reduction during session 1</td>
<td>9.6 (17.7)</td>
<td>8.4 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Session 2 baseline</td>
<td>54.4 (22.3)</td>
<td>54.5 (21.2)</td>
<td>0.109</td>
</tr>
<tr>
<td>Average reduction during session 2</td>
<td>12.0 (16.5)</td>
<td>7.8 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Average reduction during session 3</td>
<td>18.2 (-)</td>
<td>14.2 (-)</td>
<td>0.533</td>
</tr>
<tr>
<td><strong>Pain relief [mean (SD)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Session 1 (averaged)</td>
<td>2.0 (0.9)</td>
<td>1.8 (0.8)</td>
<td>0.334</td>
</tr>
<tr>
<td>Session 2 (averaged)</td>
<td>2.2 (1.0)</td>
<td>2.0 (0.9)</td>
<td>0.166</td>
</tr>
<tr>
<td>Session 3 (only collected once)</td>
<td>2.6 (1.3)</td>
<td>2.1 (1.0)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Allodynia [mean (SD)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Session 1 pain reduction</td>
<td>0.6 (0.7)</td>
<td>0.1 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Session 2 pain reduction</td>
<td>0.4 (0.6)</td>
<td>0.1 (0.6)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

* For pain intensity-0 represents no pain and 100 the worst imaginable pain.
** For pain relief: 0-worse pain, 1-no change, 2- slight relief, 3- moderate relief, 4-a lot of relief and 5-complete relief
*** For alldynia: 0-no pain or discomfort to touch, 1-uncomfortable but tolerable to touch, 2-doubles pain, looks like it hurts, 3-subject cannot stand to be touched, extremely painful etc.

Pain intensity analysed by analysis of covariance. Pain relief and allodynia were analysed by Cochran-Mantel-Haenzel test.
Assessors’ comment:
Although providing some support for the first Phase II trial, this second exploratory trial shows only small changes and the pain intensity endpoint does not show statistical significance. The Allodynia endpoint shows some evidence of benefit, although the changes are small and the pain relief endpoint provides little evidence of benefit. As with study H21, the applicant did not carry out the primary analysis using the ITT population and appropriately account for missing data. For this reason, the estimate of benefit may be over optimistic in both Phase II trials. There was an imbalance in the duration patients had PHN for, with an average of 3.05 and 4.33 years in the Lidocaine and placebo groups, respectively, which could cause a bias in the results seen. For this reason, an analysis using an ITT population and accounting for PHN duration at baseline would have been preferable.

Phase III –Study KF 10004/H32
This principal study was double-blind, randomised, placebo-controlled, two-period crossover trial conducted in two centres in the US to assess the efficacy of Lidocaine 5% medicated plaster.

Design, analysis and objectives of the study:
Patients recruited into the study were regular users of the Lidocaine 5% medicated plaster from the open-label extension studies or the compassionate use program and were rated moderate or better on the 6-point rating scale described below.

Patients were randomised to receive either 14 days of Lidocaine followed by 14 days treatment of placebo, or vice versa. There was no washout between the two treatments.

The primary endpoint for this study was the “time to exit” and patients were to withdraw from the treatment phase if their pain relief was two points lower than their usual response to Lidocaine on a 6-point rating scale (worse, no pain relief, slight relief, moderate relief, a lot of relief and complete relief). The secondary endpoint was the patient’s preference between treatments.

Patient disposition and results:
A total of 33 patients were randomised into this study of which 32 were treated. The ITT population consisted of these 32 patients and the per-protocol population excluded two patients who withdrew from the study.

The results are given below for the statistical analysis for the “time to exit” endpoint are given below.

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine 5% medicated plaster Median [95% confidence interval]</th>
<th>Placebo plaster Median [95% confidence interval]</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to exit (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment phase 1</td>
<td>&gt;14 [14.0, &gt;14]</td>
<td>2.7 [2.0, 4.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment phase 2</td>
<td>&gt;14 [14.0, &gt;14]</td>
<td>6 [4.0, &gt;14]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Overall | >14 [14.0, >14] | 3.8 [3.0, >14] | <0.001

* using the Wilcoxon non-parametric test on the primary population where patients were censored if they completed 14 days of treatment.

Three patients (9.4%) preferred the placebo plaster compared to 25 (78.1%) patients who preferred the Lidocaine plaster. The mean pain relief scores (based on the 6-point rating scale) over 14 days of treatment ranged between 2.9-3.2 on placebo and 4.4-4.6 on Lidocaine.

Two patients (No. 155 and 163) exited early in Phase B under placebo due to adverse events. One of them also stopped because of an increase in pain. Patient 155 dropped out at day 4 and Patient 163 at day 6. Both were included in the intention-to-treat analysis by using the day when they dropped out as the study exit time. This proceeding is according to the study protocol, where the primary efficacy variable is defined as time to exit during the treatment.

Assessors' comment:
There are concerns with the design of this study. An enriched population of patients who had previously responded to Lidocaine, some of whom participated in previous trials, was recruited into this study. Therefore, evidence from this study may not be independent from other studies used in this submission. It is necessary to reflect the limitations of the trial design, in particular the enriched population design, within Section 5.1 of the SmPC. The applicant has not been able to define prospectively which patients would respond. It is not clear how many patients will derive benefit.

The question to the applicant was:
The median time to exit for Lidocaine was >14 days for both treatment phases; the median time to exit for placebo was 2.7 days in treatment Phase 1 and 6 days in treatment phase 2 showing a different placebo effect in each period. The Applicant should discuss the reason for this period effect further. The Applicant should give further details on how the 95% confidence intervals were calculated for the treatment effects. The Applicant should give details on how the two patients who withdrew from the study were treated in the primary analysis.

Applicant’s Response:
A post hoc analysis for sequencing confirmed that there is no statistical difference based on sequencing, excluding a “carry-over” effect, which could be a reason for the apparent difference within both phases in time to exit for placebo-treated patients. In this regard, it might be relevant that only those patients who were on long-term treatment with a lidocaine 5% medicated plaster were included in this study.

At screening, patients were informed that they would receive an inactive plaster during the study, but also that a treatment phase would be terminated if the pain increased to a certain level two days in a row. Therefore, it can be assumed that patients having benefit from the lidocaine 5% medicated plaster over a long period of time would be sensitized at start of the trial towards identifying inactive treatment during the trial. This sensitization might be amplified by the specific study conditions, e.g. having a telephone interview every day for reporting pain intensity. As patients got used to the study conditions during the course of the trial it may be assumed that the effect diminished. This explanation is supported by the fact that not only the placebo-groups exhibited differences in time to exit. For patients on active
medication in the first phase, 4 out of 16 met “time to exit” within the predefined 14 days, while none out of 16 met time to exit in the second phase. Despite this numerical difference in ‘time to exit’, the statistical difference between active and placebo is not affected by this altered perception.

SAS procedures for evaluation of the confidence intervals were not yet available at the time of study analysis. For the calculation of the 95% confidence intervals, therefore, the method described by Simon and Lee (Simon R, Lee YJ. Non-parametric confidence limits for survival probabilities and median survival time. Cancer Treatment Report 1982; 66: 37-42) was used.

Assessors’ comment on response:
The applicant hypothesises that the period effect could be caused by patients being included into this study who are already benefiting from the Lidocaine plaster and are therefore sensitized to the plaster at the start of the study. Another reason given by the applicant for the period effect was the specific study conditions, such as daily pain assessment. The applicant also states that 4 out of the 16 patients on active treatment met “time to exit” criteria within the 14 days in the first phase compared to no patients in the second phase. It is not clear that these explanations are entirely plausible, however, given that the period effect does not alter the overall conclusions from this study this is not of major concern. An appropriate technique to calculate the confidence intervals and to deal with missing data was given by the applicant.

Study KF 10004/01
This was intended as a confirmatory study. It was conducted in 33 European Centres and was designed after consultation with the UK, German and French national authorities in 2002. The enrichment design studied a subgroup of patients with the disease who respond with a certain pain pattern to the product and aimed to measure the effect of treatment cessation. A double-blind, randomised, parallel group, withdrawal design was employed to confirm that efficacy was present in those patients who had been pre-selected as responders.

Patients who were at least a 4 on the NRS (an 11-point numeric rating scale where 0 denotes no pain and 10 pain as bad as you can imagine) were recruited to be given 8 weeks of open-label Lidocaine treatment. Only those with a positive response to the product after the 8-week open-label trial entered the randomised withdrawal. Those patients who responded (using pre-defined criteria) after the open-label phase were randomised to switch to placebo or to stay on Lidocaine treatment during a 2-week double-blind randomised withdrawal treatment phase.

For the randomised withdrawal phase, patients were assigned to either Lidocaine or placebo device, with a treatment duration of 2-14 days. The primary endpoint was the time to lack of efficacy. Multiple secondary endpoints were also assessed of daily and weekly pain intensity and pain relief, quality of sleep, quality of life, allodynia severity and pain severity, and Physicians’ Clinical Global Impression on Change. Of the 265 patients who entered the 8 week run-in phase, 137 (52%) were classified as responders with at least moderate relief from treatment with Lidocaine.

The primary endpoint for this study was the time to exit during the double-blind treatment phase due to lack of efficacy during two consecutive application days, which was defined as in study H32.
Patient disposition and results

The original study planned the recruitment of 300 patients and anticipated a high attrition rate, so that only 70 patients would be available for the randomisation phase.

A total of 116 out of 265 patients did not complete the run-in phase and 78 patients completed the run-in phase, but were not randomised as they did not meet the criteria for randomisation. This was either because of lack of compliance, or because the required number of patients for the double-blind phase, specified at 70, had been reached.

This left 71 patients who were randomised and included in the withdrawal phase of the study. Of these, 9/36 patients on active treatment and 16/35 on placebo withdrew from the double blind phase of the study because of lack of efficacy.

The results for the “time to exit” endpoint are given in the table below:

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine 5% medicated plaster Median [range]</th>
<th>Placebo plaster Median [range]</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to exit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td>13.5 [2-14]</td>
<td>9.0 [1-14]</td>
<td>0.1510</td>
</tr>
<tr>
<td>Per protocol</td>
<td>14.0 [3-14]</td>
<td>6.0 [1-14]</td>
<td>0.0398</td>
</tr>
</tbody>
</table>

*analysed using an unstratified log-rank test using the full analysis set population-defined as all patients who qualified for the double-blind treatment phase. Patients were censored if they completed 14 days of double blind treatment or if they withdrew for any other reason than lack of efficacy.

Assessors' comment:

The randomised withdrawal design of this study tests the effect of removing treatment (offset) not the usual effect of first administering treatment (onset), although the Phase II data provide some limited evidence of this. The main concern with the design of this study is that the efficacy population consists of an enriched population of patients defined as responders. As stated for Study H32, it is necessary to reflect the limitations of the trial design, in particular the enriched population design, within Section 5.1 of the SmPC.

It is noted that ICH-E10 states that randomised withdrawal studies can be used in several situations, one of which is where “drugs suppress a symptom or sign (chronic pain, hypertension, angina) but where a long-term placebo-controlled trial would be difficult”. There is concern that the 6-point rating scale used to define lack of efficacy in both the pivotal studies has more categories for patients getting better than worse and this could bias the primary endpoint. Therefore, the applicant should give details of the validation of the 6-point rating scale used in the pivotal studies.

For the FAS, the median time to exit for Lidocaine was 13.5 days compared to 9 days on placebo and the primary analysis based on the log-rank test did not show statistical significance between the treatments.
The treatment effect was smaller than that seen in the previous pivotal trial, Study H32. There could be many reasons for this, including the differences between the design and the population studied in each of the trials. It is also of interest that the applicant states that “treatment effects observed with a randomised withdrawal design may be larger than those seen in an unselected population because patients are enriched” and the treatment effect observed in this study may be larger than in a non-enriched population.

As the per-protocol results from this study were similar to the previous study, the applicant carried out post-hoc analyses to assess the possible influence of baseline imbalances on the differences seen between the FAS and per-protocol results. Estimated hazard ratios of 1.857 and 3.748 using a proportional hazards model were seen for the FAS and per-protocol populations, respectively, when not adjusting for any covariates. When adjusting for the McGill score, allodynia and PHN duration, the hazard ratios were estimated at 3.12 and 5.96, both showing statistical significant results. It should be noted that although the baseline imbalance may account for the smaller treatment effect seen compared to the previous study, it does not account for the difference between the FAS and per-protocol results. There are also concerns with this analysis as it was based on post hoc covariate selection and data driven.

The applicant was asked to address the following question in regard to studies KF10004/H32 and KF10004/0: The 6-point rating scale used to define lack of efficacy in both the pivotal studies has more categories for patients getting better than worse and this could cause a bias in the primary endpoint. Therefore the applicant should give details of the validation of the 6-point rating scale used in studies KF10004/H32 and KF10004/01.

**Applicant’s Response:**

It is correct that the 6-point rating scale used in the pivotal studies has more categories for patients getting better than worse. This does not, however, cause a bias because the scale is specifically designed to assess pain relief. The usually applied categorical scale for pain relief has the endpoints ‘no pain relief’ and ‘complete pain relief’ with different numbers of categories between the endpoints (Max & Laska, 1991).

The applicant acknowledges that the assessment of pain relief is usually not recommended for chronic pain studies due to the long recall period. However, in the aforementioned studies, the use of pain relief assessments was justified because of the short recall period during the application of lidocaine 5% medicated plaster. The plaster should be worn for no longer than 12 hours during a 24-hour period and the patients were required to wait for pain to return during the off-plaster period before the next plaster application. Under these predefined conditions, the patients were asked to report pain relief daily after plaster application compared to the pain before the same plaster application, thus having a maximum recall period of 12 hours.

Due to the randomized withdrawal design employed in the studies, an adjusted 6-point pain relief scale was used which had an additional category of ‘worse’. The randomized withdrawal design should be able to detect a worsening of pain during placebo treatment which needs to be appropriately represented in the assessment of lack of efficacy. In addition, this scale was expected to offer a higher sensitivity in comparison to the common pain relief scale.
For the adjusted 6-point rating scale as described above, it was shown in the publication by Littman et al (1985) that it correlates well with a visual analogue scale (VAS) for pain intensity and a 5-point verbal rating scale (VRS) for pain intensity (none, mild, moderate, severe, very severe): the correlation coefficients between the cumulative scores Sum of Pain Intensity Difference (SPID), Sum of Pain Analog Intensity (SPAID) and Total Pain Relief (TOTPAR) were between 0.933 and 0.896. In the same evaluation, it was also found that the relative sensitivity of the VRS for pain relief was higher than for the other pain scales. Taking these evaluations into account, the applicant considers the scale as used in the studies has been validated, a rating which is shared by several authors using the publication by Littman et al (1985) as a basis for review articles (Jensen et al 1999; Haythornthwaite & Fauerbach 2001; Caraceni et al 2002).

Assessors’ comment on response:
The applicant agrees that the 6-point scale has more categories for patients getting better than worse and states that this is more than the usually applied categorical scale for pain relief, with categories ranging from ‘no pain relief’ to ‘complete pain relief’. The applicant also presents a literature reference demonstrating that this scale correlates well with the visual analogue scale and the 5-point verbal rating scale. In addition, the small treatment effect demonstrated using the 6-point scale in the Phase II studies translates to a small treatment benefit on the VAS scale. Although this is reassuring, it does not constitute a formal validation of the 6-point scale. However, given the assessment using the 6-point scale was carried out in a placebo-controlled and blinded fashion, and that a small clinical benefit using the 6-point scale in the Phase II studies translated to a small clinical benefit using VAS scale, then any bias in the results caused by using this endpoint would not seem to alter the overall conclusion of this application. This point can be considered resolved.

For study KF 10004/01, the applicant was asked to provide further details of why the 78 patients who completed the run-in phase were not randomised and included in the withdrawal phase of the study. Specifically, what ‘general study end’ means and which randomisation criteria were not fulfilled and by how many patients are requested.

Applicant’s Response:
It is correct that 78 patients in study KF10004/01 were not included in the withdrawal phase of the study, despite having completed the 8 weeks’ run-in phase. The reasons for the non-inclusion are given below, together with a listing of the violated randomisation criteria and an explanation concerning ‘general study end’.

For 70 out of the 78 patients, the investigator documented that the randomization criteria were not fulfilled. The randomization criteria were:
1. Patients must be regularly (minimum every second day) using the lidocaine 5% medicated plaster for control of pain in the last 4 weeks of the run-in phase. The patient must wait for pain to increase before applying a new plaster.
2. The patient’s average daily pain intensity (with plaster on) must be 7 or less on an 11-point NRS (scale of 0-10) and must increase during the phases when plaster is not worn, during Week 8 of the run-in phase.
3. Before randomization, the patient must have an average relief with lidocaine 5% medicated plaster of “moderate” or better, on a 6-item scale during Week 8 of the run-in phase.
Most of the patients (41 out of 70) failed to fulfil any of the three criteria. For 22 patients, the criteria no 1 and no 2 were not fulfilled, and five patients did not meet criterion no 1. Single patients failed to meet criteria no 2 and no 3, or criteria no 1 and no 3 (Table 1).

Of the remaining eight patients, a further three patients did not meet the randomization criterion no 1, but this fact was not correctly documented in the CRF, although the patients were withdrawn from the study as required by the protocol. Two additional patients withdrew their informed consent, and one patient terminated the study because of an adverse event which was not correctly documented in the CRF. The incorrect documentation is still contained in the database and was evaluated as such. As the mistakes were only discovered after database closure and considered minor deviations, it was decided not to re-open the database for correction.

Two patients completed the run-in phase when the planned number of 70 patients had already been randomized into the double-blind phase, according to protocol. Therefore, the study was terminated (‘general study end’) before these two patients could be randomized.

**Table 1 Reasons for withdrawal for non-randomized patients who completed the run-in phase of the study (FAS-E)**

<table>
<thead>
<tr>
<th>Reason</th>
<th>NRAND, Part A fully completed (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria for randomization not fulfilled</td>
<td>70 (89.7%)</td>
</tr>
<tr>
<td>All three criteria not met</td>
<td>41 (52.6%)</td>
</tr>
<tr>
<td>Criteria 1 and 2 not met</td>
<td>22 (28.2%)</td>
</tr>
<tr>
<td>Criterion 1 not met</td>
<td>5 (6.4%)</td>
</tr>
<tr>
<td>Criteria 2 and 3 not met</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Criteria 1 and 3 not met</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Inclusion criteria No 1 for randomization in fact not fulfilled; not correctly documented in CRF.</td>
<td>3 (3.9%)</td>
</tr>
<tr>
<td>Withdrawal of informed consent; not correctly represented in the data base.</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Run-in phase completed when 71 patients had already been randomized (‘general study end’).</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>Termination due to adverse event, not correctly represented in the data base.</td>
<td>1 (1.3%)</td>
</tr>
</tbody>
</table>

FAS-E: Full analysis set of enrolled patients  
NRAND: non-randomized patients

**Assessor’s comment on response:**
The applicant states that 70 out of the 78 patients were excluded from the study for failing randomisation criteria (specifically regular use of the plaster, average pain intensity increasing when the plaster was not worn and patients not having adequate pain relief during the run-in phase). These inclusion criteria were to ensure that only an enriched population
were enrolled into the double-blind treatment phase of this study. Two patients completed the run-in phase once the planned 70 patients had already been randomised and, therefore, not included in the double-blind phase of the study and, therefore, were documented under ‘general study end’. This response seems appropriate.

**Open-Label Extension - Study KF10004/02**

This was an additional open label, uncontrolled extension study in 22 European centres. It was a study which followed-up those patients recruited for KF 10004/01 and newly recruited patients. The main objective was to assess long term safety.

Though open-label, the persistence of benefit and the development of tolerance were assessed. Efficacy was measured weekly and included pain intensity on an 11-point scale, pain relief on a 6-point scale, Clinical Global Impression of Change, Quality of Life, pain questionnaire, allodynia assessment and change in concomitant medication.

An interim report was included, as the study was not completed by the time of submission. The final study report evaluates patients up to individual treatment duration of 1 year.

**Assessors’ Conclusions on Efficacy**

For Study H32, only patients who had previously responded to Lidocaine, some of whom participated in previous trials, were recruited into this study. Therefore, evidence from this study may not be independent from other studies used in this submission. An enriched population, consisting only of those patients who ‘respond’ has been used in this study. It is difficult to prospectively define those patients who would respond and, therefore, defining the correct population in the SmPC is problematic. As no washout period was used for patients entering this study, only those patients who were randomised to placebo followed by active treatment give information about the onset of treatment, albeit in an uncontrolled fashion. It would have been beneficial for the applicant to justify that the treatment effect observed in this study could be used to infer conclusions about the onset of treatment.

For Study 01, there are concerns with the randomised withdrawal design of this study being used to assess evidence of efficacy for the onset of treatment. The main concern is that the efficacy population consists of an enriched population of patients who ‘respond’. The study was designed to randomise 70 patients and was stopped after the required number of patients was randomised. Therefore 27 patients who were still ongoing or completed at this time point, could not be considered for randomisation. 137 of the 265 enrolled patients responded, of whom 20 were not eligible for randomisation due to general study end. Therefore, the SmPC needs to include the key results from this study together with the proportion of patients who responded to Lidocaine.

In summary, the design of the pivotal studies gives only limited evidence of efficacy in an enriched population. However, the applicant has adequately addressed the points raised, and it may be considered that this product has demonstrated some clinical benefit.

**CLINICAL SAFETY**

**Study KF 10004/02**

This was an uncontrolled multi-centre, multiple-dose long-term safety study, which followed up those patients recruited for KF 10004/01 and newly recruited patients. The objective was to collect long-term safety data. In addition, the persistence of benefit and the development of
tolerance were assessed. The trial was conducted in 22 European Centres. Efficacy was measured weekly and included pain intensity on an 11-point scale, pain on a 6-point scale, Clinical Global Impression of Change, Quality of Life, pain questionnaire, allodynia assessment and change in concomitant medication. An interim report was included, as the study had not completed by the time of submission. Final study report evaluated patients up to individual treatment duration of 1 year. The study results have been submitted to the MHRA. Only data from the interim report KF10004/02 was included in the analysis below.

**Population Exposed in Clinical Trials**

In five clinical studies there were 450 patients exposed to Lidocaine 5% plaster. There were 70 patients exposed to treatment for more than 6 months. In addition, there were 155 patients exposed to placebo. The difference from placebo for most of these studies is difficult to calculate as most involved enrichment recruitment of responders.

**Deaths – Clinical Assessor’s Comment**

There were four deaths reported in association with treatment:

- A 75-year-old lady with a history of heart disease and renal insufficiency (before starting treatment). She died from complications of heart failure.
- A 78-year-old woman with a long standing history of asthma, diabetes, diabetic neuropathy, hyperlipidaemia, and hypertension, developed an exacerbation of asthma with pneumonia. She died suddenly from a diagnosis of ischaemic heart disease and coronary atheroma. The death was not considered related to study medication.
- An 80-year-old man with a history of myocardial ischaemia, hypertension and recurrent pulmonary oedema died from a recurrent pneumonia. Death was not considered related to study medication.
- A 78-year-old man with a long standing atherosclerotic cardiomyopathy and congestive heart failure died from heart failure, which was not related to study medication.

**Serious Adverse Events**

Twelve patients experienced non-fatal serious adverse events in clinical studies where 450 received active and 155 placebo. These included three pneumonia, two atrial fibrillation, and one each of recurrent atrial fibrillation, inguinal hernia, phlebothrombosis, retinal detachment, asthma, atrioventricular block, intestinal stoma complications, arthralgia, respiratory tract infection and upper abdominal pain. None of these were considered related to study drug.

**Discontinuations**

Twenty-four patients discontinued because of adverse events of these, 13 were because of skin reactions (dermatitis, pruritis, erythema, skin injury, rash, skin lesion), which were reversible and mostly drug-related.

**Non-Serious Adverse Events**

In studies KF10004/H21 and KF10004/H31 safety information was obtained using collection of AEs and by means of a symptom check list (SCL). Consequently the relative frequency of reported AEs is confounded and therefore these 2 studies were not included into the overall calculation of AE frequencies.

Spontaneous adverse event reporting alone was used in Studies KF10004/H32, KF10004/01 and KF10004/02. In a pooled safety analysis of these studies the majority of AEs were skin reactions mainly at the site of plaster administration (primary system organ classes
contributing “general disorders and administration site conditions” in 11.1% of patients and “skin and subcutaneous tissue disorders” in 8.2% of patients). Headache was the most common single AE reported in 4.9% of patients.

The active treatment did not differ significantly from placebo in terms of adverse events.

**Pregnancy and Lactation**
There was no exposure to pregnant or lactating women.

**Post Marketing Surveillance**
The product is being marketed in the USA and Switzerland since 1999. 182 million plasters have been used in the USA. Estimates of approximately 900,000 patients have been exposed to the medication up until March 2005. No safety signals of concerns were identified with the exception of anaphylactic reaction, hypersensitivity and open wound. These spontaneously reported adverse reactions are included in the proposed SmPC.

Most adverse events in the clinical studies related to tolerability at the application site in approximately 12% patients and there were of mild intensity and resolved spontaneously. Only 4.7% of all adverse reactions led to discontinuation.

Lidocaine blood concentrations observed during application of the product in study HP10004/01 are at least 10 fold lower than that needed for cardiac or anaesthetic purposes. Study report PP0018P did not show any tendency for accumulation of Lidocaine or metabolite 2,6-xylidine.

**Interactions**
No *in vitro* or *in vivo* interaction studies were carried out. The possibility of the product might interact with class 1 anti-arrhythmic drugs cannot be excluded.

**Population Sub Groups**
In two studies the incidence of adverse events were classified according to age, where the patients were above or below 65 years of age, and by gender. Adverse events were higher in the older patients, as might be expected. There were no gender differences. The company does not have data on children, or patients with renal or hepatic impairment.

**Clinical and statistical assessors’ conclusions**
It is clear that lidocaine is an effective topical analgesic. However, it remains a challenge to document an analgesic effect with this product in this complex condition.

The company came for two national scientific advice meetings at the MHRA in 2002, on 3rd April and 14th August, as well as meeting with the German and French agencies in 2002. All agencies agreed that the proposed Phase III trial should compare the active product with the administration device alone.

In 2002 the MHRA recommended that:
- Any pre-selection of the population for the trial should be reflected in the SmPC.
- The time to exclusion of non-responders should be addressed and defined in the protocol.
- Patients should be stable at baseline.
- The double-blind phase of 2 weeks was noted to be short, but the applicant wished to
submit long-term, open-label data.

On 24th June 2005, the applicant came for another meeting with the MHRA. They were concerned that their two Phase III trials showed discrepant results. It was noted that patients in the US study, KF10004/H32, were pre-selected as those who were considered to respond to the product. In contrast, in the European study, lidocaine-treatment naïve patients entered an 8-week open-label period before being randomised to continue active, or switch to the placebo patch. The MHRA noted that the disease was heterogeneous. Those patients who have c-fibres involved, which respond to topical lidocaine, cannot be defined prospectively. The applicant considered that from their clinical experience, some patients take up to 4 weeks to show a response. Interpretation of the trial data was complicated by the slow onset of efficacy and the probable efficacy of the placebo device. It was considered that the duration of treatment should be justified by the clinical data.

The key to the assessment of the risk-benefit of the data is that the product appears to be without any major safety concern. Evidence in favour of benefit is slight. Interpretation of the Phase II data suggests that there is some benefit, but this is far from robust and the clinical magnitude is small.

For the US trial, KF10004/H32, recruitment was unusual as patients were already known to regularly use the product from open-label usage and were classified as responders. The crossover period of 14 days was short, but there was reasonable evidence of efficacy.

For the European trial, KF10004/01, product-naïve patients were recruited and initially treated with the active product for 8 weeks in an open-label design. Subsequently, 71 patients entered the 2-week randomised withdrawal treatment period, where active and placebo devices were compared. Although still positive, the treatment effect was small. The time to exit is not a convincing primary endpoint, as patients may stop treatment because of lack of benefit, or possibly, because of lack of need.

In summary, there is some evidence of small clinical benefit, even though it is likely this product may have an additional placebo effect in this condition.

There does not appear to be an important safety concern and for this reason the risk benefit appears positive.

Marketing Authorisations may be granted.

**V User consultation**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
VI Overall conclusion, benefit/risk assessment and recommendation

Quality
The important quality characteristics of Versatis/Lidocaine 5% Medicated Plasters are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Non-clinical
Lidocaine, a local anaesthetic agent that interacts with voltage sensitive Na+ channels on the cell membrane, has been in medical practice since 1948. Products for the surface anaesthesia of the eye, mucous membranes and the skin are available as are product for infiltration and intravenous (i.v.) regional anaesthesia. In addition, lidocaine is used as an antiarrhythmic agent for i.v. or intramuscular administration.

Investigations in healthy human volunteers are stated to have shown that only 3% of the plaster drug contents are systemically available. From the maximum recommended use of three plasters containing 2100mg lidocaine, approximately 64mg will be systemically available per day of administration as a mean value. After the application of the maximum recommended number of three lidocaine 5% medicated plasters during a 12-hour day to healthy volunteers, $C_{\text{max}}$ of 84±36ng/ml and 125±51ng/ml were observed. Administration of lidocaine 5% medicated plasters at the maximum recommended regimen was also performed in patients with acute herpes zoster (AHZ) and with PHN. The mean maximum plasma concentrations of lidocaine were lower than in healthy volunteers (patients with PHN: 52±31ng/ml and patients with AHZ: 83±43ng/ml).

The clinical safety of lidocaine as a local anaesthetic and antiarrhythmic agent are well known. Since the plasma concentrations of lidocaine obtained with the use of lidocaine 5% medicated plaster are much lower than that observed during regional anaesthesia or antiarrhythmia treatment (approx. 50ng/ml versus 1,500-5,000ng/ml, in individual cases >5,000ng/ml), new non-clinical studies have been limited to a skin irritation test in rabbits and a skin sensitisation test in guinea pigs (modified Buehler test). In addition, plasma exposure and the toxicity of the metabolite 2,6-xylidine was evaluated following oral administration of 2,6 xylidine in rats. The results from these studies did not raise any toxicological issues.

The non-clinical overview was based almost entirely on published literature. This is considered to be acceptable in view of the clinical experience with lidocaine as a local anaesthetic and antiarrhythmic agent. In addition, the present application concerns a dermal product where the systemic exposure to lidocaine and its metabolites is much lower than that observed with other lidocaine usages.

There are no non-clinical issues and Marketing Authorisations may be granted.
Efficacy
There are two pivotal studies:

For study KF10004/H32, only patients who had previously responded to Lidocaine (some of whom participated in previous trials) were recruited into this study. Therefore, evidence from this study may not be independent from other studies used in this submission. An enriched population, consisting only of those patients who ‘respond’ has been used in this study. It is difficult to prospectively define those patients who would respond and, therefore, defining the correct population in the SmPC is problematic.

As no washout period was used for patients entering this study, only those patients who were randomised to placebo followed by active treatment give information about the onset of treatment, albeit in an uncontrolled fashion. It would have been beneficial for the applicant to justify that the treatment effect observed in this study could be used to infer conclusions about the onset of treatment.

For study KF10004/01, there are concerns with the randomised withdrawal design of this study being used to assess evidence of efficacy for the onset of treatment. The main concern is that the efficacy population consists of an enriched population of patients who ‘respond’. The study was designed to randomise 70 patients and was stopped after the required number of patients was randomised. Therefore 27 patients who were still ongoing or completed at this time point, could not be considered for randomisation. 137 of the 265 enrolled patients responded, of whom 20 were not eligible for randomisation due to general study end. The SmPC needs to include the key results from this study together with the proportion of patients who responded to Lidocaine.

In summary, the design of the pivotal studies gives only limited evidence of efficacy in an enriched population. However, the applicant has adequately addressed the points raised, and it may be considered that this product has demonstrated some clinical benefit.

Risk-benefit assessment
The quality of the product is acceptable and no new nonclinical or clinical safety concerns have been identified. Extensive clinical experience with lidocaine is considered to have demonstrated the therapeutic value of the compound. There does not appear to be an important safety concern and thus the risk-benefit appears positive and Marketing Authorisations can be granted.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the Medicines and Healthcare products Regulatory Agency website.
Versatis® 5% medicated plaster
Lidocaine

For cutaneous use only.

Do not use if the seal on the sachet is broken.

Apply immediately upon removal from sachet.

Read the package leaflet before use.

After first opening: Keep the sachet tightly closed

Do not refrigerate or freeze.

After first opening the sachet, the plasters must be used within 14 days.

Please see the package leaflet for further information.

Keep out of the sight and reach of children.

30 medicated plasters
Each 14 cm x 10 cm plaster contains 700 mg (5% w/w) lidocaine.

Self-adhesive layer (Shinetsu), liquid crystal, camphor, cedranol, propylene glycol (5120), unes, hexen lactic, parabens, alcohol, propyl alcohol, aluminium glycylate, decyl sebacate, methylparaben (E219), propyl paraben, methylparaben (E218), polyethylene oxide, purified water, parabens, hexanol, propylene glycol, polyethylene oxide, monophosphate, PE7, release liner, polyethylene terephthalate.
Versatis® 5% medicated plaster

**Lidocaine**

Each 14 cm x 14 cm plaster contains 70 mg (5%) w/w Lidocaine.

**Packaging**

Self-adhesive backing: Polyethylene terephthalate, polyethylene terephthalate, polyethylene terephthalate (PET), ethylene vinyl alcohol copolymer (EVOH), polyethylene, polyethylene terephthalate.

For disposal, please use the packaging material.

Forcutaneous use only.

Do not use if the seal on the sachet is broken.

Date opened:

Keep out of the sight and reach of children.

**Manufacturers**

Grunenthal Ltd., Regis Lakeside House, 6 Funtong Road, Stockley Park East, Uxbridge, Middlesex UB11 1SO, United Kingdom

**Marketing Authorization Holder**

Grunenthal Ltd., Regis Lakeside House, 6 Funtong Road, Stockley Park East, Uxbridge, Middlesex UB11 1SO, United Kingdom

**Reg. No.** PL/2002/0016

**Batch No.** Biox
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure numbers</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update sections 4.2 (Posology and administration) and 4.4 (Special warnings) of the SmPC and the PIL regarding warnings concerning potential increased tumourigenesis risk to patient with long term use. Additionally, Module 1.8.2 Risk Management Plan is updated to include the result of the post-approval commitment, Module 2 is updated with addenda for the clinical and non-clinical information and Module 4 with the Tier 1 preclinical study reports (TP2964, TP2967, TP2999, TP3015 and PK1135).</td>
<td>UK/H/1040/001/II/001 UK/H/1041/001/II/001</td>
<td>SmPC and PIL</td>
<td>05/08/2009</td>
<td>04/09/2009</td>
<td>Approval</td>
<td>Yes (Annex 1.1)</td>
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<td>To add new clinical data to Module 2.7 and Module 5.3.</td>
<td>UK/H/1040/001/II/015 UK/H/1041/001/II/016</td>
<td>Nil</td>
<td>24/05/2011</td>
<td>22/07/2011</td>
<td>Approval</td>
<td>Yes (Annex 1.2)</td>
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<td>To update Section 5.1 (Pharmacodynamics) of the SmPC by amending the text to describe the pain relief on a six-point scale (ranging from worse to complete relief).</td>
<td>UK/H/1040/001/IB/011/M UK/H/1041/001/IB/012/M</td>
<td>SmPC</td>
<td>18/04/2011</td>
<td>13/12/2011</td>
<td>Approval</td>
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<tr>
<td>To update sections 4.2 (posology and administration) of the Summary of Product Characteristics (SmPC) following a Mutual Recognition Repeat Use 3rd wave procedure UK/H/1040/001/E/003 (with the Netherlands as CMS), which was concluded successfully on 09.12.2013. Additionally, section 4.8 (undesirable effects) of the SmPC, and the Patient Information Leaflet (PIL) have been updated in line with the QRD template.</td>
<td>UK/H/1040/001/IB/025</td>
<td>SmPC and PIL</td>
<td>08/01/2015</td>
<td>02/02/2015</td>
<td>Yes</td>
<td>Yes (Annex 1.4)</td>
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<td>To update section 4.2 (posology and administration) of the SmPC following a Mutual Recognition Repeat Use 3rd wave procedure UK/H/1040/001/E/003 (with the Netherlands as CMS) for Versatis, which was concluded successfully on 09.12.2013. Additionally, section 4.8 of the SmPC and PIL have been updated in line with the QRD template.</td>
<td>UK/H/1041/001/IB/025</td>
<td>SmPC and PIL</td>
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<td>09/04/2015</td>
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<td>Yes (Annex 1.5)</td>
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Annex 1.1

Reference: PL 21727/0016-0017
Product: Versatis/Lidocaine 5% Medicated Plaster
Marketing Authorisation Holder: Grunenthal Limited
Active Ingredient(s): Lidocaine.

EU Procedure Number(s): UK/H/1040-1041/001/II/001

Reason: To update Sections 4.2 (Posology and administration) and 4.4 (Special warnings) of the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) regarding warnings concerning potential increased tumourigenesis risk to patient with long term use. Additionally, Module 1.8.2 Risk Management Plan is updated to include the result of the post-approval commitment (PAC), Module 2 is updated with addenda for the clinical and non-clinical information and Module 4 with the Tier 1 preclinical study reports (TP2964, TP2967, TP2999, TP3015 and PK1135).

Supporting Evidence
The following has been submitted:
- Addendum to Module 2.4 Non-Clinical Overview and Addendum to Module 2.5 Clinical Overview.
- PAC information previously circulated to CMSs on 23rd December 2008 comprising:
  5 in vitro study reports – 4 Reverse Mutation Assays (Study Numbers TP 2964, TP 2967, TP 2999 and TP 3015)
  -PK 1135 (Formation of DMHA from 2,6-xylidine on incubation with induced rat and human liver S9)
  Please note that the Marketing Authorisation Holder position paper has not been included in this variation, but has been summarised in the Non-Clinical Overview.
- Risk Management Plan (RMP) updates.

Evaluation
- Background
Versatis 5% medicated plaster and its duplicate Lidocaine 5% medicated plaster were approved in the UK in January 2007. The products then underwent a first-wave MRP with Belgium, Germany, France, Luxembourg, Sweden and Slovenia as Concerned Member States (CMSs). The procedures were referred to CMD(h) by the Swedish authority on 4th July 2007 on the grounds that the metabolic pathways of lidocaine result in the formation of several structures which raise potential serious risk to public health in relation to genotoxicity and potential carcinogenic properties (2,6-xylidine and dimethyl N-hydroxyaniline (DMHA)). There was concern that there were insufficient data to assess the magnitude of the risk, which was considered unacceptable for a long-term treatment. After the CMD (h) meeting of September 2007, consensus was reached between all CMSs that the benefit-risk-ratio was positive for these products in their intended use and that the Marketing Authorisations may be granted provided that the MAH committed to conduct further preclinical studies to generate additional data on the potential genotoxic risk of lidocaine metabolites as a post approval commitment (PAC).

The PAC consisted of a tiered approach (3 Tiers). Tier 1 comprised Ames tests with the lidocaine metabolite 2,6-xylidine and proof of dimethyl N-hydroxyaniline (DMHA) formation in the test system. The assessment of the mutagenicity of 2,6-xylidine in the bacterial test system TP2964, TP2967, TP2999 and TP3015 showed that all Ames tests were negative. Secondly, confirmation of the formation and presence of DMHA in the test system -PK1135 demonstrated that 2,6-xylidine was metabolised to DMHA and was detected in the test system. These results together with the published negative results with lidocaine indicated no mutagenic hazard and therefore no additional measures were required. The final PAC report was circulated on the 20th July 2009.
• Changes
On the 20th July 2009 the UK circulated a PAC notification informing the CMSs that the pre-clinical testing (Tier 1) had been adequately completed and that no further testing was required. However, it was concluded that warnings in Section 4.2 and 4.4 of the SmPC and PIL required strengthening to emphasise that the products should be used on a long term basis only by those patients who gain a definite benefit. No comments were received from the CMS concerning these proposals therefore they are deemed acceptable in principle.

This Type II variation has been submitted as a follow-up measure to the PAC to implement the agreed changes to the SmPC and PIL. Consequentially an updated Module 1.8.2 Risk Management Plan to include the results of the post-approval commitment has been submitted. Additionally the study reports concerned with the PAC are included in the MA dossier for completeness. These have previously been assessed and approved during the PAC.

SmPC
Sections 4.2 and 4.4
The changes are as follows:

4.2 Posology and method of administration
Adults and elderly patients
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.

The plaster must be applied to intact, dry, non-irritated skin (after healing of the shingles). Each plaster must be worn no longer than 12 hours. The subsequent plaster-free interval must be at least 12 hours.

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).

Treatment outcome should be re-evaluated after 2-4 weeks. If there has been no response to Versatis after this period or if any relieving effect can solely be related to the skin protective properties of the plaster, treatment must be discontinued as potential risks may outweigh benefits in this context (see sections 4.4 and 5.1). 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.

Use for patients under the age of 18 is not recommended because of the lack of data in this group.

4.4 Special warnings and precautions for use
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).

The plaster should be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.

One of the lidocaine metabolites, 2,6 xylidine, has been shown to be genotoxic and carcinogenic in rats (see section 5.3). Secondary metabolites have been shown to be mutagenic. The clinical
significance of this finding is unknown. Consequently long term treatment with Versatis is only justified if there is a therapeutic benefit for the patient (see section 4.2).

Comment:
SmPC updates reflect the conclusion of the PAC (previously agreed by CMSs) and are therefore acceptable.

Patient Information Leaflet
The changes are as follows:

3. **HOW TO USE VERSATIS**

Always use Versatis exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual daily dose is to use between one and three plasters of the size of the painful areas of your skin. Versatis may be cut into smaller pieces to fit the affected area. You should not use more than 3 plasters at the same time.

The plasters should be removed after 12 hours of use, so that you have a 12 hour period with no plaster.

Usually, you will feel some pain relief on the first day you use the plaster, but it may take up to 2 - 4 weeks until the full pain-relief effect of Versatis is seen. If after that time you still have a lot of pain, please talk to your doctor because the benefits of the treatment must be weighed against potential risks (see Section 2 under ‘Take special care with Versatis’).

Your doctor will check how well Versatis is working at regular intervals.

Comment:
PIL updates reflect the conclusion of the PAC (previously agreed by CMSs) and are, therefore, acceptable.

- **Update to the dossier**
The five in vitro study reports submitted in support of the PAC have been submitted as part of this variation. This information has been previously been fully assessed in the PAC and circulated by the RMS on 20th July 2009.

The non-clinical and clinical overviews have been updated to incorporate the results of the PAC.

Comment:
The update is considered satisfactory.
Risk Management Plan.
Module 1.8.2 Risk Management Plan (RMP) has been updated to include the results of the post approval commitment, i.e Module 4 with the Tier 1 preclinical study reports. The current version of the RMP (version 2) for Versatis has been updated to reflect the changes included as part of this variation. The revised RMP is version 3.

Changes included as part of the update to the RMP
The following changes were included
1. Inclusion of information on the potential for genotoxicity in section 1.1.2.1 of the RMP.
2. Updated post-authorisation safety experience in section 1.2.2.1.3
3. Inclusion of “patients who were actively and intensively immune compromised following transplantation” as a missing population in section 1.2.3.8
4. Summary of the non-clinical study post approval commitments proposed for investigating the potential genotoxicity of lidocaine metabolites, including the negative results from the first tier of these studies. As the results of the first tier were negative, tiers 2 and 3 have not been initiated.
5. Update of section 1.2.5.2 with WHO-Vigibase data for malignant neoplasms with lidocaine as suspect drug up to Q2 2009
6. Inclusion in section 1.2.10 and table 1-8 (Summary of ongoing safety concerns) of genotoxicity/carcinogenicity as a potential risk
7. Inclusion of “patients who were actively and intensively immune compromised following transplantation” as a missing population in table 1-8 (Summary of ongoing safety concerns)
8. Inclusion of genotoxicity/carcinogenicity as a potential risk and patients who were actively and intensively immune compromised following transplantation” as a missing population in table 2.1
9. Further detail on the newly available results from tier 1 of the genotoxicity studies in table 2-2
10. Inclusion of revised SmPC wording on genotoxicity/carcinogenicity in table 3-1 and section 3.1.3.2
11. Inclusion of immune compromised patients as “missing information” in table 3-1 and section 3.1.4.1
12. Inclusion of genotoxicity/carcinogenicity as a potential risk and immune compromised patients as missing information in table 5

Assessor’s comments
The MAH has included all the relevant information in version 3 of the RMP as requested. The updated RMP is satisfactory.

CONCLUSION
The proposed SmPC and PIL amendments are in-line with that requested by MHRA and MPA following the PAC. The updated RMP is satisfactory.

Decision – Approved 04 September 2009
Annex 1.2

Our Reference: PL 2172/0016-0017
Product: Versatis/Lidocaine 5% medicated plaster
Marketing Authorisation Holder: Grunenthal Limited
Active Ingredient(s): Lidocaine.

EU Procedure Number(s): UK/H/1040/001/II/015 and UK/H/1041/001/II/016

Reason:
To update Module 2.7 and Module 5.3 with new clinical data.

Supporting Evidence
New clinical data have become available, which the applicant has proposed to add to the current dossier. In Module 2.7, the order of the listing of the study synopses has changed to reflect the listing of the clinical study reports in Module 5.3. In addition, to newly added synopses of clinical studies which recently became available, synopses of studies have been added wherein the respective study reports are already included in the current Module 5.3 (i.e. synopses of the Kaken Report of the population pharmacokinetic report PP0018Pa, of KF10004/02a and of KF10004/02 interim report).

Evaluation
• Summaries
  The following summaries have been submitted in Module 2.7:
  • List of references (see below)
  • Summary of Biopharmaceutical Trials and Associated Analytical Methods dated 30 March 2010
  • Summary of Clinical Pharmacology Trials dated 30 March 2010
  • Summary of clinical safety dated 28 June 2010
  • Synopses of Individual Studies (see below)

RMS’ comments:
These summaries refer to results from studies that have either been assessed during the original MAA or in the variation applications that are ongoing MRPs in parallel with this application. No new data are included that would warrant an update to the product information.

• Study synopses
  The following are new or updated synopses:

Synopsis Kraken Report
  The full report for this synopsis is already included in Module 5.3.

Synopsis PP0018Pa
  Study PP0018P was submitted with the original dossier and the objectives were to:
  • Establish the structural population pharmacokinetic model of lidocaine and its metabolite 2,6-xylidine after topical plaster application.
  • Find covariates influencing the exposure to lidocaine and its metabolite 2,6-xylidine.
  • Estimate the general exposure to lidocaine and its metabolite 2,6-xylidine as well as the exposure in pharmacokinetic sub populations.

Pharmacokinetic data came from the following studies:
KF10004/01: “A double-blind, multicentre, multiple-dose, enriched enrolment, randomised withdrawal, parallel-group phase III study with lidocaine 5% medicated plaster and corresponding placebo plaster in patients suffering from post herpetic neuralgia (PHN)”
KF10004/02: “An open-label, multicentre, multiple-dose, phase III study with lidocaine 5% medicated plaster in patients suffering from post herpetic neuralgia (PHN)”

Study PP0018Pa was a study to evaluate the population pharmacokinetic properties of lidocaine and its metabolites, MEGX, GX, and 2,6-xylidine, after application of lidocaine 5% medicated plaster based on data coming from trial KF10004/01 and trial KF10004/02. The objectives of this study were:

- To establish the structural population pharmacokinetic model of lidocaine and its metabolites 2,6-xylidine, glycinexylidide (GX), and monoethylglycinexylidide (MEGX) after topical plaster application.
- To find covariates influencing the exposure to lidocaine and its metabolites 2,6-xylidine, GX, and MEGX.
- To estimate the general exposure to lidocaine and its metabolites 2,6-xylidine, GX, and MEGX as well as the exposure in pharmacokinetic subpopulations.

The data collected in 212 subjects with PHN up to 18 months were used to build a pharmacokinetic model to predict concentrations of lidocaine and three metabolites: MEGX, GX and 2,6-xylidine simultaneously. After multiple applications of three simultaneous plasters, the geometric mean serum concentrations for lidocaine, MEGX, GX and 2,6-xylidine were 23, 5, 6, and 5 μg/L, respectively.

The analysis resulted in the estimation of a model that provides reliable estimates of the pharmacokinetic behaviour of lidocaine after medicated plaster application. The model was qualified using simulations and showed reliable predictive properties.

The model demonstrated that steady state was reached by the 4th day of administration for the four analytes and no more accumulation would occur after that.

The investigation of the effect of long-term administration on the PK of lidocaine showed no change in PK parameters with the time in the trial, which precludes a change of exposure with time.

The result of the trial data indicated that when increasing the number of plasters from one to three plasters simultaneously, the systemic exposure increased less than proportionally to the number of plasters.

No clinically relevant effect of other covariates was found to affect the exposure to lidocaine or its metabolites.

The variability of exposure between and within subjects is large.

Synopsis KF10004/03 and Synopsis KF10004/03-PHN
Study KF10004/03 compared the efficacy of lidocaine 5% medicated plaster with that of pegabalin in patients with PHN and DPN.

This has been assessed in MRP UK/H/1040/001/II/010 & UK/H/1041/001/II/011 and also in MRP UK/H/1040/001/II/013 & UK/H/1041/001/II/014. Amendments have been proposed to section 5.1 of the SmPC.

Synopsis KF10004/02-a, Synopsis KF10004/02-ext and Synopsis Interim Report KF10004/02
Study KF10004/02 evaluated the local and systemic safety profile and the analgesic efficacy of long-term treatment with lidocaine 5% medicated plaster.
This has been assessed in MRP UK/H/1040/001/II/007 & UK/H/1041/001/II/008 and also in MRP UK/H/1040/001/II/012 & UK/H/1041/001/II/013. Amendments have been proposed to section 4.2 and 5.1 of the SmPC.

Synopsis KF10004/05 Overall Safety Summary
The objective of this study was to perform an integrated analysis of the safety profile of lidocaine 5% medicated plaster on pooled datasets from the trials KF10004/H31, KF10004/H32, KF10004/01, and KF10004/02.

In general terms, the information gathered from the pooled dataset indicates that adverse effects (AEs) occurring in the safety population showed individual relative frequencies below 5%. The most commonly reported AEs were related to the skin, in particular to the application site, namely application site erythema, application site pruritus, erythema, application site pain, rash, application site irritation, application site dermatitis, and application site hypersensitivity. Skin-related AEs were mostly considered by the Investigator as related to the use of lidocaine 5% medicated plaster.

There were 4 serious adverse effects (SAEs) leading to death (1 case in the trial KF10004/H31 and 3 cases in KF10004/02). These and the other 43 SAEs were assessed by the investigator and the sponsor as not related to the administration of lidocaine 5% medicated plaster.

No specific onset or duration pattern was observed for any of the AEs in relation to application of lidocaine 5% medicated plaster.

Results of the analysis of pooled data confirm the statements in the current Summary of Product Characteristics (SmPC).

RMS’ comments:
These additional study synopses do not provide any new data, particularly any new safety data. The adverse events occurring locally are listed in the SmPC and no further updates to the SmPC are required.

Changes to section 5.1 of the SmPC have been proposed by the applicant in response to the results of studies KF10004/02 and KF10004/03 and are the subject of MRPs that are ongoing in parallel with this application.

- Periodic Safety Updates (PSURs)
The following PSURs are added to the dossier:
PSUR covering the period July 2008 to January 2009
PSUR covering the period January 2009 to July 2009
PSUR covering the period July 2009 to July 2010
**RMS’ comments:**
The PSURs covering the period July 2008 to July 2009 have been previously submitted, assessed and accepted.

The PSUR covering the period July 2009 to July 2010 is currently under assessment in a separate MRP.

**Conclusion of the PSUR:**
Medical concepts included in ICSRs received in the period covered by this PSUR were already known to occur with lidocaine 5% medicated plaster, were evaluated as unlikely related to lido 5% medicated plaster or occurred in single ICSRs only. None of them were identified as a signal of a new adverse drug reaction or meaningful change in characteristics of known adverse drug reactions.

No action is required based on this PSUR.

- Literature Reference
  Thirty-six literature references have been submitted.

**RMS’ comments:**
The majority of these references relate to the open-label studies of lidocaine 5% medicated plaster in neuropathic pain other than Post Herpetic Neuralgia and referred to in MR Procedure UK/H/1040/001/II/010 & UK/H/1041/001/II/011

Included in the references are the CHMP Guideline on Clinical Trials in Small Populations and the ICH Guideline for Good Clinical Practice.

The applicant is reminded that literature searches for new safety information should form part of pharmacovigilance activities and should be reported in PSURs. Should new safety information come to light it is the responsibility of the applicant to submit a variation application in a timely manner in order that that safety information can be included in the product information.

**Conclusion**
The applicant has submitted updated summaries, study reports and literature references for inclusion in the dossier. For this variation application, these additional documents do not include information that required updates to the product information.

The applicant has proposed updates to the dossier and the RMS recommends that this variation application is approvable:

**Decision – Granted 22 July 2011**
Annex 1.3

Our Reference: PL 21727/0016-0017
Product: Versatis/Lidocaine 5% medicated plaster
Marketing Authorisation Holder: Grunenthal Limited
Active Ingredient(s): Lidocaine
EU Procedure Number (if applicable): UK/H/1040/001/IB/011/MR and UK/H/1041/001/IB/012/MR

Reason:
To update Section 5.1 (Pharmacodynamics) of the SmPC by amending the text to describe the pain relief on a six-point scale (ranging from worse to complete relief).

Supporting Evidence
Clinical Overview, with a Clinical Expert statement explaining the update of the SmPCs.

Evaluation
The amended sections of the SmPCs are satisfactory. These are provided below:

Amended section for the SmPC for Versatis® 5% Medicated Plaster (PL 21727/0016):

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: local anaesthetics, amides
ATC code: N01 BB02

Mechanism of action
Lidocaine when applied topically in the form of the plaster, has been shown in studies to produce a local analgesic effect. The mechanism by which this occurs is due to stabilisation of neuronal membranes, which is thought to cause down regulation of sodium channels resulting in pain reduction.

Clinical efficacy
Pain management in PHN is difficult. There is evidence of efficacy with Versatis in the symptomatic relief from the allodynic component of PHN in some cases (see section 4.2).

Efficacy of Versatis has been shown in post-herpetic neuralgia studies. Other models of neuropathic pain have not been studied.

There were two main controlled studies carried out to assess the efficacy of the lidocaine 5% medicated plaster.

In the first study, patients were recruited from a population who were already considered to respond to the product. It was a cross over design of 14 days treatment with lidocaine 5% medicated plaster followed by placebo, or vice versa. The primary endpoint was the time to exit, where patients withdrew because their pain relief was two points lower than their normal response on a six point scale (ranging from worse to complete relief). There were 32 patients, of whom 30 completed. The median time to exit for placebo was 4 days and for active was 14 days (p value < 0.001); none of those on active discontinued during the two week treatment period.

In the second study 265 patients with post-herpetic neuralgia were recruited and allocated eight weeks of open label active treatment with lidocaine 5% medicated plaster. In this uncontrolled setting approximately 50% of patients responded to treatment as measured by at least four points on a six point scale (ranging from worse to complete relief). A total of 71 patients were
randomised to receive either placebo or lidocaine 5% medicated plaster given for 2-14 days. The primary endpoint was defined as lack of efficacy on two consecutive days because their pain relief was two points lower than their normal response on a six point scale (ranging from worse to complete relief) leading to withdrawal of treatment. There were 9/36 patients on active and 16/35 patients on placebo who withdrew because of lack of treatment benefit.

Post hoc analyses of the second study showed that the initial response was independent of the duration of pre-existing PHN. However, the notion that patients with longer duration of PHN (>12 months) do benefit more from active treatment is supported by the finding that this group of patients was more likely to drop out due to lack of efficacy when switched to placebo during the double-blind withdrawal part of this study.

**Amended section for the SmPC for Lidocaine® 5% Medicated Plaster (PL 21727/0017):**

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local anaesthetics, amides

ATC code: N01 BB02

Mechanism of action

Lidocaine when applied topically in the form of the plaster, has been shown in studies to produce a local analgesic effect. The mechanism by which this occurs is due to stabilisation of neuronal membranes, which is thought to cause down regulation of sodium channels resulting in pain reduction.

Clinical efficacy

Pain management in PHN is difficult. There is evidence of efficacy with Lidocaine 5% medicated plaster in the symptomatic relief from the allodynic component of PHN in some cases (see section 4.2).

Efficacy of Lidocaine 5% medicated plaster has been shown in post-herpetic neuralgia studies. Other models of neuropathic pain have not been studied.

There were two main controlled studies carried out to assess the efficacy of the Lidocaine 5% medicated plaster.

In the first study, patients were recruited from a population who were already considered to respond to the product. It was a cross over design of 14 days treatment with Lidocaine 5% medicated plaster followed by placebo, or vice versa. The primary endpoint was the time to exit, where patients withdrew because their pain relief was two points lower than their normal response on a six point scale (ranging from worse to complete relief). There were 32 patients, of whom 30 completed. The median time to exit for placebo was 4 days and for active was 14 days (p value < 0.001); none of those on active discontinued during the two week treatment period.

In the second study 265 patients with post-herpetic neuralgia were recruited and allocated eight weeks of open label active treatment with Lidocaine 5% medicated plaster. In this uncontrolled setting approximately 50% of patients responded to treatment as measured by at least four points on a six point scale (ranging from worse to complete relief). A total of 71 patients were randomised to receive either placebo or Lidocaine 5% medicated plaster given for 2-14 days. The primary endpoint was defined as lack of efficacy on two consecutive days because their pain relief was two points lower than their normal response on a six point scale (ranging from worse to complete relief) leading to withdrawal of treatment. There were 9/36 patients on active and 16/35 patients on placebo who withdrew because of lack of treatment benefit.
Post hoc analyses of the second study showed that the initial response was independent of the duration of pre-existing PHN. However, the notion that patients with longer duration of PHN (>12 months) do benefit more from active treatment is supported by the finding that this group of patients was more likely to drop out due to lack of efficacy when switched to placebo during the double-blind withdrawal part of this study.

**Conclusion**
The proposed SmPCs amendments are satisfactory and there are no objections to approval.

**Decision – Approved 13 December 2011**
Annex 1.4

Our Reference: PL 21727/0016
Product: Versatis medicated plaster 5%w/w
Marketing Authorisation Holder: Grunenthal Limited
Active Ingredient(s): Lidocaine

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/1040/001/IB/025

Reason:
To update sections 4.2 (posology and administration) of the Summary of Product Characteristics (SmPC) following a Mutual Recognition Repeat Use 3rd wave procedure UK/H/1040/001/E/003 (with the Netherlands as CMS), which was concluded successfully on 09.12.2013. Additionally, section 4.8 (undesirable effects) of the SmPC, and the Patient Information Leaflet (PIL) have been updated in line with the QRD template.

Supporting Evidence
Revised SmPC fragments and updated PIL text have been provided.

Evaluation
The updated sections of the SmPC are in line with the latest QRD template and are satisfactory.

The amendment to the PIL text is satisfactory.

Conclusion
The amendments to the SmPC fragments and the PIL text can be approved.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision - Approved on 02 February 2015.
## Annex 1.5

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<td><strong>Marketing Authorisation Holder:</strong></td>
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<td><strong>EU Procedure Number (if applicable):</strong></td>
<td>UK/H/1041/001/IB/025</td>
</tr>
</tbody>
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**Reason:**
To update section 4.2 (posology and administration) of the Summary of Product Characteristics (SmPC) following a Mutual Recognition Repeat Use 3rd wave procedure UK/H/1040/001/E/003 (with the Netherlands as CMS) for Versatis, which was concluded successfully on 09.12.2013. Additionally, section 4.8 of the SmPC, and the Patient Information Leaflet (PIL) have been updated in line with the QRD template.

**Supporting Evidence**
Revised SmPC and PIL have been provided.

**Evaluation**
The marketing authorisation holder (MAH) has updated sections 4.2 of the SmPC to bring it in line with section 4.2 of the SmPC for Versatis 5 % medicated plaster (PL 21727/0016), with respect to guidance for the prescriber if pain relief is solely related to the skin protective properties of the plaster, rather than the active substance. Furthermore, section 4.8 of the SmPC is updated to include the UK wording for the reporting of suspected adverse reactions. The introductory paragraph of the PIL has been updated in line with the QRD template.

No other changes have been proposed.

**Conclusion**
The proposed changes to the SmPC and PIL are acceptable.

In accordance with Directive 2010/84/EU, the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for products granted marketing authorisations at a national level are available on the Medicines and Healthcare products Regulatory Agency website.

**Decision** - Approved on 09 April 2015.