HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

05 May 2010

LAMICTAL 2 mg, dispersible / chewable tablet
B/30 (CIP: 354 581-7)
LAMICTAL 5 mg, dispersible / chewable tablet
B/30 (CIP: 344 835-6)
LAMICTAL 25 mg, dispersible / chewable tablet
B/30 (CIP: 338 984-3)
LAMICTAL 50 mg, dispersible / chewable tablet
B/30 (CIP: 341 471-3)
LAMICTAL 100 mg, dispersible / chewable tablet
B/30 (CIP: 338 986-6)
LAMICTAL 200 mg, dispersible / chewable tablet
B/30 (CIP: 341 473-6)

LAMICSTART 25 mg, tablet
B/21 (CIP: 366 191-4)
LAMICSTART 50 mg, tablet
B/42 (CIP: 366 192-0)

Applicant: GLAXOSMITHKLINE

Lamotrigine
ATC code: N03AX09
List I

Date of the Marketing Authorisations (mutual recognition procedure):
LAMICTAL 2 mg: 26/06/2000
LAMICTAL 5 mg: 25/11/1997
LAMICTAL 25 mg and 100 mg: 02/05/1995
LAMICTAL 50 mg and 200 mg: 31/07/1996
LAMICSTART 25 mg and 50 mg: 09/03/1998
Amendment: 06/01/2009

Reason for the request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use in the extension of indication “”Monotherapy treatment for typical absence seizures in children and adolescents aged 2 to 12 years”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Lamotrigine

1.2. Indications

Old wording:

LAMICTAL 2 mg, 5 mg, 25 mg, 50 mg, 100 mg and 200 mg (MA of 20/06/2007):

"Adults and children over 12 years of age:
Either as monotherapy or combined with another antiepileptic treatment:
- Treatment of generalised epilepsy: tonic, clonic, tonic-clonic, absence, myoclonic and atonic seizures; Lennox-Gastaut syndrome.
- Treatment of partial epilepsy: partial seizures with or without secondary generalisation.

Children aged 2 to 12 years:
In combination with another antiepileptic treatment when this is of insufficient efficacy:
- Treatment of generalised epilepsy: tonic, clonic, tonic-clonic, absence, myoclonic and atonic seizures; Lennox-Gastaut syndrome.
- Treatment of partial epilepsy: partial seizures with or without secondary generalisation."

LAMICSTART 25 mg and 50 mg (MA of 10/05/2007):

"These packs of 25-mg and 50-mg tablets, called LAMICSTART, are restricted:
- to the first month of treatment with lamotrigine,
- in adults and children aged over 12 years,
- for LAMICSTART 25 mg: in cases of combined use with sodium valproate and/or other antiepileptics such as phenytoin, carbamazepine, phenobarbital and primidone;
- for LAMICSTART 50 mg: in cases of combined use with phenytoin, carbamazepine, phenobarbital and primidone.

These three conditions must be met in order to use this pack.

In adults and children aged over 12 years:
In combination with another antiepileptic treatment:
- Treatment of generalised epilepsy: tonic, clonic, tonic-clonic, absence, myoclonic and atonic seizures; Lennox-Gastaut syndrome.
- Treatment of partial epilepsy: partial seizures with or without secondary generalisation."

New wording (MA of 06/01/2009):

LAMICTAL 2 mg, 5 mg, 25 mg, 50 mg, 100 mg and 200 mg and LAMICSTART 25 mg and 50 mg:

"Epilepsy

Adults and adolescents aged 13 years and over:
- Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.
- Seizures associated with Lennox-Gastaut syndrome. Lamictal is given as adjunctive therapy, but may be the initial antiepileptic drug in the treatment of Lennox-Gastaut syndrome.

Children and adolescents aged 2 to 12 years:
- Adjunctive treatment of partial and generalised seizures, including tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome.
- **Monotherapy of typical absence seizures.**

Bipolar disorder (this extension of the indication will be the subject of a separate notification)

Adults aged 18 years and above

- Prevention of depressive episodes in patients with type I bipolar disorder who experience predominantly depressive episodes.

Lamictal is not indicated for the acute treatment of maniac or depressive episodes."

LAMICSTART 25 mg and 50 mg:

"These packs of 25-mg and 50-mg tablets, called LAMICSTART, are restricted:

- to the first month of treatment with lamotrigine,
- in adults and children aged 13 years and over with epilepsy and in adults aged 18 years and over with bipolar disorder;
- for LAMICSTART 25 mg: in cases of combined use with sodium valproate and/or other medications for which the pharmacokinetic interactions with lamotrigine are unknown;
- for LAMICSTART 50 mg, in cases of combined use without sodium valproate and with inducers of lamotrigine glucuronidation.

These three conditions must be met in order to use this pack."

1.3. Dosage (see appendix and SPC)

"Epilepsy

The recommended dose escalation and the maintenance doses for adults and adolescents aged 13 years and older (Table 1) and for children and adolescents aged 2 to 12 years (Table 2) are given below. Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see SPC).

When concomitant antiepileptics are withdrawn or other antiepileptics/medicinal products are added to a therapeutic protocol containing lamotrigine, consideration should be given to the effect this may have on the pharmacokinetics of lamotrigine (see SPC).

To ensure that a therapeutic dose is maintained, the weight of the child must be monitored and the dose reviewed as weight changes occur. It is likely that patients aged two to six years will require a maintenance dosage at the higher end of the recommended range.

If epileptic control is achieved with adjunctive treatment, concomitant AEDs may be withdrawn and patients maintained on Lamictal monotherapy.

Children aged less than 2 years

There are limited data on the efficacy and tolerance of lamotrigine for adjunctive therapy of partial seizures in children aged 1 month to 2 years (see SPC). There are no data in children below one month of age. Thus Lamictal is not recommended for use in children below 2 years of age. If, based on clinical need, a decision to treat is nevertheless taken, see sections 4.4, 5.1 and 5.2."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

N : Nervous system
N03 : Antiepileptics
N03A : Antiepileptics
N03AX : Other antiepileptics
N03AX09 : Lamotrigine

2.2. Medicinal products in the same pharmacotherapeutic category

None

2.3. Medicinal products with a similar therapeutic aim

These are medicinal products indicated in children for monotherapy and/or in combination with another antiepileptic treatment in the treatment of generalised epilepsy including absence seizures:

ethosuximide

ZARONTIN 250 mg/ 5 ml syrup (children aged 3 years and over)

clobazam

URBANYL 10 mg and 20 mg, scored tablet

clonazepam

RIVOTRIL 2 mg, quarter-scored tablet (children aged 6 years and over)
RIVOTRIL 2.5 mg/ml, oral solution

sodium valproate

DEPAKINE 200 mg and 500 mg, tablets and generics
DEPAKINE 200 mg/ml, oral solution and generics; 57.64 mg/ml, syrup
DEPAKINE CHRONO 500 mg, sustained-release scored tablets and generics (children aged 6 years and over)
MICROPAKINE LP 100, 250, 500, 750, 1000 mg, sustained-release granules in a single-dose sachet

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Following examination of the data from pivotal studies, due to the differences in indications in the SPC for lamotrigine within the European Union, the EMA harmonised the SPC, which led in particular to an indication extension for monotherapy treatment of typical absence seizures in children and adolescents aged 2 to 12 years.

3.1.1 Data presented by the company

The file submitted in support of this indication extension is based on 2 studies (see Table 1).

Table 1: description of the studies submitted by the company for monotherapy of typical absence seizures in children

Study	Design	N	Treatment	Duration
US44	Open-label phase	45	lamotrigine	4-18 weeks
	Double-blind phase	28	- placebo (following tapering of lamotrigine) - lamotrigine at the same effective dose as was determined during the open-label phase	4 weeks
LAM100118	Open-label study	54	Lamotrigine dose escalation phase	up to 20 weeks
		30	Maintenance phase: lamotrigine	12 weeks

Study US44

This randomised, double-blind, placebo-controlled study was performed in previously untreated children and adolescents aged 2-16 years with a new diagnosis of typical absence seizures. The diagnosis of typical absence seizures was confirmed by electroencephalography (EEG) in at least one of 2 hyperventilation tests lasting 3 minutes.

Treatments:

During the open-label phase of 4 to 18 weeks, the patients were treated with escalating doses of lamotrigine: 0.5 mg/kg/day for the first 2 weeks, 1 mg/kg/day for the following 2 weeks and 1 mg/kg/day per week until the dose enabling absence of seizures. The dosage could be escalated up to 15 mg/kg/day.

Responder patients, defined as seizure-free patients as confirmed by two negative EEG hyperventilation tests, were randomised to receive lamotrigine monotherapy, at the optimal dosage as determined during the open-label phase, or placebo, following tapering of lamotrigine over 2 of the 4 weeks of the double-blind phase.

Primary endpoint: % responders remaining seizure-free during the 4-week double-blind phase (confirmed by two 3-minute EEG hyperventilation tests).

Results:

In the double-blind phase, the mean age of patients was 8.8 years in the lamotrigine group and 6.9 years in the placebo group.

Of the 45 patients included in the open-label phase, 28 (62%) responded to lamotrigine treatment and were randomised to receive lamotrigine or placebo. During the 4-week double-blind treatment phase in children who had responded to lamotrigine in the open-label phase, 9 of 14 patients in the lamotrigine group remained seizure-free versus 3 out of 14 in the placebo group (p=0.02) in the ITT analysis.

The results in the PP analysis were similar (7/12 vs 3/13; p=0.05).

In the seizure-free patients, the median dose of lamotrigine was 5 mg/kg/day (2-15 mg/kg/day) and in those who did not remain seizure-free, it was 6 mg/kg/day (2-10 mg/kg/day).

Study LAM100118

Open-label study to evaluate lamotrigine monotherapy in previously untreated children and adolescents under 13 years of age with newly diagnosed typical absence seizures. The diagnosis of typical absence seizures was confirmed by EEG in at least one of 2 hyperventilation tests lasting 5 minutes.

Treatments:

Over a 20-week period, the patients received monotherapy with escalating doses of lamotrigine: 0.3 mg/kg/day for the first 2 weeks, 0.6 mg/kg/day for the following 2 weeks and 0.6 mg/kg/day per week until the dose enabling absence of seizures. The dosage could be escalated up to 10.2 mg/kg/day.

Responder patients, defined as seizure-free patients, confirmed by a one-hour EEG hyperventilation test, continued the study with a maintenance phase of 12 weeks.

Primary endpoint: proportion of patients free of typical absence seizures during 2 consecutive weeks of the dose-escalation phase (confirmed clinically and by means of a one-hour EEG hyperventilation test).

Results:

The mean age of the 54 patients included was 7.3 years. During the 4 weeks preceding the study, these patients had experienced absence seizures for a mean of 25.5 days.

In week 20 of lamotrigine treatment, 30 of the 54 patients (56%) did not experience seizures for 2 consecutive weeks (see Table 2).

Between week 20 and week 32 of lamotrigine treatment, approximately 85% of the 30 patients who had responded by week 20 remained seizure-free. The median dose of lamotrigine during this maintenance phase was 6 mg/kg/day (3-11.8 mg/kg/day).

Table 2: Percentage of patients free of typical absence seizures (study LAM100118)

Study LAM100118	**Lamotrigine monotherapy n=54**	
	seizure-free patients[1]	
	number	percentage
Week 2	1	2%
Week 4	1	2%
Week 5	2	4%
Week 6	2	4%
Week 7	4	7%
Week 8	7	13%
Week 9	9	17%
Week 10	14	26%
Week 11	16	30%
Week 12	18	33%
Week 13	19	35%
Week 14	20	37%
Week 15	22	41%
Week 16	23	43%
Week 17	25	46%
Week 18	27	50%
Week 19	29	54%
Week 20	30	56%

[1] A seizure-free patient is defined as a patient without any typical absence seizures during 2 consecutive weeks in the 20-week phase (confirmed by an EEG hyperventilation test lasting one hour) A patient is considered to be seizure-free at a given visit if absence of seizures was confirmed during the following week's visit.

3.1.2 Literature data

A comparative study (T. Glauser) and a review of the literature concerning the management of epileptic absence seizures by monotherapy were identified during an analysis of the literature.

The efficacy of lamotrigine, ethosuximide and valproic acid were compared in a randomised, double-blind study[2] conducted in 453 children with newly diagnosed epileptic absence seizures of infancy. The patients were treated with escalating doses over a period of 16 weeks.
The primary endpoint was the percentage of children without treatment failure in week 16 or week 20.
Treatment failure was defined as the persistence of seizures in week 16 or week 20 or the presence of generalised tonic-clonic seizures or of toxicity.
The median age of the children was 7.5 years. In total, 209 of the 446 children (47%) did not experience treatment failure. After 16 or 20 weeks of treatment, the percentage of children without treatment failure was similar in the ethosuximide (53%) and valproic acid (58%) groups. The percentage of children without treatment failure with lamotrigine (29%) was lower than in the ethosuximide ($p<0.001$) and valproic acid ($p<0.001$) groups.

A Cochrane literature review was published in 2005[3] concerning ethosuximide, valproate and lamotrigine in the treatment of absence seizures. This included 5 studies: one study comparing lamotrigine with placebo (study US44 described above), one comparing lamotrigine with valproate and 3 comparing valproate with ethosuximide. The authors of this review concluded that the available data, derived mainly from studies of poor methodological quality (small groups, open-label studies, older studies), were incapable of demonstrating the superiority of one [anti]epileptic over another.

3.2. Adverse effects

Study US44

Adverse events were reported in 44 out of 45 patients.
During the open-label and double-blind phases, the most common adverse events were: infection (37%), headache (33%), rhinitis (26%), abdominal pain (24%), rash (22%), cough (22%), fever (17%) and pharyngitis (17%).
Serious adverse events were reported in 2 patients (one attempted suicide and one hospital admission, probably due to gastroenteritis).
No patient discontinued the study because of an adverse event.

Study LAM100118

The overall incidence of adverse events was 87% (47/54).
The commonest adverse events were: headache (37%), cough (22%), abdominal pain (19%), nasal congestion (19%), pharyngitis (15%), pyrexia (13%), rash (11%).
One serious adverse event (exacerbation of seizures) was observed.
Of the 54 patients, 26 (48%) withdrew from the study: 21 patients withdrew due to lack of efficacy and 3 due to adverse events (namely dizziness, convulsions, tremor).

According to the SPC

Adverse events reported as being very common (≥1/10) were: headache, drowsiness, ataxia, sensations of vertigo, diplopia, blurred vision, nausea, vomiting, skin rash.
Adverse events reported as being common (≥1/100, <1/10) were: aggression, irritability, tremor, insomnia, nystagmus, tremor, insomnia, diarrhoea, fatigue.

No data are available concerning the effect of lamotrigine on growth, sexual maturation and cognitive, emotional and behavioural development in children.

[2] Glauser T. Cnaan A, Shinnar S et al. Ethosuximide, valproic acid and lamotrigine in childhood absence epilepsy N Engl J Med 2010 ; 362:790-9
[3] Posner EB, Mohamed K, Marson AG Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents (Review), Cochrane Database Syst Rev. 2005 Oct 19;(4):CD003032

Risk of skin rash

Cutaneous adverse events have been reported, usually occurring during the first 8 weeks of treatment with lamotrigine.

Most of the rashes are benign and transient, but serious skin rashes (including one case of Stevens-Johnson syndrome and one case of Lyell's syndrome), which required hospital admission and discontinuation of lamotrigine, have also been reported. This risk of serious skin rashes is higher in children than in adults. The study data that are available suggest that the incidence of rashes in epileptic children resulting in hospital admission will be of the order of 1/300 to 1/100.

In order to limit the risk of serious skin rash and hypersensitivity, the dosage regimen for lamotrigine must be appropriate and the dose escalated progressively.

Suicide risk

Suicidal thoughts and behaviour have been reported in patients treated with antiepileptics for several indications. A meta-analysis of randomised studies evaluating antiepileptics versus placebo has shown a slight increase in the risk of suicidal thoughts and behaviour. The causes are not known and the available data do not exclude the possibility of an increased risk in the case of lamotrigine.

The incidence of suicidal thoughts and behaviour was analysed in 6,467 patients included in studies conducted with lamotrigine versus placebo for several indications. In the studies conducted on epilepsy, the incidence of these events was 0.6% (6/1073) for lamotrigine and 0.3% (2/805) for placebo (non-significant difference).

3.3. Conclusion

The efficacy and tolerance of lamotrigine in monotherapy have primarily been evaluated in 2 studies in previously untreated children over 2 years of age with newly diagnosed typical absence seizures.

After an open-label phase of 4 to 18 weeks of lamotrigine treatment, 28 out of the 45 patients included had not experienced a typical absence seizure. During the double-blind phase conducted over a period of 4 weeks in the 28 patients who had responded to lamotrigine in the open-label phase, 9 out of the 14 patients randomised into the lamotrigine group remained seizure-free versus 3 out of 14 in the placebo group (p=0.02).

In another study, in week 20 of open-label lamotrigine treatment, 30 of the 54 patients (56%) had not experienced a typical absence seizure during 2 consecutive weeks. Between week 20 and week 32 of lamotrigine treatment, approximately 85% of the 30 patients who had responded by week 20 remained seizure-free.

In addition, data on the efficacy of lamotrigine compared to other antiepileptics indicated for absence seizures are limited.

Very common adverse events (≥1/10) reported with lamotrigine during the studies conducted on epilepsy were : headache, drowsiness, ataxia, sensations of vertigo, diplopia, blurred vision, nausea, vomiting, skin rash.

Serious skin rashes were observed. This risk of serious skin rashes is higher in children than in adults. The precautions for use should be respected.

Suicidal thoughts and behaviour have been reported in patients treated with antiepileptics for several indications. The available data do not exclude the possibility of this risk being increased with lamotrigine, as with any antiepileptic.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Typical absence seizures can occur within various generalised epilepsy syndromes such as infantile absence epilepsy, juvenile absence epilepsy and juvenile myoclonic epilepsy.
Typical absence seizures are characterised by a brief alteration in consciousness, with an abrupt start and finish, manifesting as an interruption in activity. The electroencephalogram shows a generalised bilateral synchronous spike-wave discharge at 3 Hz interrupting the normal tracing. Typical absence seizures are frequently provoked by hyperventilation.

These medicines are intended for use as part of symptomatic therapy.

The efficacy/adverse effects ratio for these products is average, particularly due to cutaneous tolerance.

Public health benefit:

The public health burden of typical absence seizures in children aged 2 to 12 years is low, taking into account the limited number of children affected by this disease, which is mostly controlled by treatment and does not persist into adulthood. There is no identified public health need.

In view of the available data, this product is expected to have a low impact on morbidity and mortality in monotherapy treatment of typical absence seizures in children aged 2 to 12 years. It is not expected to have any impact on the health system.

Consequently, in light of the other treatments that are currently available, LAMICTAL is not expected to benefit public health in this indication.

These products can be used as first-line treatment.

Alternative medicinal products exist.

The actual benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit (IAB)

LAMICTAL and LAMICSTART do not provide an improvement in actual benefit (IAB V) in the management by monotherapy of typical absence seizures in children and adolescents aged 2 to 12 years.

4.3. Therapeutic use

Consensus is lacking in France concerning the treatment of generalised epilepsy syndromes including typical absence seizures in children and adolescents.
The medicinal products that are usually prescribed are: ethosuximide, sodium valproate or lamotrigine.
The first-line management of newly diagnosed typical absence seizures is based on monotherapy. Combinations such as sodium valproate and lamotrigine at low doses can be used following failure of the available monotherapies.
In rare cases, clonazepam and clobazam can be an adjunctive treatment, particularly when the absence seizures have a myoclonic component, but the long-term use of benzodiazepines should be avoided.
Other antiepileptic agents can be used as a treatment of last resort, but they do not have an MA for this indication (levetiracetam, topiramate, zonisamide).

According to the International League Against Epilepsy[4], the optimal strategy for the initial management of absence seizures using monotherapy cannot be established due to the lack of a study with rigorous methodology.
According to European experts[5], valproate is the treatment of choice for first-line monotherapy of absence seizures in childhood, with the alternatives being ethosuximide and lamotrigine. In the event of failure of ethosuximide, these experts considered that valproate is the backup treatment, with lamotrigine being an alternative. In juvenile absence epilepsy, valproate and lamotrigine can be used as first-line treatments due to their activity in generalised tonic-clonic seizures, in contrast to ethosuximide, which is a specific antiepileptic agent for absence seizures. In the event of failure of valproate, lamotrigine would be an option.

In childhood absence epilepsy, the experts agree on a recommendation for the progressive withdrawal of treatment in children who are free of absence seizures for 1 to 2 years and whose EEG has normalised[6]

The role of the product in the therapeutic strategy
Lamotrigine monotherapy is one of the first-line alternatives in the management of typical absence seizures in children and adolescents aged 2 to 12 years.

4.4. Target population

The target population for LAMICTAL and LAMICSTART in this indication extension consists of children and adolescents aged 2 to 12 years and treated with monotherapy for typical absence seizures.

It can be estimated on the basis of the following elements:

- the number of children aged 2 to 12 years on 1st January 2010[7]: 8,756,601;
- the prevalence of children with an epileptic syndrome was estimated to be 4 in 1000 according to a retrospective study conducted in Finland on a cohort of 329 children aged 0 to 15 years[8], this corresponds to 35,026 children aged 2 to 12 years;
- the prevalence of children with absence epilepsy: between 10% and 12%[6] of cases of epilepsy in children under 16 years of age, corresponding to between 3,500 and 4,200 children;
- the proportion of children treated with monotherapy: 83% according to a retrospective study conducted in Canada[9] between 1991 and 2007 in 52 children aged over 2 years with absence epilepsy of childhood, corresponding to between 2,900 and 3,500 children.
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Based on these estimates, the target population for LAMICTAL and LAMICSTART is between 2,900 and 3,500 children.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicinal products approved for use by hospitals and various public services in the marketing authorisation's extension of indication and dosage.
The Committee requests that an oral formulation adapted for children under the age of 6 years should be made available.

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[4] Glauser T, Ben-Menachem E et al. International League Against Epilepsy Treatment Guidelines: Evidence-based analysis of anti-epileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, Epilepsia, 2006 ; 47:1094-1120
[5] Wheless J, Clarke D et al. Treatment of pediatric epilepsy: European expert opinion 2007. Epileptic Disorder 2007 ; 9 : 353-412
[6] Roger J Bureau M et al. Les syndromes épileptiques de l'enfant et de l'adolescent, 4ème édition
[7] http://www.insee.fr/fr/ppp/bases-de-donnees/donnees-detaillees/bilan-demo/xls/pyramide-des-ages-2010.xls
[8] Eriksson KJ. Koivikko MJ Prevalence, classification and severity of epilepsy and epileptic syndromes in children Epilepsia 1997 Dec ; 38(12):1275-82
[9] Nadler B., Shevell MI. Childhood absence epilepsy requiring more than one medication for seizure control Canadian Journal of Neurological Sciences 2008, 35(3) : 297-300

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 65%

APPENDIX: Dosage recommendations in epilepsy (see SPC)

Table: Children and adolescents aged 2 to 12 years – total daily dosage in mg/kg body weight/day

Type of treatment	Weeks 1 + 2	Weeks 3 + 4	Usual maintenance dosage
Monotherapy of typical absence seizures:	0.3 mg/kg/day (in one or 2 doses per day)	0.6 mg/kg/day (in one or 2 doses per day)	1-10 mg/kg/day, nevertheless some patients will require higher doses (up to 15 mg/kg/day) in order to achieve the desired response (in 1 or 2 doses per day) In order to obtain the maintenance dosage, the doses should be escalated in maximum increments of 0.6 mg/kg/day every 1 to 2 weeks until the optimal response is achieved
Treatment in combination WITH valproate (inhibitor of lamotrigine glucuronidation – see SPC):			
This dosage should be used with valproate, without taking into account any other concomitant treatment	0.15 mg/kg/day* (one dose per day)	0.3 mg/kg/day (one dose per day)	1-5 mg/kg/day (in 1 or 2 doses per day) In order to attain the maintenance dosage, the doses should be escalated in maximum increments of 0.3 mg/kg every 1 to 2 weeks until the optimal response is achieved, the maximum maintenance dosage being 200 mg/day.
Treatment in combination WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see SPC):			
This dosage should be used without valproate, but with: phenytoin carbamazepine phenobarbital primidone rifampicin lopinavir/ritonavir	0.6 mg/kg/day (in 2 doses per day)	1.2 mg/kg/day (in 2 doses per day)	5-15 mg/kg/day (in 1 or 2 doses per day) In order to attain the maintenance dosage, the doses should be escalated in maximum increments of 1.2 mg/kg every 1 to 2 weeks until the optimal response is achieved, the maximum maintenance dosage being 400 mg/day
Treatment in combination WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see section 4.5):			
This dosage should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation	0.3 mg/kg/day (in 1 or 2 doses per day)	0.6 mg/kg/day (in 1 or 2 doses per day)	1-10 mg/kg/day (in 1 or 2 doses per day) In order to attain the maintenance dosage, the doses should be escalated in maximum increments of 0.6 mg/kg every 1 to 2 weeks until the optimal response is achieved, the maximum maintenance dosage being 200 mg/day
In the case of patients taking medicinal products for which the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the recommended dosage for lamotrigine in combination with valproate should be used.			

* If the calculated daily dosage for patients taking valproate is 1 mg or more, but less than 2 mg, then Lamictal 2 mg dispersible tablets or chewable tablets can be administered every other day during the first 2 weeks. If the calculated daily dosage for patients taking valproate is less than 1 mg, then Lamictal should not be administered.