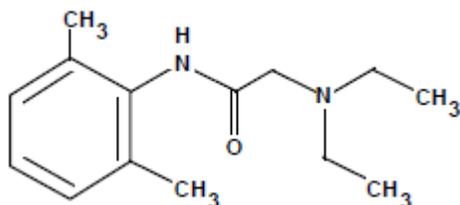


VERSATIS (Lignocaine) 5% w/w, Dermal Patch

NAME OF THE MEDICINE

Lignocaine

Structural Formula:



Chemical Name: 2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide

Molecular Formula: C₁₄H₂₂N₂O

Molecular Weight: 234.3

CAS Number: 137-58-6

DESCRIPTION

Versatis is a white hydrogel patch containing adhesive material, which is applied to a non-woven polyethylene terephthalate backing embossed with 'Lidocaine 5%' and covered with a polyethylene terephthalate film release liner.

Each 10 cm x 14 cm patch contains 700 mg (5% w/w) lignocaine (50 mg lignocaine per gram adhesive base).

Lignocaine is a white or almost white crystalline powder, practically insoluble in water, very soluble in ethanol, and freely soluble in ether. The pKa is 7.9. The coefficient (log D) is defined as the ratio of the equilibrium concentrations of a single molecular species in a 1-octanol/aqueous buffered solution 2-phase system at pH 7.4. The value of log D for lignocaine in 1-octanol/water is 1.61.

PHARMACOLOGY

Pharmacotherapeutic group: local anaesthetics, amides

Pharmacodynamics

Lignocaine is a local anaesthetic of the amide type which stabilises excitable membranes by inactivation of sodium channels. Its action on neuronal membranes prevents neuronal conduction. When applied topically in the form of the patch, lignocaine produces a local analgesic effect.

Lignocaine 5% dermal patch has a dual mode of action: the pharmacological action of lignocaine diffusion and the mechanical action of the hydrogel patch that protects the hypersensitive area. The lignocaine contained in the 5% dermal patch diffuses continuously into the skin, providing a local analgesic effect.

Pharmacokinetics

Absorption

The amount of lignocaine systemically absorbed from lignocaine 5% dermal patch is directly related to both the duration of application and the surface area over which it is applied. When lignocaine 5% dermal patch is used according to the maximum recommended dose (3 patches applied simultaneously for 12 h) about $3\pm 2\%$ of the total applied lignocaine dose is systemically available and similar for single and multiple administrations. Maximum systemic concentrations of lignocaine were observed between 9 and 12 h after application of the patch.

A population kinetics analysis of the clinical efficacy studies in patients suffering from post-herpetic neuralgia (PHN) revealed a mean maximum concentration for lignocaine of 45 ng/mL after application of 3 patches simultaneously 12 h per day after repeated application for up to one year. This concentration is in accordance with the observation in pharmacokinetic studies in PHN patients (52 ng/mL) and in healthy volunteers (85 ng/mL and 125 ng/mL).

For lignocaine and its metabolites MEGX, GX, and 2,6-xylidine no tendency for accumulation was found; steady state concentrations were reached within the first four days.

The population kinetic analysis indicated that when increasing the number from 1 to 3 patches worn simultaneously, the systemic exposure increased less than proportionally to the number of used patches.

Distribution

After intravenous administration of lignocaine to healthy volunteers, the volume of distribution was found to be 1.3 ± 0.4 L/kg (mean \pm S.D., n = 15). The lignocaine distribution volume showed no age-dependency; however it is decreased in patients with congestive heart failure and increased in patients with liver disease. At plasma concentrations produced by application of the patch, approximately 70% of lignocaine is bound to plasma proteins. Lignocaine crosses the placental and blood brain barriers presumably by passive diffusion.

Biotransformation

Lignocaine is metabolised rapidly in the liver to a number of metabolites. The primary metabolic route for lignocaine is N-dealkylation to monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which are less active than lignocaine and available in low concentrations. These are hydrolyzed to 2,6-xylidine, which is converted to 4-hydroxy-2,6-xylidine and the N-hydroxylation product N-(2,6-dimethylphenyl)-hydroxylamine (DMHA).

The metabolite, 2,6-xylidine, has unknown pharmacological activity but has shown carcinogenic potential in rats (see **Carcinogenicity**). A population kinetics analysis revealed a mean maximum concentration for 2,6-xylidine of 9 ng/mL after repeated daily applications for up to one year. This finding is confirmed by a phase I pharmacokinetic study.

Lignocaine may undergo metabolism in the skin.

Elimination

Lignocaine 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 lignocaine 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. The elimination half-life of lignocaine after patch application in healthy volunteers is 7.6 hours. After multiple administration of lignocaine 5% dermal patch in healthy subjects, the elimination half-lives of MEGX, GX and 2,6-xylidine are 6.4 h, 13 h, and 15 h respectively. The systemic clearance of lignocaine is 0.635 ± 0.175 L/min.

The excretion of lignocaine and its metabolites may be delayed in cardiac, renal or

hepatic insufficiency.

CLINICAL TRIALS

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.

There were two key controlled studies carried out to assess the efficacy of the lignocaine 5% dermal patch. A third study provides information on maintenance of effect.

Efficacy was demonstrated in a multicentre, enriched enrolment, double-blind placebo-controlled, multiple dose randomised-withdrawal, parallel group study with lignocaine 5% dermal patch and corresponding placebo patch. This study had an initial 8-week run-in, open label phase in which patients with PHN responding to treatment were randomised to a 2-week, double-blind treatment period with either lignocaine 5% dermal patch or placebo patch. PHN was defined as neuropathic pain persisting for at least 3 months after healing of a herpes zoster skin rash.

Patients aged 50 years and older, suffering from PHN and having an average pain intensity (during last week prior to screening and enrolment visit) of at least 4 on the 11 point numeric rating scale (NRS) applied lignocaine 5% dermal patch for up to 8 weeks. Only those patients who reported regular use of the lignocaine 5% dermal patch during the last 4 weeks of the run-in phase, an average daily pain intensity of 7 or less on the 11-point NRS in the last week prior to randomisation, increase in pain intensity when the patch was not worn, and an average pain relief of 'moderate' or better at randomisation (recall period of 1 week prior to the visit) were considered to be responders and were eligible for randomisation.

The primary endpoint was the time-to-exit during the double-blind phase due to lack of efficacy (decrease of pain relief score by two or more categories on a 6-item pain relief scale on two consecutive application days in comparison to the average pain relief in last week on treatment with lignocaine 5% dermal patch before randomisation in run-in phase).

Of the 265 patients, 137 (52%) entered the run-in phase and responded to lignocaine 5% dermal patch. Of these, 71 were randomised to the double-blind phase. About 40% of patients randomised to each treatment group were not regularly taking any concomitant medication for PHN pain at study entry. The median time to exit the

double-blind period was 13.5 days for patients randomised to active patch (n = 36) and 9.0 days for those randomised to placebo patch (n = 35). This difference was not statistically significant. For the *per protocol* population, median time to exit was 14 days for the active patch (n = 17) and 6 days for the placebo patch (n = 17). This difference between groups was statistically significant.

Post hoc analyses of this 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.

A double-blind, placebo-controlled, cross-over trial was conducted to test whether patients who had been using lignocaine 5% dermal patch could distinguish between the lignocaine patch and a placebo patch. Half of the patients were randomised to receive lignocaine 5% dermal patch as first treatment and half received the placebo patch as first treatment then *vice versa* in the second treatment phase. After up to 14 days in the first phase patients were directly switched to second treatment phase. The primary endpoint was 'time to exit' comparing treatment phases.

Patients were to withdraw from the treatment phase if their pain relief was 2 points lower than their usual response to lignocaine 5% dermal patch on a 6-point verbal rating scale (worse, no pain relief, slight relief, moderate relief, a lot of relief, complete relief). The secondary end-point was patient's preference between treatments. Of the 33 patients with PHN in this study, 32 of them received the investigational products and completed the study. In general, patients used up to 3 patches per application with only three exceptions (two patients used up to 4 and one patient 5 patches per application). The median times to exit in each treatment arm were >14 days for lignocaine 5% dermal patch and 3.8 days for placebo patch (across both treatment periods) $p < 0.001$. Three patients (9.4%) preferred placebo patch, 25 patients (78.1%) preferred lignocaine 5% dermal patch, and 4 patients (12.5%) had no preference.

Maintenance of efficacy was assessed over up to 12 months in an open-label, multicentre, multiple-dose study conducted in 259 patients aged 50 years and older with PHN for >3m after herpes zoster (HZ) rash healing who participated in an earlier efficacy study, or had PHN with average pain intensity of ≥ 4 (0–11 scale) over last week prior to screening. At 12 months, 143 patients had completed the study. Pain relief was generally maintained.

INDICATIONS

For the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (PHN).

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. The patch is also contraindicated in patients with known hypersensitivity to other local anaesthetics of the amide type e.g. bupivacaine, etidocaine, mepivacaine and prilocaine.

The patch must not be applied to inflamed or injured skin, such as active herpes zoster lesions, atopic dermatitis or wounds.

PRECAUTIONS

The patch should not be applied to mucous membranes. Eye contact with the patch should be avoided.

The patch contains propylene glycol which may cause skin irritation. It also contains methyl hydroxybenzoate and propyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

Excessive dosing

Excessive dosing by applying lignocaine 5% dermal patch to larger areas or for longer than the recommended wearing time could result in increased absorption of lignocaine and higher blood concentrations, which may lead to systemic adverse drug reactions (see **ADVERSE EFFECTS**). The blood concentration of lignocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients or impaired elimination may all contribute to increasing the blood concentration of lignocaine. Lignocaine toxicity could be expected at lignocaine blood concentrations above 5 µg/mL. With recommended dosing of lignocaine 5% dermal patch, the average peak blood concentration is about 0.13 µg/mL, but individual concentrations up to 0.28 µg/mL have been observed in clinical trials.

Cardiac, renal and hepatic insufficiency

The patch should be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment. The excretion of lignocaine and

its metabolites may be delayed in patients with these conditions. These patients therefore have more potential for developing higher systemic concentrations of lignocaine.

External heat sources

Placement of external heat sources, such as heating pads or electric blankets, over lignocaine 5% dermal patch is not recommended as this has not been evaluated and may increase plasma lignocaine levels.

Accidental exposure

Even a used lignocaine 5% dermal patch contains a large amount of lignocaine (at least 665 mg). The potential exists for a small child or pet to suffer serious adverse effects from chewing or ingesting a new or used lignocaine 5% dermal patch, although the risk with this formulation has not been evaluated. It is important for patients to store and dispose of the lignocaine 5% dermal patch out of the reach of children, pets and others.

Lignocaine metabolite toxicity

The lignocaine metabolite, 2,6-xylidine, has been shown to be genotoxic and carcinogenic in rats and a secondary metabolite has been shown to be mutagenic (see **Carcinogenicity** and **Genotoxicity**). The clinical significance of these findings is unknown. Consequently long term treatment with Versatis is only justified if there is a therapeutic benefit for the patient (see **DOSAGE AND ADMINISTRATION**).

Use in pregnancy (Category A)

Lignocaine crosses the placenta. However, there are no adequate data from the use of lignocaine in pregnant women. Animal studies are incomplete with respect to effects on pregnancy, embryo-fetal development, parturition or postnatal development.

Lignocaine had no effect on general reproductive performance in rats at plasma concentrations up to 130-fold those observed in patients. No adverse effects were seen in an embryofetal / teratogenicity study in rats at plasma concentrations more than 200-fold that observed in patients.

The potential risk for humans is unknown. Therefore, Versatis should not be used during pregnancy unless clearly necessary.

Use in lactation

Lignocaine is excreted in milk. However, there are no studies of the Versatis patch in breast-feeding women. Since the metabolism of lignocaine is relatively rapid and almost completely in the liver, only very low levels of lignocaine are expected to be excreted into milk.

Use in children

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

Carcinogenicity

Carcinogenicity studies have not been performed with lignocaine. A two year dietary study in rats with the metabolite 2,6-xylidine noted inflammation and hyperplasia of the nasal olfactory epithelium and carcinomas and adenomas in the nasal cavity.

Tumorigenic changes were also found in the liver and subcutis. Estimated 2,6-xylidine exposure (plasma AUC) at the lowest tumorigenic dose was at least 60-fold clinical exposure at the maximum recommended human dose (MRHD) of Versatis dermal patch. Because the risk to humans is unclear, long term treatment with high doses of lignocaine should be avoided.

Genotoxicity

Lignocaine itself has shown no evidence of genotoxicity when investigated *in vitro* or *in vivo*. Metabolites of lignocaine, 2,6-xylidine and N-(2,6-dimethylphenyl)-hydroxylamine (DMHA), have shown genotoxic activity in several assays

Effects on fertility

No clinical data regarding fertility are available for lignocaine. Animal studies have not shown effects on female fertility.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed. No clinically relevant interactions have been observed in clinical studies with the lignocaine 5% dermal patch.

Antiarrhythmic drugs

Although normally the absorption of lignocaine from the skin is low, the patch must be used with caution in patients receiving Class I antiarrhythmic medicinal products (e.g. tocainide, mexiletine) since the cardiac effects (including arrhythmia) and CNS effects (including convulsions, CNS depression) may be additive and potentially synergistic.

Local anaesthetic agents

When lignocaine 5% dermal patch is used concomitantly with other products containing local anaesthetic agents, the amount absorbed from all formulations must be considered.

Effects on ability to drive or use machines

No studies on the effects on the ability to drive and use machines have been performed. An effect on the ability to drive and use machines is unlikely because systemic absorption is minimal (see **Pharmacokinetics**).

ADVERSE EFFECTS

Systemic adverse drug reactions following the appropriate use of the patch are unlikely since the systemic concentration of lignocaine is very low (see **Pharmacokinetics**). Systemic adverse drug reactions to lignocaine are similar in nature to those observed with other amide local anaesthetic agents (see **OVERDOSAGE**).

Adverse events identified in clinical trials

Adverse events occurring in at least 1.5% of patients treated for up to 6 months are displayed in **Table 1**. The adverse events listed may be associated with the underlying disease and concomitant medications.

Table 1: Percentage of patients with reported adverse events $\geq 1.5\%$ (independent from causal relationship) in the safety population of 3 clinical trials

MedDRA primary system organ class	Preferred term	Patients valid for safety analysis (n = 306) Percentage of patients with adverse events
Total number of events	-	256
Total percentage of patients with adverse events	-	36.9%
Cardiac disorders	-	3.6%
Eye disorder	-	2.0%
Gastrointestinal disorder	-	4.6%
	Nausea	2.0%
General disorders and administration site conditions	-	11.1%
	Application site burning	1.6%
	Application site erythema	3.6%
	Application site pain	1.6%
Infections and infestations	Application site pruritus	2.0%
	Nasopharyngitis	6.9%
Injury, poisoning, and procedural complications	-	2.0%
Investigations	-	2.9%
Musculoskeletal and connective tissue disorders	-	1.6%
Nervous system disorders	-	6.9%
	Headache	4.9%
Psychiatric disorders	-	1.6%
Respiratory, thoracic, and mediastinal disorders	-	1.6%
Skin and subcutaneous tissue disorders	-	8.2%
	Erythema	3.3%
	Pruritus	2.0%
Vascular disorders	Rash	2.3%
	-	2.0%

Adverse drug reactions identified in clinical trials

Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Approximately 16% of patients can be expected to experience adverse drug reactions. These are localised reactions due to the nature of the medicinal product.

The most commonly reported adverse drug reactions were skin reactions (such as erythema, rash, application site pruritus, application site burning, application site dermatitis, application site erythema, application site vesicles, dermatitis, skin irritation, and pruritus).

The table below lists adverse drug reactions that have been reported in studies of post herpetic neuralgia patients receiving the patch. They are listed by system organ class and frequency. Frequencies are defined as very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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

All adverse drug reactions were predominantly of mild and moderate intensity. Of those less than 5% lead to treatment discontinuation.

Post-marketing experience

Additionally, the following adverse drug reactions have been observed in patients receiving the patch under post-marketing conditions:

Body system	Frequency	Adverse Drug Reaction
Injury, poisoning and procedural complications	Very rare	Open wound
Immune system disorders	Very rare	Anaphylactic reaction, hypersensitivity

All adverse drug reactions were predominantly of mild and moderate intensity. Of those less than 5% lead to treatment discontinuation.

DOSAGE AND ADMINISTRATION

Adults and elderly patients

The painful area should be covered with the patch once daily for up to 12 hours within a 24 hour period. Only the number of patches that are needed for an effective treatment should be used. When needed, the patches may be cut into smaller sizes with scissors prior to removal of the release liner. In total, not more than three patches should be used at the same time.

The patch must be applied to intact, dry, non-irritated skin (after healing of the shingles).

Each patch must be worn no longer than 12 hours. The subsequent patch-free interval must be at least 12 hours.

The patch 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 patch, treatment must be discontinued as potential risks may outweigh benefits in this context (see **PRECAUTIONS** and **Pharmacodynamics**). Treatment should be reassessed at regular intervals to decide whether the amount of patches needed to cover the painful area can be reduced, or if the patch-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.

OVERDOSAGE

Overdose with the patch is unlikely but it cannot be excluded that inappropriate use, such as use of a higher number of patches at the same time, with prolonged application period, or using the patch on broken skin might result in higher than normal plasma concentrations. Possible signs of systemic toxicity will be similar in nature to those observed after administration of lignocaine as a local anaesthetic agent, and may include the following signs and symptoms: dizziness, vomiting, drowsiness, dysgeusia, seizures, mydriasis, bradycardia, arrhythmia, and shock.

In addition, known drug interactions related to systemic lignocaine concentrations with beta-blockers, CYP3A4 inhibitors (e.g. imidazole derivatives, macrolides) and antiarrhythmic agents might become relevant with overdose.

In case of suspected overdose the patch should be removed and supportive measures taken as clinically needed. Contact the Poisons Information Centre on 13 11 26 for advice on management. If there is any suspicion of lignocaine overdose, drug blood concentration should be checked. There is no antidote to lignocaine.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Versatis patches are contained in a re-sealable sachet composed of paper / polyethylene / aluminium / ethylene meta-acrylic acid co-polymer containing 5 patches.

Each 10 cm x 14 cm patch contains 700 mg (5% w/w) lignocaine (50 mg lignocaine per gram adhesive base).

Each carton contains 5, 10, 20, 25 or 30 patches. Not all pack sizes may be marketed.

Excipients

Self adhesive layer: glycerol, sorbitol solution (70%) (crystallising), carmellose sodium, propylene glycol, urea, heavy kaolin, tartaric acid, gelatin, polyvinyl alcohol, aluminium glycinate, disodium edetate, methyl hydroxybenzoate, propyl hydroxybenzoate, polyacrylic acid, sodium polyacrylate, purified water.

Backing fabric and release liner: Polyethylene terephthalate (PET).

Storage

Store below 25°C. Do not refrigerate or freeze.

After first opening: Keep the sachet tightly closed.

Use opened sachets within 14 days.

Special precaution for disposal

After use the patch still contains active substance. After removal, the used patches should be folded in half, adhesive side inwards so that the self-adhesive layer is not exposed, and the patch should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE

S4

AUST R 175178

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

16 March 2012

DATE OF MOST RECENT AMENDMENT

24 July 2015