HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

6 October 2010

VERSATIS 5%, medicated plaster
B/5 (CIP code: 382 852-1)
B/20 (CIP code: 382 854-4)
B/30 (CIP code: 382 856-7)

Applicant: GRUNENTHAL

Lidocaine
ATC code: N01BB02

List II

Date of initial Marketing Authorisation (by mutual recognition): 5 December 2007
(This medicinal product was approved for prescription in France under the temporary authorisation for use by a named patient and groups of patients, in February 2007).

Reason for request: Reassessment of the actual benefit (AB) and improvement in actual benefit (IAB).

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Lidocaine[1]
Each medicated plaster[2] (size 10 cm x 14 cm) contains 700 mg (5% w/w) lidocaine (equivalent to 50 mg lidocaine per gram adhesive base).

1.2. Indication

"VERSATIS 5% is indicated for the symptomatic relief of postherpetic neuropathic pain (PHN)".

1.3. Dosage

Adults and elderly patients: "The painful area should be covered with the plaster once daily for up to 12 hours within a 24-hour period. Not more than three plasters should be used at the same time.

Treatment outcome should be re-evaluated after 2 to 4 weeks. If there has been no response, or if any relieving effect is related solely to the skin protective properties of the plaster, treatment must be discontinued [3] as potential risks associated with treatment may outweigh the expected benefits. 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 of 12 hours can be extended.

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

Method of administration: "The plaster must be applied intact to dry, non-irritated skin (after healing of the shingles)". "Hairs in the affected area must be cut off with scissors (not shaved)". The plaster must not be worn for more than 12 hours. "The subsequent plaster-free interval must be at least 12 hours."

N.B.: The SPC states (special warnings and precautions for use) that:
" - Versatis 5% must not be applied to mucous membranes. Eye contact with the plaster should be avoided. It should be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.
- 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)."

1 According to the SPC, local applications of lidocaine (VERSATIS 5%) showed a local analgesic effect during clinical trials. It is thought that the mechanism of action is due to stabilisation of the neuronal membranes, leading to down-regulation of the sodium channels and thus eventually reducing pain.
2 Characteristics of the plaster: white hydrogel plaster with an adhesive base, applied to a non-woven polyethylene terephthalate backing embossed with "lidocaine 5%" and covered with a polyethylene terephthalate film release liner.
3 The MA was revised on 24 February 2010, and now states that "long-term treatment with VERSATIS 5% is justified only if the patient is observed to derive therapeutic benefit" as "The potential risks associated with treatment may outweigh the expected benefits".

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2010):

N : Central nervous system
N01 : Anaesthetics
N01B : Local anaesthetic
N01BB : Amide
N01BB02 : Lidocaine

2.2 Medicines in the same therapeutic category

2.2.1 Comparator medicines: none.
Reminder
Other lidocaine-based proprietary medicinal products for application to the skin are available, but they are not indicated for the symptomatic treatment of chronic neuropathic pain. The products in question are:

- EMLAPATCH 5%, adhesive skin dressing containing 5% lidocaine + prilocaine, indicated in the local anaesthesia of healthy skin.
- EMLA 5% cream (lidocaine) indicated in the local anaesthesia of healthy skin, anaesthesia of the genital mucous membranes in adults and the local anaesthesia of skin ulcers requiring long, painful mechanical detersion.

2.3 Medicines with a similar therapeutic aim

- Medicinal products indicated for the treatment of peripheral neuropathic pain in adults, including post-herpetic pain:

Anti-epileptics and tricyclic antidepressants[4]:

INN	BRAND NAME	Indication wording on the marketing authorisation
Gabapentin	NEURONTIN	peripheral neuropathic pain such as diabetic neuropathy and post-herpetic neuralgia in adults.
Pregabalin	LYRICA	peripheral and central neuropathic pain in adults
Carbamazepine	TEGRETOL	treatment of neuropathic pain in adults
Imipramine	TOFRANIL	peripheral neuropathic pain in adults / intractable pain
Amitriptilyne	LAROXYL	peripheral neuropathic pain in adults
Clomipramine	ANAFRANIL	peripheral neuropathic pain in adults

- Medicinal products indicated in the treatment of intractable or chronic pain in adults, including opioids.

4 Duloxetine (CYMBALTA) is indicated in the “treatment of peripheral diabetic neuropathic pain in adults.”

3. ANALYSIS OF AVAILABLE DATA

The efficacy of VERSATIS 5% has been assessed in the treatment of post-herpetic neuropathic pain with allodynia.

3.1. Reminder of the conclusions of the previous opinion (May 2008)

This opinion was produced on the basis of the findings of two placebo-controlled studies (studies KF10004/H32[5] and KF10004/01), data on the use of VERSATIS in the context of a group temporary authorisation for use, the results of a Cochrane meta-analysis[6] clinical studies of 5% lidocaine as a local application to the skin and those of a systematic review[7] of symptomatic treatments for post-herpetic neuropathic pain (including 5% lidocaine applied to the skin).

The Committee concluded that "VERSATIS 5% has been found to be effective compared to placebo in two clinical studies of the symptomatic treatment of allodynia associated with post-herpetic neuropathic pain. VERSATIS 5% has not been studied for the treatment of other forms of neuropathic pain. Compared to placebo, pain relief achieved after local cutaneous application of lidocaine 5% was poor. According to a Cochrane meta-analysis carried out in 2007 of placebo-controlled studies of acceptable methodological quality which assessed local cutaneous application of 5% lidocaine, the level of evidence showing the efficacy of lidocaine in the treatment of post-herpetic pain in adults is limited and the extent of the proven analgesic effect is low. The efficacy of VERSATIS 5% has not been assessed in comparison with that of other medicinal products indicated for this clinical situation: tricyclic antidepressant, antiepileptic or oral opioid in particular. The role of VERSATIS 5% plaster opinion in treatment strategy remains to be defined. It is currently based on the views of experts. Local cutaneous application of 5% lidocaine appears to be well tolerated in most patients taking part in clinical studies. The risk of significant local reactions due to the lidocaine or excipients contained in the VERSATIS plaster seems low, and systemic adverse effects seem unlikely to occur."

3.2. New efficacy data

The pharmaceutical firm has submitted the results of a non-inferiority clinical study (study KF10004/03). This was a randomised, open-label, controlled parallel group study lasting four weeks, comparing the efficacy and tolerance of VERSATIS with those of pregabalin (LYRICA) in patients suffering from post-herpetic neuropathic pain (PHN) and diabetes-related neuropathy (off-label use).

The patients taking part, aged 18 or over, were suffering from worsening PHN for more than three months. The average intensity of pain, calculated on the last three days before the randomisation visit, was more than 4 on the NRS-3 numerical scale[8.] Patients were seen again on D14 and D28. Patients with renal insufficiency, defined as creatinine clearance above 60 ml/mn, were not included.

5 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.

6 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.

7 Hempenstall K. et al. Analgesic therapy in postherpetic neuralgia : a quantitative systematic review. Plos Med 2005;2(7):164.

8 The patients assessed their pain over the past 24 hours each evening, using the 11-point NRS (Numerical Rating Scale). The NRS runs from 0 (no pain) to 10 (worst conceivable pain).

The patients were randomised to receive:
- either one VERSATIS plaster a day (to be left on for up to 12 hours) for 28 days;
- or oral pregabalin: 150 mg/d in two doses in week one and 300 mg/d in week two. If the patient's pain intensity was still above 4 on the NRS-3 scale after two weeks, the dose could be increased to 600 mg/d for the following two weeks.

The emergency pain relief treatments permitted were paracetamol (up to 2 g/d) and selective serotonin reuptake inhibitors. Transcutaneous electrostimulation was not permitted during the study.

The primary efficacy was the responder rate after 4 weeks, defined as a reduction of at least 2 points on the 11-point NRS-3 scale compared to baseline, or an absolute NRS-3 score of ≤ 4 after 4 weeks. All patients who stopped treatment prematurely were considered as non-responsive.
The non-inferiority limit was set at -8%, with a unilateral significance threshold of 2.5% for all patients in respect of the primary endpoint (responder rate after 4 weeks). In order for VERSATIS to be found not inferior to pregabalin, the lower limit of the unilateral 97.5% confidence interval or of the bilateral 95% confidence interval of the difference between the responder rate in the VERSATIS group at D28 and in the pregabalin group at D28 had to be above -8%.

Results

The opinion only analysed the results for PHN: randomisation was stratified according to indication, and VERSATIS has not been granted marketing authorisation for the treatment of diabetes-related neuropathic pain.

98 of the 148 patients selected in 33 centres in Europe were randomised as follows: 50 to the VERSATIS group and 48 to the pregabalin group. 24 of these patients withdrew from the study prematurely: 7 in the VERSATIS group and 17 in the pregabalin group. The patients in the two groups were similar in respect of average age (64.5 +/- 12.16), average duration of pain (36.1 months +/- 58.41), the site and average intensity of pain (6.6 to 6.7 +/- 1.3), including the severity of allodynia. More than 70% of patients were taking analgesics on one of the three WHO pain ladder steps (36.7% of them were taking an opioid).

Fewer than 20% were taking an antidepressant or anti-epileptic.

After 4 weeks of treatment, the responder rate was 62.2% (28/45) in the VERSATIS group and 46.5% (20/43) in the pregabalin group. This is a difference in favour of VERSATIS of 15.7% (95% CI: - 7.7% to 36.9%), p = 0.002.

The study therefore established the non-inferiority of VERSATIS compared to pregabalin.

Among the secondary criteria, it should be noted that the severity of allodynia was only reduced for patients treated with VERSATIS, and that the proportion of patients reporting 'very good' or 'excellent' when asked how satisfied they were with their treatment was higher in the VERSATIS group (44.5%) than in the control group (23.3%).

Discussion
- From a methodological point of view, a study assessing an analgesic must include a placebo arm and be of double-blind design, even if the galenic forms are different. However, it could be argued that "deblinding" could occur as a result of the adverse effects caused by pregabalin.
- The pain assessment scale was validated to assess spontaneous pain in the same way as the visual analogue or verbal scale. Allodynia needs to be assessed at the patient's bedside in a specific way: very little information was provided as to how allodynia was

assessed, and data on this point is sparse. The primary efficacy endpoint (% of responders) is in line with the EMEA recommendations[9]
- This finding is also backed up by published data[10].

3.3. Adverse effects

In the non-inferiority study, adverse effects were reported more often in patients in the pregabalin group than in those in the VERSATIS group. The most common adverse effects in the VERSATIS group were disorders at the application site (erythema, paresthesia, rash with a frequency of 1%). These events were slight to moderate in intensity. The most commonly reported effects among patients in the pregabalin group were nervous system disorders [dizziness (18.8%), somnolence (6.3%), lethargy (4.2%) and balance disorders (4.2%)], general disorders and gastrointestinal disorders. Frequency rates were 45.1% at the 150 mg dosage (titration phase), 35.4% at the 300 mg dosage and 15.9% at the 600 mg dosage.

The SPC for VERSATIS states that adverse effects have been observed in around 16% of patients, and that most of these were local reactions caused by the pharmaceutical form of the product. Skin irritation may also be linked to the presence of propylene glycol in the plaster. Similarly, the presence of preservatives (methyl parahydroxybenzoate (E128) and propyl parahydroxybenzoate (E216)) may trigger contact eczema. In exceptional cases, immediate skin reactions with urticaria and bronchial spasms may occur.

Lidocaine is unlikely to cause systemic adverse effects because of the low concentration in the bloodstream. The adverse effects reported are similar to those observed with other local amide anaesthetics.

3.4. Observational data obtained from the group temporary authorisation for use scheme and the use of VERSATIS for named patients in the temporary authorisation for use scheme

3.3.1 The indication for the group temporary authorisation for use was treatment of PHN if treatment with an antidepressant or antiepileptic failed, was contraindicated or not tolerated, or if these treatments were not recommended.

The records of 625 patients included during a nine-month period were analysed to assess the trend in consumption of analgesic treatments, and describe associated treatments prescribed, adverse effects and suspensions of treatment. The analysis was conducted on the total population and the monitored population (patients who had at least one follow-up visit). The average age of the patients was 73.6; 68.9% (184 patients) were over 70. 62.0% of the patients over 70 were women. The median duration of PHN was 13.5 months.

In the monitored population (273 patients), the temporary authorisation for use was in place for 2.4±2.5 months on average (median = 1 month).

- The number of associated analgesic treatments per patient fell significantly between the start and end of the temporary authorisation for use period ($p<0.001$): 2.56±1.71 (median=2) associated analgesic treatments at the start of the TAU period as against 1.64±0.83 (median=1) at the end of the TAU period ($p < 0.001$).

9 http://www.ema.europa.eu/pdfs/human/ewp/025203enfin.pdf
10 Baron R et al. Efficacy and safety of combination therapy with 5% lidocaine medicated plaster and pregabalin in post-herpetic neuralgia and diabetic polyneuropathy. Curr.Med.Res.Opin. 2009;25(7):1677-87.

- Prescriptions of step 2 analgesics (mild opioids), step 3 analgesics (strong opioids) and tricyclic antidepressants fell between the start and end of the TAU period (p=0.009; p=0.001 and p=0.003 respectively): 34.4% (n=94), 11.4% (n=31) and 18.3% (n=50) of patients took step 2 or 3 analgesics or tricyclic antidepressants at the start of the TAU period as against 27.8% (n=76), 6.6% (n=18) and 12.1% (n=33) at the end of the TAU period.

3.3.2 The pharmaceutical firm, Laboratoires Grünenthal, also submitted an analysis of data obtained from a temporary authorisation for use by a named patient (ATU nominative in French) between 2001 and February 2007. The analysis was conducted on 88 patients suffering from PHN. The primary objective was to assess the efficacy of VERSATIS in the treatment of neuropathic pain, especially post-herpetic pain (NHP) in patients who were already undergoing treatment but who did not obtain sufficient relief, or who had adverse effects when under treatment.

90.0% of the patients (53.8% of whom were women, n=42) were aged over 61: 35.0% (n=28) were over 80, 30.0% (n=24) were between 71 and 80 and 25.0% (n=20) were between 61 and 70. 13.8% of the patients (n=11) had been suffering from neuropathic pain for between 6 months and a year, and 22.5% of them (n=18) had been suffering from it for two to three years. 45.5% (n=35) of the patients had been in pain for less than six months, 16.9% (n=13) for six months to a year and 20.8% (n=16) for two to three years. Taking all the patients together, the analgesic treatments initially prescribed were mainly anti-epileptics (85.2%) and step 2 analgesics (60.2%).

- A maximum reduction in pain intensity of over 30% was observed in 60.0% of the patients who were monitored, while a reduction of over 50% was observed in 25.7%.
- 24 patients had pain relief of over 50% on the VAS, and only 2 patients experienced no improvement at all.
- At the last consultation, there was an overall reduction in the prescription of analgesics and co-analgesics (tricyclic antidepressants and anti-epileptics). In patients aged over 70, this reduction in prescription related to step 2 analgesics and imipramine antidepressants.

3.5. Conclusion

Local cutaneous application of 5% lidocaine (VERSATIS) was at least as effective as treatment with pregabalin in terms of the number of responsive patients. It was also better tolerated. These were the findings after four weeks of treatment in 98 patients experiencing post-herpetic neuropathic pain.

Observational data indicate that VERSATIS may reduce prescriptions of other analgesics (mild and strong opioids) and co-analgesics (tricyclic antidepressants and anti-epileptics); the tolerance profile of these other treatments is less favourable than that of VERSATIS, especially among elderly patients.
The short-term tolerance of VERSATIS was good in most patients taking part in clinical studies, except for irritation and paresthesia at the application site. The risk of significant local reactions due to the lidocaine or excipients contained in the VERSATIS plaster seems low, and systemic adverse effects seem unlikely to occur.

Only a small number of clinical studies have clearly established the efficacy of VERSATIS. The size of the effect and its long-term persistence remain to be clarified.

TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Reassessment of actual benefit

Herpes, which is caused by reactivation of the varicella zoster virus (VZV), is normally a benign condition. The main complication is neuropathic pain. No consensus exists on the definition of post-herpetic neuropathic pain (PHN). This chronic pain arises once the skin lesions have healed, and can last for several months or even several years. PHN normally takes the form of continuous spontaneous pain (a burning sensation) and/or paroxysmal pain ("flashes of pain"), but can also involve pain caused by a stimulus which is not normally painful (friction allodynia) and itching. It is located in the dermatome connected to the lymph node in which the VZV was reactivated. Characterised by their chronic evolution and resistance to medical treatment, PHN can have a major psychosocial impact and severely affect the patient's quality of life.
PHN becomes more prevalent with age, especially after 60. Some patients are at greater risk of complications than others (immunosuppressed patients, elderly patients, individuals who have had ophthalmic zoster).

Public health benefit:

The frequency and psychosocial impact of peripheral neuropathic pain (causing fatigue, anxiety and depression) as well as the impact of chronic pain on quality of life and everyday activities means that they are considered to represent a moderate public health burden. The burden represented by post-herpetic neuropathic pain can however be regarded as low because of the smaller number of patients concerned.

Improved management of pain is a public health need that is part of the established priorities (Public Health Policy Act of 9 August 2004, Pain Management Improvement Plan 2006-2010).

In the light of the data available from comparative studies versus placebo, and a single non-inferiority study versus pregabalin, it is difficult to assume that VERSATIS would have any additional impact in terms of morbidity (including quality of life), particularly in the long term. However, this proprietary medicinal product has a better tolerance profile than the antidepressants and anti-epileptics prescribed in this situation. It could therefore reduce the use of these other treatments.

The transferability of the results of the study versus pergabaline to practice appears to be acceptable.

VERSATIS is not expected to impact on the health system. It is unlikely to provide a supplementary response to the identified public health need.

Consequently, in the current state of knowledge and in view of the other fact that therapies are currently available, it is not expected that VERSATIS will benefit public health.

The efficacy/adverse effect ratio for VERSATIS is high.

Alternative medicinal products exist.

The use of VERSATIS can be considered as a first-line symptomatic treatment for PHN, especially in elderly subjects. Its prescription could reduce the use of anti-epileptics and tricyclic antidepressants, which have been shown to be effective but which have a worse tolerance profile than VERSATIS.

Conclusion: the actual benefit of VERSATIS is substantial.

4.2 Reassessment of the improvement in actual benefit (IAB)

The new clinical data available indicates that VERSATIS provides a minor improvement in actual benefit (level IV) in the management of post-herpetic pain in adults.

4.3 Reassessment of the role of VERSATIS in treatment strategy

Post-herpetic neuropathic pain responds poorly, if at all, to the usual analgesic treatments (NSAIDs, paracetamol). The medicinal products used to treat post-herpetic neuropathic pain are: imipramine antidepressants (amitriptilyne, clomipramine, imipramine), which are regarded as the standard treatment; anti-epileptics (particularly gabapentin and pregabalin); and opiates (morphine, oxycodone, tramadol). They have been shown to be effective[11,12,13,14,15,16] but their risks mean that their use must be limited, and some require a titration phase before efficacy is obtained. Local non-drug treatments can also be considered.

Role of lidocaine 5% plasters (VERSATIS) in the treatment of post-herpetic neuropathic pain

The role of VERSATIS was not well established in 2008 (poor pain relief compared to placebo, selection of "responsive" patients, no clinical data on efficacy compared to other drugs indicated for the treatment of PHN).

A comparative randomised study has since been carried out which established that VERSATIS is not inferior to pregabalin (LYRICA). Reduction of allodynia was only seen in patients in the group treated with VERSATIS.

Recommendations issued by experts[17,**18,19**] indicate that lidocaine medicated plasters are first-line treatment when the lesions are localised, especially for elderly subjects suffering from allodynia and for whom systemic treatments are contraindicated or not advisable.

VERSATIS must not be applied to skin that is injured (active herpes lesions, dermatitis, wounds) or inflamed. It is suitable for prescription only when the painful area is small and accessible to medicated plasters. Lidocaine is contraindicated for patients who are known to be hypersensitive to other local amide anaesthetics (bupivacaine and levobupivacaine, mepivacaine, ropivacaine).

Long-term efficacy has not been determined, and prescription must therefore be reassessed at regular intervals. The product should only be continued if a therapeutic benefit is observed.

4.4 Target population

Definition: the target population for VERSATIS 5% medicated plasters is made up of patients suffering from post-herpetic neuropathic pain.
In quantitative terms, elderly patients are the largest group.

11 Eisenberg E, McNicol ED, Carr DB. Opioids for neuropathic pain. Cochrane Database of Systematic Reviews 2009, Issue 4.
12 Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews 2009, Issue 4.
13 Wiffen PJ, McQuay HJ, Rees J, Moore RA. Gabapentin for acute and chronic pain. Cochrane Database of Systematic Reviews 2010, Issue 1.
14 Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 4.
15 Attal N et al. EFNS guidelines on pharmacological treatment of neuropathic pain; 2010 revision. European Journal of Neurology 2010;17:1113-23.
16 Toni Tan, Peter Barry, Stefanie Reken, Mark Baker, on behalf of the Guideline Development Group. Guidelines : Pharmacological management of neuropathic pain in non-specialist settings : summary of NICE guidance BMJ 2010; 340:707-709.
17 Lang P-O et al. Zona des sujets âgés. Presse Med 2009; 38:571-583.
18 V. Martinez, N. Attal, D. Bouhassire, M. Lantéri-Minet, Les douleurs neuropathiques chroniques : diagnostic, évaluation et traitement en médecine ambulatoire. Recommandations pour la pratique clinique de la Société française d'étude et de traitement de la douleur. Douleur analg . 2010; 11:3-21.
19 V. Martinez, M. Lantéri-Minet. Traitements pharmacologiques actuels, recommandations et perspectives des douleurs neuropathiques. Douleur analg. 2010; 23:93-98

The target population may be estimated from the following data:
- Acute herpes is thought to affect 1.3 to 2.1 in a thousand individuals a year in the USA and Europe.
According to data from the *Sentinelles* French epidemiology network, the incidence of herpes diagnosed by general practitioners was 3.9 cases per thousand individuals, or 235,000 new cases a year in 2005. These figures are close to those reported in other French studies, which put the incidence of herpes at 3.2 to 4.8 cases per thousand individuals a year (Hanslik et al 2007).
The number of new cases of herpes per year in France is thought to be between 202,000 and 303,000.

The incidence of PHN is difficult to establish as no consensus exists regarding the definition of this condition:
- The *Sentinelles* network defines PHN as pain persisting more than four weeks after the herpes attack, and puts the incidence of PHN at 18% (Sentinelles 2004).
- A study carried out among general practitioners in Iceland (Helgason et al. 2000) put the incidence of PHN at:
  - 19.2% for pain persisting for 1 month after the start of the herpes attack,
  - 7.1% for pain persisting for 3 months afterwards,
  - 3.3% for pain persisting for 12 months afterwards.

On the basis of the above, the target population for VERSATIS would be 14,300 to 58,200 patients.

4.5 Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use 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: 65%