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1. NAME OF THE MEDICINAL PRODUCT

Versatis® 700 mg 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 with known effect: Methyl parahydroxybenzoate 14 mg Propyl parahydroxybenzoate 7 mg Propylene glycol 700 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medicated plaster

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Versatis® 700 mg is indicated for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN) in adults.

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 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).

Treatment outcome should be re-evaluated after 2-4 weeks. If there has been no response to Versatis® 700 mg 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® 700 mg 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.

Renal impairment

In patients with mild or moderate renal impairment a dosage adjustment is not required. Versatis® 700 mg 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® 700 mg should be used with caution in patients with severe hepatic impairment (see section 4.4).

Paediatric population

Versatis® 700 mg is not indicated in children below 18 years. No data are available.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in 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 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® 700 mg 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 Fertility, pregnancy and lactation

Pregnancy

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

Animal studies do not indicate a teratogenic potential for lidocaine (see section 5.3).

The potential risk for humans is unknown. Therefore, Versatis® 700 mg should not be used during pregnancy unless clearly necessary.

Breast-feeding

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.

Fertility

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

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 (such as burning, dermatitis, erythema, pruritus, rash, skin irritation, and vesicles).

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 ($\geq 1/10$); 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	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:

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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>).

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

Versatis® 700 mg 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® 700 mg plaster diffuses continuously into the skin, providing 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® 700 mg in the symptomatic relief from the allodynic component of PHN in some cases (see section 4.2).

Efficacy of Versatis® 700 mg has been shown in post-herpetic neuralgia studies.

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.

In a controlled open-label study Versatis® 700 mg suggested comparable efficacy to pregabalin in 98 patients with PHN with a favourable safety profile.

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 $3 \pm 2\%$ 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 \pm 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 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:

purified water
liquid sorbitol (70%)
glycerol
polyacrylic acid solution (20% w/w)
sodium polyacrylate
carmellose sodium
propylene glycol (E1520)
urea
heavy kaolin
tartaric acid
gelatin
polyvinyl alcohol
aluminium glycinat
disodium edetate
methyl parahydroxybenzoate (E218)
propyl parahydroxybenzoate (E216)

Backing fabric:

Polyethylene terephthalate (PET)

Release liner:

Polyethylene terephthalate
Non-woven fabric

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Not more than 30°C. Do not refrigerate or freeze.

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

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 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. Registration number: 161-98-35316-00

8. Manufacturer:

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9. License holder:

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