



Clinical utility of a new divisible lamotrigine tablet (Plexxo®): a post marketing surveillance study

M. Wangemann¹, A. Retzow²

¹Desitin Pharmaceuticals, GmbH, Weg beim Jäger 214, D-22335 Hamburg, Germany

²Biopharmaceutical Consulting, Paul-von-Schoenaichstrasse 25, D-23858 Reinfeld, Germany

Clinical utility of a new divisible lamotrigine tablet (Plexxo®): a post marketing surveillance study

M. Wangemann, A. Retzow

Abstract

Background

Post marketing surveillance studies (PMS) are non-interventional studies assessing the prescription pattern and the clinical utility of an approved drug in clinical practice.

Methods

A PMS study on a new divisible lamotrigine tablet was conducted by epilepsy specialists in Poland and Romania to obtain information regarding the prescription pattern in daily practice. During the admission visit, demographic data, epilepsy history, previous antiepileptic treatment and the number of seizures during the last 8 weeks were recorded. Details of the treatment with the new lamotrigine preparation including the reasons for change as well as dosage changes of concomitant antiepileptic medication (AED) and adverse drug reactions were recorded. At the final examination approximately after 8 weeks the number of seizures was assessed including global ratings of efficacy and tolerability by both the patient and the physician.

Results

From April 2004 to September 2005 1421 patients entered the study including a subset of 1245 patients who had received AEDs previously. The most

frequently administered AEDs were valproate (43.2%), carbamazepine (31.0%) and lamotrigine (22.2%). The seizure frequency per 28 days decreased from a mean of 4.6 (95% CI: 3.8 - 5.4) during the retrospective assessment to 1.6 (95% CI: 1.2 - 2.1) in the 8 week prospective observational period. The mean intraindividual difference between the prospective and the retrospective period was -5.7 (95% CI: -6.8 - -4.6). The percentage of patients with more than 5 seizures per 28 days decreased from 14.1% (95% CI: 12.4 - 16.1%) to 3.5% (95% CI: 2.7 - 4.6%). The percentage of seizure-free patients increased from 9.1% (95% CI: 7.8 - 10.8%) to 40.6% (95% CI: 38.1 - 43.2%). More than 1000 patients (75.4%) experienced a decrease in seizure frequency by 50% or more. An increase was observed in 44 patients only.

Conclusions

This observational study supports the clinical utility of the new divisible lamotrigine preparation as an AED for single and adjunctive therapy in patients with partial and generalised seizures under the routine conditions of daily practice. A transfer from the previous lamotrigine formulation or other AEDs to the new divisible lamotrigine drug preparation was well tolerated and safe.

Background

Lamotrigine is an AED of the phenyltriazine class chemically unrelated to other AEDs. Its mechanism of action is not yet fully elucidated; in vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilising neuronal membranes and consequently modulating presynaptic neurotransmitter release of excitatory amino acids, notably glutamate and aspartate. Clinical experience for more than two decades has shown the broad spectrum of AED activity, as it is effective against partial and secondarily generalised tonic-clonic seizures as well as idiopathic generalised epilepsy in adults and children [1,2]. Lamotrigine has been demonstrated to exert a beneficial influence on vigilance, cognition and mood and may thus considerably improve the epilepsy patients' quality of life [3]. In addition, lamotrigine has proved efficacy in the maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes [4].

The new lamotrigine formulation which was studied here, is a divisible tablet available at different dosage strength of 25 mg, 50 mg and 100 mg lamotrigine, thus allowing precise individual dose adjustment to the

optimum effective dose. In healthy volunteers, average bioequivalence with regard to both extent and rate of absorption had been proven for the new divisible tablet formulation in comparison to the plain and the dispersible/chewable originator tablet formulation [5]. Although generics are bioequivalent, substitution from original AEDs which have a narrow therapeutic to generic formulations have raised concerns [6]. These concerns were based on the fact that minute changes of bioavailability within the range of bioequivalence as a consequence of substitution may have adverse effects in individual patients. If the bioavailability of the new product is lower, seizures may occur. If it is higher, better seizure control may be a benefit, although in some patients, it may lead to adverse effects.

PMS studies are a useful tool to obtain data on seizure control and side effects when patients are switched from one drug product to another. In addition, the prescribing pattern and adherence to the prescribed doses can be evaluated.

Methods

This PMS study was conducted in Poland and Romania in order to obtain information on seizure control and tolerability of the novel lamotrigine preparation Plexxo^{®*} following its marketing authorisation in these countries. In Romania, the National Drug Agency (*reg. no. 9096/22.12.2003*) and the Ethics Committee (*reg. no. 1563/22.12.2003*) were noti-

fied about the study conduct, while such notification was not required in Poland. Specifically, information regarding the prescription pattern in daily practice, with special emphasis on change-over from other AEDs including other lamotrigine preparations, and adherence to the recommendations given in the Summary of Product Characteristics were investigated.

The PMS study is a non-comparative, strictly non-intervening prospective study in which patients had to receive the drug in accordance with the drug's marketing authorisation. Eligible patients included children (at least 2 years of age) and adults with partial or generalised seizures including tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome insufficiently controlled by other antiepileptic drugs. Each physician was responsible for observing the labelled indication and the dosage. Patients in whom Plexxo[®] treatment was replacing another lamotrigine drug preparation, the suggestion was to change at a dose ratio of 1:1 without titration. For patients without lamotrigine pre-treatment the initial dose and the dose increases were given according to the detailed dosage recommendations in the SPC. The participating physicians were advised not to exceed the initial dose and subsequent dose escalations in order to minimise the risk of rash.

During the admission visit, patient demographic data, epilepsy history, previous antiepileptic treatment, the number of seizures during the last 8 weeks and the occurrence of any adverse drug reactions of

the previous treatment were recorded. Details of the Plexxo[®] treatment (mono or combination therapy, time course of stabilisation on or change-over) including the reasons for change as well as dosage changes of concomitant AEDs were recorded. Concomitant medication and adverse drug reactions were documented during the observational period.

At the final examination scheduled approximately 8 weeks after the admission visit seizure control was assessed again and global ratings of efficacy and tolerability by the physician and the patient were documented.

The assessment of seizure control was based on the comparison of the frequency of seizures between the retrospective baseline period and the prospective observation period. Efficacy outcome measures included (a) mean intra-individual difference in the incidence of seizures per 28 days, (b) responder rate (defined as a reduction of seizure frequency per 28 days by at least 50% compared to the retrospective baseline) and (c) the global evaluation of treatment by the investigator and patient. For a better comparability the number of seizures documented retrospectively and prospectively were converted to seizure frequency per 28 days. For the retrospective pre-study phase a lengths of eight weeks was always assumed, whereas the length of the observational period was calculated from the dates of admission and the final visit.

The tolerability was primarily assessed on the basis of adverse drug reaction reports (coded

* Desitin Pharmaceuticals

according to WHO Adverse Reaction Terminology) and the global tolerability ratings obtained from patients and treating physician.

All data contained in the case report forms were documented in a case-wise data listing. Data were represented in concise descriptive statistical tables stating mean \pm standard deviation (SD) or frequencies in absolute numbers or %. If appropriate, tabulations were broken down by subgroups based on previous antiepileptic treatment. 95% confidence intervals (CI) were calculated for clinical relevant variables.

Results

Patient Characteristics

From April 2004 to September 2005 a total of 1421 patients were documented by 88 physicians in Poland ($n=657$) and by 59 physicians in Romania ($n=764$). The physicians were epilepsy specialists in private practices and outpatient clinics. About 95% of the patients completed the 8-week period of observation as scheduled with a mean duration of 77 days (median 72 days). Only 55 patients terminated prematurely or regular completion could not be documented. The most frequent reasons for premature termination were adverse drug reactions (1.9%) followed by poor drug adherence (0.8%).

In both participating countries about half of the patients were male and female. At inclusion patients were between <1 and 84 years of age with mean of 25 years. In Romania more than half of the patients were

children or adolescents whereas the patients in Poland were on average slightly older. The percentage of patients below 12 years of age was with 30.6% higher in Romania than with 18.7% in Poland. All patients suffered from epilepsy. The most frequent seizure types were generalised tonic-clonic seizures occurring in 45% and partial seizures in about 40% of patients. No significant differences in distribution were observed between the two countries with the exception of generalised tonic-clonic which occurred in patients in Romania 4 times more frequent than in patients in Poland. The reported aetiology was symptomatic in 36% and idiopathic in about 34%. The time between first diagnosis and start of this investigation varied from 0 to 52 years with a mean of 6.8 years.

Antiepileptic Drug Treatment

During the last eight weeks before the start of the observational period, 1245 of the 1421 patients received AED treatment, 176 patients were untreated newly diagnosed patients. The most frequently administered AEDs were valproate (43.2%), carbamazepine (31.0%) and lamotrigine (22.2%). Of those 316 patients receiving already lamotrigine, 139 received monotherapy and 177 took lamotrigine in combination with at least one additional AED. A total of 929 patients (65.4%) received pre-treatment with antiepileptic drugs (mono- or adjunctive therapy) that did not include lamotrigine. No relevant differences with regard to AED pre-treatment were found between the countries.

Out of the 1421 patients, 460 (32.4%) were transferred to monotherapy with the new divisible lamotrigine formulation while 890 patients (62.6%) received combination therapy with at least one other AED. No information was available for 71 (5.0%) patients.

In patients with AED pre-treatment, the main reasons for switching were (1) insufficient seizure control, (2) pharmacoeconomic reasons and (3) intolerance to previous treatment. Patients were observed prospectively for 77 ± 24 days (range 1 - 216 days); 93% of the patients were participating for at least 8 weeks.

A titration to the lamotrigine maintenance dose was performed in nearly 80% of the patients including a number of patients receiving already lamotrigine in either mono- or combination therapy. Up-titration was performed in 23% of patients with monotherapy and in 26% of patients receiving combination therapy. Down-titration was done only in single patients. The titration phase was generally of shorter duration (10 and 20 days) than the titration phase in patients not treated with lamotrigine (44 and 35 days). An average maintenance dose of 145.7 ± 83.5 mg/day (range: 1 - 500 mg/day) was reached. The initial and maintenance doses administered in Poland were higher than in Romania, regardless of the type of previous treatment (*Table 1*). Across all subgroups the average initial dose in Poland exceeded the one in Romania by a factor of 1.8, and the average maintenance dose was higher by a

factor of 1.5. The lower doses in Romania cannot be explained by the larger percentage of young children and the lower average age of patients in this country alone. On the contrary, the same findings were observed in all subsets of patients defined by age (Table 1).

Seizure Control

The seizure frequency per 28 days decreased from a mean of 4.6 (95% CI: 3.8 - 5.4) during the retrospective assessment to 1.6 (95% CI: 1.2 - 2.1) in the observational period after the initiation of the treatment with the new lamotrigine for-

mulation. The mean intraindividual difference between the prospective and the retrospective period was -5.7 (95% CI: -6.8 - -4.6). Following a median frequency of two seizures per 28 days during the retrospective assessment, a reduction of the frequency to 0.3 seizures per 28 days was observed. This corresponded to an intra-individual median decrease by three seizures per 28 days, or by 75% of the baseline value. Differences between the countries were only negligible.

Before and during the study patients with add-on treatment (with or without lamotrigine) had higher average seizure frequencies than patients receiving no previous drug treatment or monotherapy with or without lamotrigine. The percentage of patients with more than 5 seizures per 28 days decreased from 14.1% (95% CI: 12.4 - 16.1%) to 3.5% (95% CI: 2.7 - 4.6 %). Furthermore, the percentage of seizure-free patients increased from 9.1% (95% CI: 7.8 - 10.8%) to 40.6% (95% CI: 38.1 - 43.2%) during the observational period (Figure 1). The responder rate

Table 1: Maintenance dose in mg/day (mean ± SD) by country and previous treatment (number of valid cases in brackets) and by country and age

	Poland	Romania
LTG monotherapy	219.3 ± 80.9 (N=61)	134.9 ± 71.2 (N=77)
LTG add-on therapy	230.7 ± 98.4 (N=74)	173.4 ± 79.1 (N=102)
Other AED than LTG	165.3 ± 82.2 (N=468)	107.1 ± 63.9 (N=458)
No previous LTG	155.8 ± 73.8 (N=48)	105.8 ± 58.2 (N=124)
<hr/>		
11 years and younger	112.7 ± 74.8 (N=122)	86.5 ± 56.1 (N=234)
12-17 years	176.9 ± 81.9 (N=117)	142.9 ± 62.8 (N=137)
18-59 years	200.4 ± 82.0 (N=350)	131.8 ± 75.4 (N=302)
60 years and older	196.9 ± 72.3 (N=24)	99.3 ± 40.6 (N=37)

Almost 80% of those patients with previous lamotrigine monotherapy and about 64% with previous lamotrigine combination therapy were changed over to the same dose of the new lamotrigine formulation, while the dose was increased in about 16% and 33%, respectively.

In about 80% of the patients, a twice daily dose regimen was observed, while about 15% of the patients in Romania and only about 3% of patients in Poland were administered lamotrigine once daily. This is possibly related to the higher percentage of patients receiving lower doses. The remainder of patients took lamotrigine three times daily.

mulation. The mean intraindividual difference between the prospective and the retrospec-

Figure 1: Seizure frequency per 28 days during the retrospective baseline and during the prospective treatment period

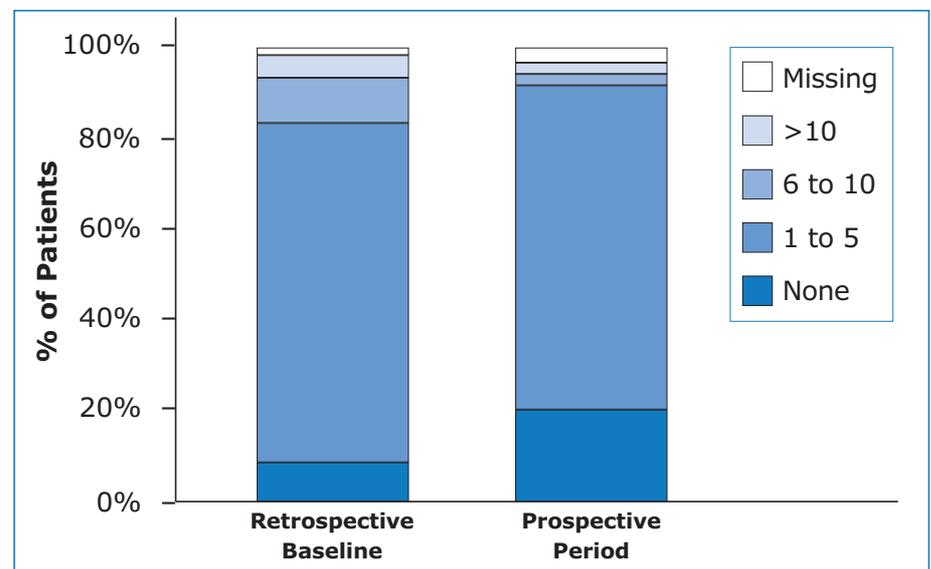
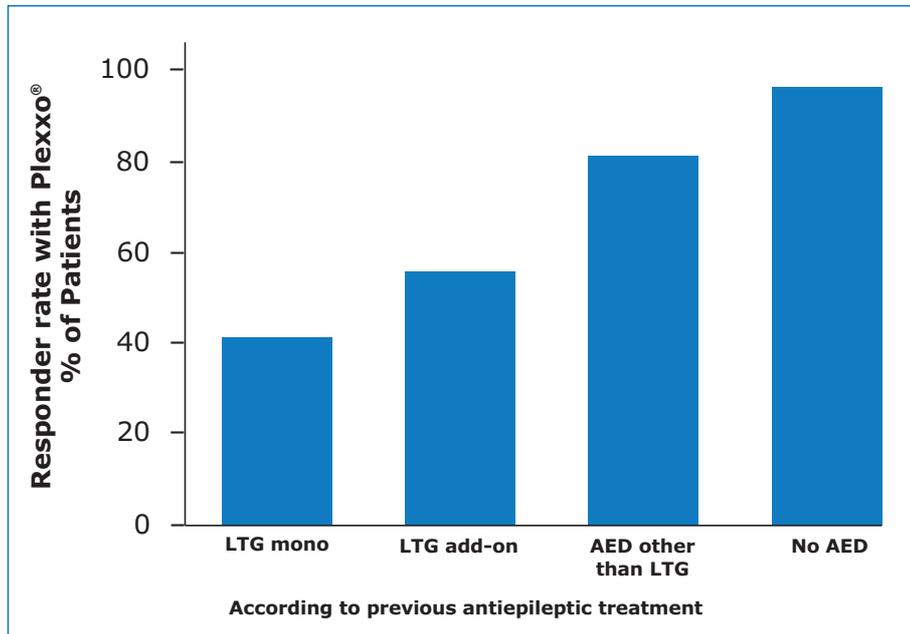


Figure 2: Responder rate (% of patients with a >50% reduction in seizure frequency) between retrospective baseline and prospective treatment period by previous antiepileptic treatment (LTG=lamotrigine)



by previous antiepileptic treatment is displayed in *Figure 2*. More than 1000 patients (75.4%) experienced a decrease in seizure frequency by 50% or more which is a commonly considered response criterion for seizure control for chronic epilepsy. An increase of seizure frequency was observed in 44 patients including six patients who had no seizures during the baseline period. According to the global evaluation obtained from the investigator at the final examination, the efficacy was rated as very good and good in more than 90% of the patients and as moderate or poor in only less than 4% of patients. This assessment was largely comparable to the patient self-ratings.

Safety

In the retrospective 8-week baseline period 166 of 1421 patients (11.7%; 95% CI: 10.1 - 13.5%) reported a total of 242 adverse drug reactions (ADR)

compared to 111 ADRs by 88 patients (6.2%; 95% CI: 5.1 - 7.6%) during the prospective assessment. None of the ADRs were classified as serious. No systematic relationship between dose and ADR rate was observed. The most frequently reported ADRs were somnolence (1.3%), headache (1.7%), and rash (1.0%). All other ADRs appeared in less than 1% of the participants. No rash occurred in patients with previous lamotrigine treatment. Rash was only observed in patients switched from other AEDs to lamotrigine (14 events) or in drug-naïve patients (4 events).

The global tolerability was rated by the investigator as very good or good in about 95% of the patients, comparable ratings were given by the patients. The investigators thus intended to continue the lamotrigine treatment beyond the end of the observational period in about 95% of patients.

Discussion

In this PMS study performed in Poland and Romania information regarding tolerability and seizure control after transfer to a new divisible lamotrigine formulation (Plexxo®) was obtained in more than 1400 patients. When discussing the results of an observational study the methodological limitations must be taken into account. Due to absence of a control group observational studies cannot be used for the assessment of efficacy of a drug. In addition, the absence of a prospective baseline hampers the attribution of the observed changes in seizure control to the new drug. Nevertheless, PMS studies are useful because they show how the drug is used in clinical practice and what the outcome of such treatment is. As more than 85% of the participants were already on AEDs (in 22% of the cases on another lamotrigine preparation), we focussed on switching to and addition of our new lamotrigine preparation. In lamotrigine-naïve patients, a low starting dose and a gradual dose escalation scheme was observed. Those patients who were on lamotrigine were switched 1:1 with subsequent slightly increased maintenance dose. Our scored tablet allows a better individual titration to the effective dose. The maintenance doses of lamotrigine administered in Poland were mainly in the medium range of the recommendations of Summary of Product Characteristics. In Romania, however, patients received predominantly lower doses (total and in mg/kg) which interestingly did not seem to result in lower seizure control

compared to treatment with a higher dose in Poland.

The ultimate goal of antiepileptic drug treatment is seizure freedom. During the retrospective 8-week period, only about 10% of patients were seizure-free. Following the switch-over and increase of dose in some patients as described above more than 40% were seizure free during the 8-week observational period. Another benefit was a lower proportion of cases with five and more seizures. These data should, however, be interpreted cautiously as the observational period was short, in particular for those patients with a low seizure frequency. In controlled efficacy studies the observation period is at least 3 months. In addition, patients may have received increased attention by their physicians which by itself may have improved compliance, well-feeling and possibly seizure control - independent of the specific properties of the new medication.

Our data show that switching to the new drug from another lamotrigine formulation is possible without harm. In this context, it should be noted that bioequivalence for both rate and extent of absorption of the new drug was in a the range with a confidence interval of 95% to 108% which is a smaller margin than the generally accepted bioequivalence range of 80% to 125% [4].

The most important fact is that the switch was well tolerated and less patients experienced side effects as compared to baseline. No rash was observed in patients with prior lamotrigine therapy.

Conclusions

This observational study demonstrated the clinical utility of the new lamotrigine preparation as an antiepileptic drug in patients with partial and generalised seizures receiving mono and combination AED therapy. Starting treatment and switching to the new divisible lamotrigine drug preparation improved seizure control and was not associated with increased side effects. The study also indicated that switching from another lamotrigine preparation to the new divisible lamotrigine formulation is safe.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AR drafted the manuscript based on the biometric report of Psy Consult. MW critically revised the manuscript and made substantial contributions to the discussion of the study. Both authors read and approved the final manuscript.

Acknowledgements

We thank Andreas Voelp, Psy Consult, Frankfurt (Germany) for the statistical analysis and the comprehensive biometric report.

References

1. Fitton A, Goa KL: **Lamotrigine. An update of its pharmacology and therapeutic use in epilepsy.** *Drugs* 1995, 50: 691-713
2. Culy C, Goa KL: **Lamotrigine. A review of its use in childhood epilepsy.** *Paediatr Drugs* 2000, 2: 299-330
3. Meador KJ, Baker GA: **Behavioral and cognitive effects of lamotrigine.** *J Child Neurol* 1997, 12 (Suppl 1): S44-S47
4. Goldsmith DR, Wagstaff AJ, Ibbotson T, Perry CM: **Lamotrigine. A review of its use in bipolar disorder.** *Drugs* 2003, 63: 2029-2050
5. Wangemann M, Retzow A, Pohlmann-Eden B: **In vivo biopharmaceutical characterisation of a new formulation containing the antiepileptic drug lamotrigine in comparison to plain and dispersible/chewable lamotrigine tablets.** *Arzneim-Forsch/ Drug Res* 2005, 55: 429-435
6. Krämer G, Dennig D, Schmidt D, Schmitz B, Stefan H, Steinhoff BJ, Stephani U, Stodieck S: **Generika in der Epilepsitherapie: Was ist zu beachten?** *Akt Neurol* 2005, 32:275-278

Imprint

The Neurology-Portal
www.NeuroNews.de

Editorship for special publications:
Dr. med. Susanne Schweizer

Publication in the Internet available:
www.neuronews.de/media/se_lamotrigine_8-2006

Managing director: Beate Döring

Publishing house:
MedienCompany GmbH
Medizin-Medienverlag
Zeppelinstr. 71-73
D-81669 Munich/Germany
Phone: ++49 (0)89 - 45835-301
Fax: ++49 (0)89 - 45835-306

www.mediencompany.de

www.medizin-medienverlag.de

Email: info@mediencompany.de

ISSN 1619-7577 (Print)

ISSN 1619-7585 (Online)

© 2006 | Medizin-Medienverlag

Munich / Germany

Printed in Germany