HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 May 2008

VERSATIS 5%, medicated plasters
- Medicated plasters in sachet presentation (paper/PE/aluminium/methacrylic acid copolymer), box of 5 (CIP: 382 852-1)
- Medicated plasters in sachet presentation (paper/PE/aluminium/methacrylic acid copolymer), box of 20 (CIP: 382 854-4)
- Medicated plasters in sachet presentation (paper/PE/aluminium/methacrylic acid copolymer), box of 30 (CIP: 382 856-7)

Applicant: GRUNENTHAL

Lidocaine

ATC code: N01BB02

List II

Marketing Authorisation (MA) date (mutual recognition procedure): decision dated 5 December 2007
This proprietary drug has held a cohort ATU since February 2007.

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance (B/5 and B/20) and approved for use by hospitals (B/5, B/20 and B/30).

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Lidocaine[1]

Each medicated plaster[2] (10 cm x 14 cm in size) contains 700 mg (5% w/w) of lidocaine (equivalent to 50 mg of lidocaine per gramme of adhesive base).

1.2. Indication

"VERSATIS 5% is indicated for the symptomatic treatment of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia, PHN)".

1.3. Dosage

In adults and elderly patients: the plasters are applied to the painful area once a day and left in place for up to 12 hours within a 24 hours period. No more than three plasters may be used at the same time. The plaster must not be left in place for more than 12 hours. A gap of 12 hours must be left before applying the next plaster.

The efficacy of treatment should be assessed after two to four weeks. It must be withdrawn if it is ineffective or if the improvement is due only to the protective effect of the plaster on the skin. Treatment must be reassessed regularly in order to reduce the number of plasters needed, if appropriate, or to extend the plaster-free period of 12 hours during which the patient does not use a plaster.

Instructions for application: plasters must be applied as they are to dry, non-irritated skin (after healing of the shingles). Hairs in the area of pain to which the plaster is to be applied must be cut off with a pair of scissors (not shaved).

The use of VERSATIS 5% for patients under the age of 18 is not recommended because of the lack of data in this group.

1 According to the SPC, local applications of lidocaine (VERSATIS 5%) had a local analgesic effect during clinical studies. It is thought that the mechanism of action is related to stabilisation of the neuronal membranes, leading to a decline in the activity of sodium channels and consequently a reduction in pain.

2 Characteristics of the plaster: white hydrogel plaster with an adhesive base, applied to a non-woven polythene terephthalate backing, embossed with "lidocaine 5%" and covered with a polyethylene terephthalate film release liner.

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2007)

N:	Central nervous system
N01:	Anaesthetic
N01B:	Local anaesthetic
N01BB:	Amide bond local anaesthetic
N01BB02:	Lidocaine

2.2 Medicines in the same therapeutic category

2.2.1 Comparator medicines: none

Reminder
Other lidocaine-based pharmaceutical proprietary products designed for application to the skin are available: they are not indicated in the symptomatic treatment of chronic neuropathic pain:

- EMLAPATCH 5% adhesive skin dressing (lidocaine + prilocaine) is indicated in the context of local anaesthesia on healthy skin.
- EMLA 5% cream (lidocaine) is indicated for local anaesthesia of healthy skin, anaesthesia of the genital mucosa in adults, and local anaesthesia of leg ulcers requiring long, painful mechanical detersion.

2.3 Medicines with a similar therapeutic aim

- Proprietary products indicated in the treatment of peripheral neuropathic pain in adults, including post herperic neuralgia (PHN):

Antiepileptics:

- gabapentin: NEURONTIN
- pregabalin: LYRICA
- carbamazepine: TEGRETOL

Tricyclic antidepressants:

- amitriptilyne: LAROXYL
- clomipramine: ANAFRANIL
- imipramine: TOFRANIL

- Medicinal products indicated in the treatment of stubborn pain in adults, including opiates.

3. ANALYSIS OF AVAILABLE DATA

The efficacy of VERSATIS 5% has only been assessed in PHN with allodynia. It has been assessed primarily by means of two controlled studies versus placebo (cf. SPC). Data relating to the use of VERSATIS in the context of the cohort ATU is presented. The findings of a Cochrane meta-analysis (2007) of clinical studies of lidocaine 5% in local cutaneous application and those of a systematic review (2005) of symptomatic treatments of post-herpes zoster neuropathic pain (including lidocaine 5% applied to the skin) are also available.

NB: The findings of an exploratory study of repeated administrations of lidocaine 5% (KF10004/H31, Rowbotham et al., 1996; only an abstract is available) were considered in the Cochrane meta-analysis (Khalic et al, 2007); they are not discussed in detail in this opinion.

3.1 Efficacy

3.1.1 **Study KF10004/H32 (Galer et al., 1999)**[3]

Methodology: randomised comparative double-blind study versus placebo on patients selected among a population regarded as responding to the product. This was a cross-over study, i.e. the patients were treated with VERSATIS 5% for 14 days and then given a placebo plaster for the next 14 days, or vice versa.

NB: This study was not included in the Cochrane meta-analysis (see 3.1.3) because of its methodological characteristics.

The primary endpoint was time to exit due to pain increase. Pain was assessed using a scale of 0 to 5, where 0 represents no relief and 5 represents complete relief. Worsening of pain was defined by a reduction of two points in the score (compared to the score previously obtained with VERSATIS)[4]. The proportion of patients experiencing relief (qualitative assessment) was a secondary efficacy endpoint.

Results

30 of the 32 patients recruited completed the study. The time to exit *(N.B.: mean time according to the SPC, median time according to the company's dossier)* was 14 days under VERSATIS 5% versus 4 days under the placebo, $p < 0.001$.

Table 1: Primary efficacy endpoint result of the KF10004/H32 study

Treatment phase	Type of plaster	time to exit		P
		Median (days)	95% Confidence interval	
First 14 days (first phase of cross-over)	VERSATIS (n=16) Placebo (n=16)	>14 2.7	[14.0 ; >14] [2.0 ; 4.0]	<0.001
Last 14 days (second phase of cross-over)	VERSATIS (n=16) Placebo (n=16)	>14 6	[14.0 ; >14] [4.0 ; >14]	<0.001
Total	VERSATIS (n=16) Placebo (n=16)	>14 3.8	[14.0 ; >14] [3.0 ; >14]	<0.001

Pain relief (secondary efficacy endpoint) described as "moderate", "significant" or "total" was reported by 29 patients using VERSATIS versus 13 patients using the placebo.

3 Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain 1999;80:533-8.

4 According to the SPC, the primary endpoint was "time to exit from the trial due to pain worsening"; patients were withdrawn from the trial if the pain relief score fell by at least two points on a six-point assessment scale".

None of the patients using VERSATIS 5% withdrew from the study during the two weeks of treatment (see SPC).

3.1.2 **Study KF10004/01**

Methodology: randomised, double-blind comparative study versus placebo in patients selected as responders.

- In the first study period, 265 patients suffering from post-herpes zoster pain were given VERSATIS 5% for eight weeks. About 50% of the patients experienced pain relief of more than two points on a six-point pain assessment scale.
- In the second study period, 71 "responder" patients were allocated at random to receive either a placebo plaster or VERSATIS 5% for up to 14 days.

The inclusion criteria were:

- age ≥ 50 on inclusion,
- PHN for at least three months after the skin rash had healed,
- pain intensity of at least 4/10 on a numerical assessment scale (VAS) at the first (preselection) appointment and the fifth (randomisation) appointment.

Patients were regarded as being responsive to VERSATIS if the following criteria were met:

- they used VERSATIS regularly for at least four weeks in the first period,
- their daily pain intensity when using VERSATIS was ≤ 7 on an eleven-point NRS scale, and it increased if they did not use the plaster,
- they experienced at least moderate pain relief when using VERSATIS.

The primary endpoint was time to exit from the study in the second period. The withdrawal criterion was defined by a relief of two points less than that obtained previously with VERSATIS (as in the previous study, a six-point scale was used).
N.B.: according to the SPC: the primary endpoint was lack of efficacy for two consecutive days, leading to premature discontinuation of treatment.

Results
Among the 71 randomised patients, those in the placebo group had a shorter duration of illness, more intense allodynia and a lower pain questionnaire score (McGill score).

Table 2: Time to exit from the trial during the comparative phase of the study (KF10004/01)

	VERSATIS		Placebo		Difference *(%)
	Number of patients	Number of days	Number of patients	Number of days	
FAS population					
Median (min-max)	**36**	**13.5 (2 – 14)**	**35**	**9.0 (1 – 14)**	**4.5 (33.3%)**
Mean±SD	**36**	**10.1±4.7**	**35**	**8.7±5.0**	**1.4 (13.9%)**
PP population					
Median (min-max)	**17**	**14.0 (3 – 14)**	**17**	**6.0 (1 – 14)**	**8.0 (57.1%)**
Mean±SD	**17**	**11.6±4.2**	**17**	**7.6±5.2**	**4.0 (34.5%)**

*** Number of days on VERSATIS - Number of days on placebo / Number of days on VERSATIS**

Notes:
- According to the SPC, nine out of the 36 patients in the VERSATIS group withdrew from the study prematurely versus 16 of the 35 patients in the placebo group, p < 0.001.
- A post-hoc analyses showed that the initial was independant from the duration of pre-existing PHN. However, in the second phase of the study, after randomisation, patients who had been suffering from PHN for more than twelve months continued to benefit from the active treatment, while those on the placebo withdrew from the study sooner due to a lack of efficacy. (see SPC).

3.1.3 **Other clinical data**

- A systematic review, or **Cochrane meta-analysis**[5] assessed the efficacy and adverse effects of lidocaine 5% applied cutaneously in the symptomatic treatment of post-herpes zoster pain[6] on the basis of controlled and randomised (or "quasi-randomised"[7]) clinical studies which assessed lidocaine in the form of patches or dermal gel.

Methodology: three comparative clinical studies *versus* placebo have been taken into consideration:

- two double-blind, cross-over, randomised studies (Rowbotham 1995[8]; Rowbotham 1996a[9])
- one study published in the form of an abstract (Rowbotham 1996b[10]): this study involved 150 of the 314 patients (48%) included in these three clinical studies. Additional data supplied by the FDA were taken into account for this study.

These three studies included 314 patients with allodynia; 182 of them received topical lidocaine.
The duration of treatment ranged from 8 - 24 hours (two studies) to 28 days (Rowbotham 1996b study).

Results
The primary efficacy endpoint in both studies (Rowbotham 1996 a and Rowbotham 1996b) was pain relief. The meta-analysis of these two studies showed that locally applied lidocaine 5% was more effective than a placebo in obtaining pain relief (p=0.003).
The third study also found lidocaine 5% to be more effective than placebo in relieving pain (Rowbotham 1995, p=0.003). However, this was a secondary efficacy endpoint, and fewer patients took part in this study (47 patients were given lidocaine).

The quantitative effect shown by a pain relief assessment scale (score ranging from 1 to 5) was low: 0.50 (95% CI: 0.12 to 0.88) in the study with the larger number of participants and 0.42 (95% CI: 0.14 to 0.69), p=0.003 for the meta-analysis.
Taking the additional data supplied by the FDA for the Rowbotham 1996b study into account indicates that there is no significant difference between lidocaine and placebo, except for patients who were treated with lidocaine for three to four weeks.

There was no difference between patients in both arms as regards skin tolerance.

- Another **quantitative systematic review**[11] **(**2005) assessed the efficacy and adverse effects of treatments investigated in studies of post-herpes zoster pain from which subjects had been suffering for at least three months. This review looked at double-blind randomised studies performed on adult patients in whom pain assessment had been carried out. Thirty-one (31) clinical studies *versus* placebo were accepted for the meta-analysis.

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5 Khaliq W, Alam S, Puri N. Topical lidocaine for the treatment of postherpetic neuralgia. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD004846. DOI: 10.1002/14651858.CD004846.pub2.

6 This pain had to have been present for at least one month after the rash first developed.

7 The authors took the view that studies whose protocols forecasted a randomisation but that might have been open to bias because of the method used are "quasi-randomised".

8 Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves post-herpetic neuralgia. Annals of neurology 1995;37:246-53.

9 Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain 1996;65:39-44.

10 Rowbotham MC, Davies PS, Galer BS. Multicenter double-blind, vehicle-controlled trial of long term use of lidocaine patches for post-herpetic neuralgia (abstract). 8th World Congress on pain – Abstracts. Seattle: IASP Press,1996:274.

11 Hempenstall K. et al. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. Plos Med 2005;2(7):e164, 17 pages (0628-0644).

Results for lidocaine 5%, dermal gel or patch form
The analgesic effect of this product has been investigated in three studies (Galer et al, 1999; Rowbotham 1995; Rowbotham 1996). Only the study (Galer et al., 1999) which included 33 patients (64 patient-episodes) was taken into consideration in estimating the effect size (NNT = 2, 95% CI: 1.43-3.31), which limits the relevance of the effect size estimate.

3.2 Adverse effects

Overall findings from the studies available [12] (511 patients)
The average age was 74.4 (range 45 to 97), and 56% of the subjects were female. The average duration of the PHN was 4.5 years. Approximately 16% of the patients using topical local lidocaine 5% were observed to have adverse effects. The most frequent adverse effects were local reactions at the application site: erythema, rash, pruritis at the application site, burning sensation, dermatitis, erythema, vesicles, dermatitis, skin irritation and pruritis. These effects were slight to moderate in intensity and led to suspension of treatment in less than 5% of patients.

The SPC for VERSATIS states that skin irritation might also be due to the presence of propylene glycol in the plaster. Similarly, contact eczema can be triggered by preservatives: methyl parahydroxybenzoate (E128) and propyl parahydroxybenzoate (E216); in exceptional cases this features immediate reactions with urticaria and bronchospasm.
Lidocaine is unlikely to provoke systemic adverse effects in view of the low concentrations in the bloodstream. The adverse effects that have been reported are similar to those observed with other local amide anaesthetics.

Data obtained from use in the context of the cohort ATU (since 2 April 2007):
The indication established for the cohort ATU was more restrictive than that established for the MA: "post-herpes zoster pain in the event of failure, contraindication or intolerance of an antidepressant or antiepileptic treatment, or where these treatments are not recommended".
This procedure applied to 376 patients (data processed at the end of October 2007). The average age was 73 (range +/-11.9), and 56% of the subjects were female. Half of the patients were suffering from chronic pain and had been receiving treatment for over a year. At the initial appointment, 55% were taking pain control products more than twice a day: in half of the cases these were antiepileptics and in a third of the cases they were antidepressants and weak analgesics. These patients used on average 1.87 plasters per day. Eleven suspensions of treatment were reported, in five cases because of local adverse effects.

3.3 Conclusion

The efficacy of VERSATIS 5% versus placebo has been established in two clinical studies of the symptomatic treatment of allodynia associated with post-herpes zoster neuropathic pain. VERSATIS 5% has not been studied for other forms of neuropathic pain.
Compared to placebo, the relief of this pain following local cutaneous application of lidocaine 5% was weak.

12 Among these studies, the open-label study KF10004/02 (abstract, Baron et al 2006) included patients who had taken part in the KF10004/01 study and patients who had not done so. The objective of this prospective 12-month study was to assess the local and systemic tolerance of VERSATIS. The protocol provided for patients having the opportunity to apply one or more plasters a day, depending on the size of the painful area, for 12 hours a day. 259 patients took part in this study. Tolerance was assessed in 249 of them. One hundred and forty three (143) patients (57.4%) continued to receive treatment for 12 months. The clinical properties of the study population were similar to those of the efficacy studies described above.

A Cochrane meta-analysis conducted in 2007 on placebo-controlled studies of acceptable methodological quality which had assessed local cutaneous application of lidocaine 5% found the level of evidence supporting the efficacy of lidocaine in treating post-herpes zoster pain in adults to be limited and the pain control effect size determined to be low.

The efficacy of VERSATIS 5% has not been compared to that of other medicinal products indicated for this clinical situation: tricyclic antidepressants, anti-epileptics or oral opioids in particular. The role of VERSATIS 5% in treatment strategy remains to be defined. It is currently based on experts' opinions.

Most patients taking part in clinical studies appear to tolerate local cutaneous application of lidocaine 5% well. The risk of significant local reactions due to lidocaine or the excipients contained in VERSATIS plasters appears to be low, and systemic adverse effects are unlikely to occur.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Herpes zoster is caused by reactivation of the varicella-zoster virus (VZV virus). This normally takes a benign path. Neuropathic pain is the main complication. No consensus has been established on a definition of PHN. This chronic pain arises after the skin lesions have healed, and can persist for several months or several years. PHN takes the form of continuous spontaneous pain (burning sensation) and/or paroxysmal pain ("lightning-flash pain"), but also through pain triggered by a stimulus that does not normally cause pain (friction allodynia) and pruritis. It is located at the level of the dermatoma closest to the ganglion in which the VZV virus was reactived. Characterised by their chronic evolution and resistance to medical treatment, PHN pain may have a major psychosocial impact and severely affect the patient's quality of life.

PHN becomes more common with age, especially after the age of 60. Some patients are at greater risk of complications than others (immunosuppressed patients, elderly subjects, individuals who have contracted ophthalmic herpes zoster).

Public health benefit:

In view of its frequency and psychosocial repercussions (tiredness, anxiety and depression), neuropathic pain is a moderate public health burden. The burden caused by PHN, however, is low, because of the smaller number of patients concerned.

The need for improved pain management may be considered a public health priority, as identified by GTNDO (National Technical Group for Defining Public Health Objectives). For neuropathic pain, including post-herpes zoster pain, the therapeutic need is only partly covered by the available treatments.

It is difficult to assume that VERSATIS could have an impact on morbidity (including quality of life) insofar as the clinical studies have been carried out only versus placebo and over a too short period for a public health approach. Furthermore, it is not certain that these studies would readily translate into practice because the profile of patients treated in actual practice may be different from that of patients taking part in these studies (where patients with allodynia, patients already regarded as being more responsive, and patients with long-established pain were selected). Therefore, VERSATIS is not likely to offer any additional contribution to the identified public health need.

Consequently, in the current state of knowledge and in view of the existence of other currently available treatments, VERSATIS is not expected to benefit public health in this indication. *Groupe Technique National de Définition des Objectifs [National Technical Objective Definition Group] (DGS-2003)

Pain relief was low in placebo-controlled clinical studies and in patients selected as being "responsive" (see analysis of clinical studies). VERSATIS was well tolerated in the studies available. The efficacy/safety ratio for lidocaine 5% plasters is moderate.

There are alternative drugs available. Opioids/tricyclic antidepressants (LAROXYL: amitriptyline; TOFRANIL: impiramine; ANAFRANIL: clomipramine) and anti-epileptics (gabapentin: NEURONTIN; LYRICA: pregabalin; TEGRETOL: carbamazepine) are particularly indicated.

The role of VERSATIS in treatment strategy remains to be defined. The use of VERSATIS 5% plasters can be considered as a first-line symptomatic treatment for PHN (experts' opinions).

Conclusion: the actual benefit of VERSATIS 5% lidocaine plasters in the treatment of PHN is low in view of its weak efficacy demonstrated versus placebo.

4.2 Improvement in actual benefit

VERSATIS offers no improvement in actual benefit compared to the current treatment strategy (IAB V).

4.3 Therapeutic use

Symptomatic treatment of PHN must not be based on non-specific analgesics (such as paracetamol or NSAIDs). The medicinal products used are: tricyclic antidepressants/imipramine-based products (amitriptyline, clomipramine, imipramine), which are regarded as the standard treatment; anti-epileptics (in particular gabapentin and pregabalin); and opiates (morphine, oxycodone, tramadol). The efficacy of these medicinal products is partial. A titration phase (stepped dose increase) is necessary when initiating systemic treatments.
Non-pharmaceutical local treatments can also be considered.

Role of VERSATIS 5% plasters in the treatment of PHN [13] [14] [15]

The role of VERSATIS in treatment strategy has not yet been clearly established. Pain relief was low in placebo-controlled clinical studies and in patients selected as being "responsive" (see analysis of clinical studies). No clinical data is available comparing the efficacy of VERSATIS with other medicinal products indicated in the treatment of PHN.

The long-term efficacy of VERSATIS has not been established. If prescribed, it must therefore be regularly reassessed and continued only if a real therapeutic benefit is observed. It must be withdrawn if it is ineffective or if the improvement is due only to the protective effect of the plaster on the skin.

This medicinal product must not be applied to skin that is damaged (active herpes zoster lesions, dermatitis of various kinds, wounds) or in case of inflammation. It is only suitable for prescription if the painful area is small and accessible to plasters. Lidocaine is contraindicated in patients who are known to be hypersensitive to other local amide anaesthetics (bupivacaine and levobupivacaine, mepivacaine, ropivacaine).

4.4 Target population

Definition: the target population for VERSATIS 5% plasters is made up of patients suffering from PHN that is clearly localised and accessible to plasters.

In numerical terms, elderly patients represent the largest population group.

13 Attal N, Bouhassira D. Traitement pharmacologique des douleurs neuropathiques [Pharmacological treatment of neuropathic pain]. Neurologie 2005: 44-54.
14 Gilron I et al. Neuropathic pain : a practical guide for the clinician. CMAJ 2006 ;175(3) :265-275.
15 Warenham D., Breuer J. Herpes zoster. BMJ 2007 ; 334:1211-5.

The target population may be estimated from the following data:
The incidence of acute herpes zoster is thought to be between 1.3 and 2.1 per thousand people a year in the USA and Europe.
The incidence of herpes zoster diagnosed in general practice has been assessed at 3.9 cases per thousand people, or 235,000 new cases per year in 2005, according to data from the Sentinelles network [the French communicable diseases network]. These figures are close to those established in other French studies, which assess the incidence of herpes zoster at between 3.2 and 4.8 cases per thousand people per year (Hanslik et al., 2007).
This would put the number of new cases of herpes zoster per year in France at between 202,000 and 303,000.

The incidence of PHP is difficult to determine as there is no consensus as to their definition:

- The Sentinelles network defines PHN as pain persisting for more than four weeks after the attack of herpes zoster, and puts the incidence of the condition at 18% (Sentinelles 2004).
- A study conducted among general practitioners in Iceland (Helgason et al., 2000) put the incidence of PHP at:
- 19.2% for pain persisting for one month after the start of the attack of herpes zoster,
- 7.1% for pain persisting for three months after the attack,
- 3.3% for pain persisting for twelve months after the attack.

Based on this data, the target population of VERSATIS would be 14,300 to 58,200 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals and various public services in the indication and at the dosage in the Marketing Authorisation.

4.5.1 Packaging: appropriate for the prescription conditions.

4.5.2 Reimbursement rate: 35%