SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VERSATIS 5 % medicated plaster

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each plaster contains 700 mg (5 % *m/m*) lidocaine in an aqueous adhesive base (50 mg lidocaine per gram adhesive base).
Area containing the active substance: 10 cm x 14 cm.

Excipients with known effect:
Propylene glycol 700 mg
Preservatives:
Methyl parahydroxybenzoate 0,1 % *m/m*
Propyl parahydroxybenzoate 0,05 % *m/m*
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Medicated plasters.
The medicated plaster is 14 cm long and 10 cm wide. It is a white to pale yellow polymeric adhesive material with a faint characteristic odour, spread on one side of non-woven fabric, and covered with a plastic film. The non-woven fabric is embossed “Lidocaine 5 %”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VERSATIS 5 % medicated plaster 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

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

Apply not more than three plasters to cover the painful area *once daily* for up to 12 hours within a 24-hour period.
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 can be applied during the day or during the night.
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). When needed, plasters may be cut into smaller sizes with scissors prior to removal of the release liner.
Treatment outcome should be re-evaluated after 2-4 weeks. If there has been no response to **VERSATIS 5 %** after this period (during the wearing time and/or during the plaster-free interval), treatment must be discontinued as potential risks may outweigh benefits in this context (see sections 4.4 and 5.1). Long-term use of **VERSATIS 5 %** in clinical studies showed that the number of plasters used decreased over time. Therefore, 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.

Date of approval: 10 February 2025

Special populations

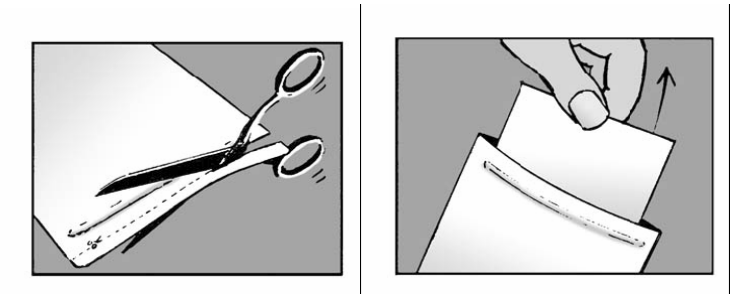
Renal impairment
In patients with mild or moderate renal impairment a dosage adjustment is not required.
VERSATIS 5 % should be used with caution in patients with severe renal impairment (see section 4.4).

Hepatic impairment
In patients with mild or moderate hepatic impairment a dosage adjustment is not required.
VERSATIS 5 % should be used with caution in patients with severe hepatic impairment (see section 4.4).

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

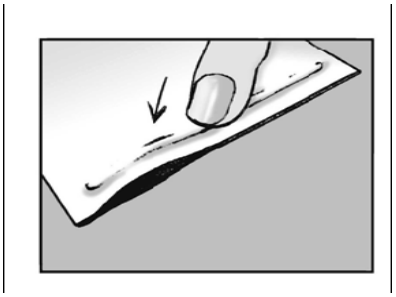
Instructions to apply the plaster on skin:

Step 1: Open the sachet and remove one or more plasters



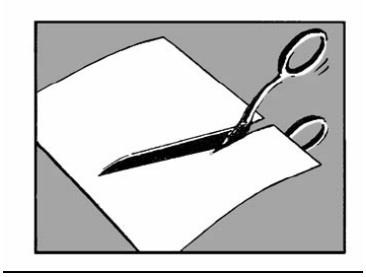
- tear open or cut the sachet along the dotted line
- when using scissors, be careful not to damage the plasters
- take out one or more plasters depending on the size of the painful area on your skin.

Step 2: close the sachet



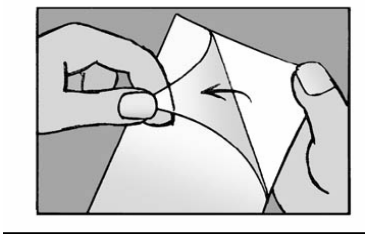
- close the sachet tightly after use
- the plaster contains water and will dry out if the sachet is not closed properly.

Step 3: cut the plaster, if necessary



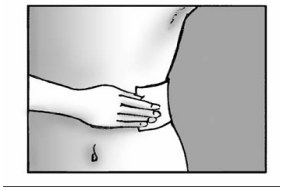
- if required, cut the plaster to the required size to fit the painful area of skin before removing the liner.

Step 4: remove the liner



- remove the transparent liner from the plaster
- try not to touch the sticky part of the plaster.

Step 5: apply the plaster and press it firmly onto the skin



- apply up to three plasters to the painful area of skin
- press the plaster onto your skin
- press for at least 10 seconds to make sure the plaster sticks firmly
- make sure that all of it sticks to your skin, including the edges.

Leave the plaster on for 12 hours only



It is important that **VERSATIS 5 %** is in contact with your skin for only 12 hours. For example, if you have more pain at night you might want to apply the plaster at 7 pm in the evening and remove it at 7 am in the morning.
If you have more pain during the day than at night you might want to apply **VERSATIS 5 %** at 7 am in the morning and remove it at 7 pm in the evening.
Do not exceed the recommended dose.

4.3 Contraindications
Hypersensitivity to lidocaine or to any of the inactive ingredients of **VERSATIS 5 %** (see section 6.1). 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 must be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.
The plaster must not be applied to inflamed or injured skin, such as active herpes zoster lesions, atopic dermatitis or wounds (see section 4.3). The plaster must not be applied to mucous membranes. Eye contact with the plaster must be avoided.

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 5 %** is only justified if there is a therapeutic benefit for the patient (see section 4.2).

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).

4.5 Interaction with other medicines 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 antidysrhythmic medicines (e.g. tocainide, mexiletine) and other local anaesthetics since the risk of additive systemic effects cannot be excluded.

4.6 Fertility, pregnancy and lactation
Pregnancy
Safe use of **VERSATIS 5 %** medicated plasters in pregnancy and lactation has not been established.
Lidocaine crosses the placenta. Therefore, **VERSATIS 5 %** should not be used during pregnancy.
Breastfeeding
Lidocaine is excreted in breast milk. Breastfeeding is not recommended.
Fertility
No clinical data regarding fertility are available.

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
a. Summary of the safety profile
Within each frequency grouping, side effects are presented in order of decreasing seriousness.
Approximately 16 % of patients can be expected to experience adverse reactions. These are localized 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.

b. Tabulated list of adverse reactions

The table below lists adverse reactions that have been reported in studies of post herpetic neuralgia patients receiving the plaster. They are listed by class and frequency. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 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 lesions
General disorders and administration site conditions: Very Common	Administration site reactions
Injury, poisoning and procedural complications: Uncommon	Skin injury

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

Body System & frequency	**Adverse drug reaction**
Immune system disorders: Very rare	Anaphylactic reaction, hypersensitivity
Injury, poisoning and procedural complications: Very rare	Open wound

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

c. Description of selected adverse reactions

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).

VERSATIS 5 % may cause methaemoglobinaemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Alternatively side effects can be reported to Adcock Ingram Pharmacovigilance department by e-mail to Adcock.Aereports@adcock.com, fax to +27 86 553 0128 or call 011 635 0134.

4.9 Overdose

Symptoms

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, dysrhythmia, and shock.

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

Treatment
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: A 3.2.3. Analgesic Topical Agent

Mechanism of action
Lidocaine is a local anaesthetic of the amide group.
VERSATIS 5 % has a dual mode of action; the pharmacological action of lidocaine diffusion and the mechanical action of the hydrogel plaster that protects the hypersensitive area.
The lidocaine contained in the **VERSATIS 5 %** plaster diffuses continuously into the skin, providing a local analgesic effect without inducing unwanted numbness.

Clinical efficacy
Pain management in PHN is difficult. There is evidence of efficacy with **VERSATIS 5 %** in the symptomatic relief from the allodynic component of PHN in some cases (see section 4.2).
Efficacy of **VERSATIS 5 %** has been shown in post-herpetic neuralgia studies. There were two main controlled studies carried out to assess the efficacy of the lidocaine 700 mg 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 700 mg 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 700 mg 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 700 mg 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.
In a controlled open-label study **VERSATIS 5 %** suggested comparable efficacy to pregabalin in 98 patients with PHN with a favourable safety profile.

Clinical safety
Overall, no significant difference concerning safety was observed between the active and placebo treatments in any of the aforementioned trials. Extensive clinical experience with

VERSATIS 5 % is considered to have demonstrated therapeutic value of the compound.

5.2 Pharmacokinetic properties

Absorption

When lidocaine 5 % medicated plaster is used, about 3 ± 2 % of the applied lidocaine dose is systemically available.

A mean maximum serum concentration for lidocaine of 84 ng/ml to 125 ng/ml was seen after the application of 3 plasters simultaneously for 12 hours in healthy volunteers.

Pharmacokinetic studies in post herpetic neuropathy (PHN) patients found a mean serum concentration of 52 ng/ml.

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

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; range 0.9 - 2.3 l/kg). The lidocaine distribution volume showed no age-dependency. 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.

Biotransformation

Lidocaine is metabolised 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 hydrolysed 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 metabolite, 2,6-xylidine, has unknown pharmacological activity but shows carcinogenic potential in rats. 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 mean half-life of lidocaine elimination from the plasma following multiple administration of the plaster 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 general toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating 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, female fertility or embryo-foetal development/teratogenicity in rats at plasma concentrations up to more than 50-fold those observed in patients.
Animal studies are incomplete with respect to male fertility, parturition or postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Self-adhesive layer:
Aluminium glycinate
Carmellose sodium (E466)
Disodium edetate
Gelatin
Glycerol
Heavy kaolin
Liquid sorbitol (E420)
Methyl parahydroxybenzoate
Polyacrylic acid
Polyvinyl alcohol
Propylene glycol (E1520)
Propyl parahydroxybenzoate
Purified water
Sodium polyacrylate
Tartaric acid (E334)
Urea
Backing fabric:
Polyethylene terephthalate (PET)
Release liner:
Polyethylene terephthalate (PET)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.
Once the sachet is opened, the plasters must be used within 14 days.

6.4 Special precautions for storage

Store at or below 25 °C.
Keep the sachet tightly closed after first opening.
Do not refrigerate or freeze.

6.5 Nature and contents of container

Re-sealable white sachet composed of paper/polyethylene/aluminium/ethylene meta-acrylic acid co-polymer containing 5 plasters.
Each carton contains 5, 10, or 30 plasters packed in 1, 2, or 6 sachets, respectively.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
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 out of the reach of children.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand,
South Africa
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER
43/3.2.3/0382

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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