SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Versatis 5% medicated plaster

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 cm x 14 cm plaster contains 700 mg (5% w/w) lidocaine
(50 mg lidocaine per gram adhesive base)

Excipients:
Methyl parahydroxybenzoate 14 mg
Propyl parahydroxybenzoate 7 mg
Propylene glycol 700 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medicated plaster

White hydrogel plaster 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Versatis is indicated for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN).

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.

4.3 Contraindications

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

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

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).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No clinically relevant interactions have been observed in clinical studies with the plaster.

Since the maximum lidocaine plasma concentrations observed in clinical trials with the plaster were low (see section 5.2), a clinically relevant pharmacokinetic interaction is unlikely.

Although normally the absorption of lidocaine from the skin is low, the plaster must be used with caution in patients receiving Class I antiarrhythmic medicinal products (e.g. tocainide, mexiletine) and other local anaesthetics since the risk of additive systemic effects cannot be excluded.

4.6 Pregnancy and lactation

Pregnancy

Lidocaine crosses the placenta. However, there are no adequate data from the use of lidocaine in pregnant women.

Animal studies are incomplete with respect to effects on pregnancy, embryo-foetal development, parturition or postnatal development (see section 5.3).

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

Lactation

Lidocaine is excreted in breast milk. However, there are no studies of the plaster in breast-feeding women. Since the metabolism of lidocaine occurs relatively fast and almost completely in the liver, only very low levels of lidocaine are expected to be excreted into human milk.

4.7 Effects on ability to drive and 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 section 5.2)

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

The most commonly reported adverse reactions were administration site reactions including 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 reactions that have been reported in studies of post herpetic neuralgia patients receiving the plaster. They are listed by system organ class and frequency. Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Body system	**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

The following reactions have been observed in patients receiving the plaster under post-marketing conditions:

Body system	**Adverse drug reaction**
Injury, poisoning and procedural complications	
Very rare	Open wound
Immune system disorders	
Very rare	Anaphylactic reaction,

	hypersensitivity

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

Systemic adverse reactions following the appropriate use of the plaster are unlikely since the systemic concentration of lidocaine is very low (see section 5.2). Systemic adverse reactions to lidocaine are similar in nature to those observed with other amide local anaesthetic agents (see section 4.9).

4.9 Overdose

Overdose with the plaster is unlikely but it cannot be excluded that inappropriate use, such as use of a higher number of plasters at the same time, with prolonged application period, or using the plaster 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 lidocaine as a local anaesthetic agent, and may include the following signs and symptoms:

dizziness, vomiting drowsiness, seizures, mydriasis, bradycardia, arrhythmia, and shock.

In addition, known drug interactions related to systemic lidocaine 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 plaster should be removed and supportive measures taken as clinically needed. There is no antidote to lidocaine.

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 two points lower than their normal response 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 endoint was defined as lack of efficacy on two consecutive days 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.

5.2 Pharmacokinetic properties

Absorption

When lidocaine 5% medicated plaster is used according to the maximum recommended dose (3 plasters applied simultaneously for 12 h) about 3 ± 2% of the total applied lidocaine dose is systemically available and similar for single and multiple administrations.

A population kinetics analysis of the clinical efficacy studies in patients suffering from PHN revealed a mean maximum concentration for lidocaine of 45 ng/ml after application of 3 plasters 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 lidocaine 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 plasters worn simultaneously, the systemic exposure increased less than proportionally to the number of used plasters.

Distribution

After intravenous administration of lidocaine to healthy volunteers, the volume of distribution was found to be 1.3 ± 0.4 l/kg (mean ± S.D., n = 15). The lidocaine distribution volume showed no age-dependency, it 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 glycinexylidide (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.

The metabolite, 2,6-xylidine, has unknown pharmacological activity but shows carcinogenic potential in rats (see section 5.3). 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. 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. The elimination half-life of lidocaine after plaster application in healthy volunteers is 7.6 hours. The excretion of lidocaine and its metabolites may be delayed in cardiac, renal or hepatic insufficiency.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

In toxicological studies described in the literature using systemic administration of lidocaine, cardiovascular effects (tachycardia or bradycardia, decreases in cardiac output and blood pressure, cardiac arrest) and central nervous system effects (convulsion, coma, respiratory arrest) were observed at exposures considered sufficiently in excess of the maximum human exposure following treatment with Versatis. This indicates that these effects have little relevance to clinical use.

Lidocaine HCl has shown no genotoxicity when investigated *in vitro* or *in vivo*. Its hydrolysis product and metabolite, 2,6-xylidine, showed mixed genotoxic activity in several assays particularly after metabolic activation.

Carcinogenicity studies have not been performed with lidocaine. Studies performed with the metabolite 2,6-xylidine mixed in the diet of male and female rats resulted in treatment-related cytotoxicity and hyperplasia of the nasal olfactory epithelium and carcinomas and adenomas in the nasal cavity were observed. Tumorigenic changes were also found in the liver and subcutis. Because the risk to humans is unclear, long-term treatment with high doses of lidocaine should be avoided.

Lidocaine had no effect on general reproductive performance or female fertility in rats at plasma concentrations up to 130-fold those observed in patients. No adverse effects were seen in an embryo-foetal/teratogenicity study in rats at plasma concentrations more than 200-fold that observed in humans.

Animal studies are incomplete with respect to effects on pregnancy, embryofoetal development, parturition or postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Self-adhesive layer*:*

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,

purified water.

***Backing fabric**:*

Polyethylene terephthalate (PET)

***Release liner**:*

Polyethylene terephthalate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Do not refrigerate or freeze.
After first opening: Keep the sachet tightly closed.

6.5 Nature and contents of container

Re-sealable sachet composed of paper/polyethylene/aluminium/ethylene meta-acrylic acid co-polymer containing 5 plasters.

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

6.6 Special precautions for disposal

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

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

7. MARKETING AUTHORISATION HOLDER

Grünenthal GmbH- - Zieglerstrasse 6 - 52078 Aachen - Germany

8. DATE OF REVISION OF THE TEXT

July 2009