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 Marketing Authorisation (mutual recognition procedure):
LAMICTAL 2 mg: 26 June 2000
LAMICTAL 5 mg: 25 November 1997
LAMICTAL 25 mg and 100 mg: 02 May 1995
LAMICTAL 50 mg and 200 mg: 31 July 1996
LAMICSTART 25 mg and 50 mg: 09 March1998
Variations: 06 January 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 for adults aged 18 years and older:
“Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes.
Lamictal is not indicated for the acute treatment of manic or depressive episodes."

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Lamotrigine

1.2. Indications

LAMICTAL 2mg, 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 older

- 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 (AE) 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 (this extension of indication will be the subject of a separate opinion).

Bipolar disorder

Adults aged 18 years and older

- **Prevention of depressive episodes in patients with bipolar I 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:

"Packs of 25 mg and 50 mg tablets, called LAMICSTART, are restricted:

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

All three conditions must be met to use these packs."

1.3. Dosage (see appendix)

"Bipolar disorder

The recommended dose escalation and maintenance doses for adults of 18 years of age and older are given in the tables below.

The transition regimen involves escalating the dose of lamotrigine to a maintenance stabilisation dose over six weeks (Table 1) after which other psychotropic medicinal products and/or antiepileptics can be withdrawn, if clinically indicated (Table 2). The dose adjustments following the addition of other psychotropic medicinal products and/or antiepileptics are also provided below (Table 3).

Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded (see SPC). "

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 therapeutic category

None

2.3. Medicinal products with the same therapeutic aim

Medicinal products indicated for the prevention of recurrent bipolar disorder and whose indications do not overlap with those of LAMICTAL:

- Mood stabilisers:

TERALITHE (lithium carbonate), tablet, oral suspension
TERALITHE LP (lithium carbonate), tablet

Prophylaxis of recurrent bipolar disorder and intermittent schizoaffective states
Treatment of episodes of mania or hypomania

- Antiepileptics:

DEPAKOTE (sodium divalproate) 250 and 500 mg, gastro-resistant tablet

In adults:

Treatment of manic episodes in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after the manic episode could be considered in patients who have responded to this medicinal product for acute mania.

DEPAMIDE (valpromide) 300 mg, film-coated, gastro-resistant tablet

In adults:

Treatment of bipolar disorder when lithium and carbamazepine are contraindicated or not tolerated.
The efficacy of Depamide has not been demonstrated in the treatment of acute manic or depressive episodes occurring during bipolar disorder

TEGRETOL (carbamazepine) 200 mg, tablet; 200 mg and 400 mg, prolonged release tablet; 20 mg/ml, oral suspension

Psychiatry:

Prophylaxis of bipolar disorder relapse, especially in patients with relative resistance, contraindications or lithium intolerance
Treatment for manic or hypomanic states

- *Atypical antipsychotics:*

ABILIFY (aripiprazole), tablet and orodispersible tablet

Treatment of moderate to severe manic episodes in bipolar I disorder and prevention of new manic episodes in patients who have experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment

ZYPREXA (olanzapine), coated tablet
ZYPREXA VELOTAB (olanzapine), orodispersible tablet.

Treatment of moderate to severe manic episodes
Prevention of recurrence of bipolar disorder in patients for whom a manic episode responded to treatment with olanzapine.

3. ANALYSIS OF AVAILABLE DATA

The present dossier is based on 2 randomised, double-blind studies with 3 groups: lamotrigine, lithium and placebo (SCAB2003 and SCAB2006).

3.1. Efficacy

The aim of studies SCAB2003 and SCAB2006 was to conduct a double-blind evaluation of the tolerance and efficacy of lamotrigine versus placebo over 76 weeks in the prevention of relapse and recurrence of depression and/or mania in adult subjects with bipolar I[1] disorder who responded to 8 to 16 weeks of open-label lamotrigine treatment. The patients included in study SCAB2003 had bipolar I disorder with a recent or ongoing depressive episode, while those in study SCAB2006 had a recent or ongoing manic or hypomanic episode.
The 2 studies were of similar design (see table 1).

Table 1: Description of studies SCAB2003 and SCAB2006

Study	Design	Patients included	N	Treatment	Duration
SCAB2003	Open-label phase	Patients with a recent depressive episode (HAMD-17 total score ≥ 18)	996	Lamotrigine alone or with a psychotropic agent	8-16 weeks
	Double-blind phase	CGI-S score [2] ≤ 3 for at least 4 weeks prior to randomisation	463	- lamotrigine (fixed dose): 50, 200, 400 mg/d - lithium {0.8-1.1 mEq/L} - placebo	76 weeks
SCAB2006	Open-label phase	Patients with a recent manic (MRS-11 score ≥ 14) or hypomanic episode	349	Lamotrigine alone or with a psychotropic agent	8-16 weeks
	Double-blind phase	CGI-S score ≤ 3 for at least 4 weeks prior to randomisation	175	- lamotrigine (flexible dose): 100-400 mg/day - lithium {0.8-1.1 mEq/L} - placebo	76 weeks

In the 8- to 16-week open-label phase, the patients were treated with escalating doses (25 mg up to 200 mg/day) of lamotrigine (alone or in combination with a psychotropic treatment) over a 6-week period.
Patients randomised in the double-blind phase to receive lamotrigine only, lithium only or placebo only musts have discontinued the additional psychotropic treatment at least one week prior to randomisation to have improved or to have become stabilised (CGI-S score ≤ 3).
Since discontinuing the psychotropic drugs was obligatory for randomisation in the double-blind phase, efficacy data for lamotrigine in combination treatment are not available.

Since the randomised treatments were initiated early after the end of the open-label phase, it seems to be difficult to distinguish recurrences (new episodes) from relapses (aggravation of symptoms during an ongoing episode) during the double-blind phase.

[1] According to the DSM IV: Bipolar I disorder is essentially characterised by the occurrence of one or more manic or mixed episodes. Subjects also often have had one or more major depressive episodes. Bipolar II disorder is essentially characterised by the occurrence of one or more major depressive episodes accompanied by at least one hypomanic episode. The existence of a manic or mixed episode rules out the diagnosis of bipolar II disorder.
[2] CGI-s scale: Clinical Global Impression-severity - scores range from 1 (normal) to 7 (very ill).

Primary endpoint: time to intervention for a mood episode during the double-blind phase, defined as the interval between the randomisation and the intervention, which is defined as an additional pharmacological treatment or electroconvulsive therapy deemed by the investigator to be necessary to treat a relapse or recurrence of a manic, hypomanic, depressive or mixed episode.

Among the secondary endpoints:
- time to intervention for a mood episode requiring treatment for a depressive episode
- time to intervention for a mood episode requiring treatment for a manic, hypomanic or mixed episode.

Results:
In both studies, more than 90% of patients experienced a depressive or manic episode classified as moderate or severe according to the DSM-IV. In the year preceding inclusion in the open-label phase, the patients experienced approximately three mood episodes on average, with 1.7 depressive episodes in study SCAB2003, and 1.4 manic episodes as well as 0.3 hypomanic episodes in study SCAB2006.

o Primary endpoint (see table 2):

In both studies, the analysis of the survival curves at 76 weeks showed that the time to intervention for a mood episode relapse or recurrence was longer in the lamotrigine (100-400 mg) and lithium groups than in the placebo group.

Table 2: Results for the primary endpoint: time to intervention for mood episodes (SCAB2003, SCAB2006 and pooled studies)

Study	Treatment	N	Number of subjects with an intervention (%)	Median time to intervention (days) 95% CI	p for log rank test *vs.* placebo
SCAB2003	lamotrigine 200-400[3] lithium placebo	165 120 119	123 (75%) 83 (69%) 98 (82%)	110 (63, 150) 105 (85, 158) 58 (33, 85)	0.004 0.006
SCAB2006	lamotrigine 100-400 lithium placebo	59 46 70	37 (64%) 25 (57%) 55 (80%)	86 (66, 315) 202 (98, 366) 82 (37, 111)	0.023 0.006
Pooled analysis (SCAB2003 and 2006)	lamotrigine lithium placebo	223 164 188	160 (72%) 108 (66%) 153 (81%)	97 (70, 146) 123 (94, 166) 58 (44, 85)	<0.001 <0.001

o Secondary endpoints (see table 3):

In both studies, the analysis of the survival curves at 76 weeks showed that the time to intervention for a relapse or recurrence:
- of a depressive episode was longer in the lamotrigine group than in the placebo group and did not differ between the lithium and placebo groups
- of a manic episode was longer in the lithium group than in the placebo group and did not differ between the lamotrigine and placebo groups.

3 Combined lamotrigine 200 mg and 400 mg subgroups (the lamotrigine 50 mg/day subgroup was excluded from this analysis).

Table 3: Results for secondary endpoints: time to intervention for depressive and manic episodes (SCAB2003, SCAB2006 and pooled studies)

			Depressive episode			Manic episode		
Study	**Treatments**	**N**	**Number of subjects with an intervention (%)**	**p vs. placebo**	**Median time to intervention (days) 95% CI**	**Number of subjects with an intervention (%)**	**p vs. placebo**	**Median time to intervention (days) 95% CI**
SCAB2003	lamotrigine 200-400[4]	165	57 (35%)	0.047	ND	26 (16%)	NS	ND
	lithium	120	46 (38%)	NS	197 (119, ND)	10 (8%)	0.026	ND
	placebo	119	47 (39%)		162 (93, ND)	19 (16%)		ND
SCAB2006	lamotrigine 100-400	59	8 (14%)	0.015	ND	20 (34%)	NS	ND
	lithium	46	10 (23%)	NS	ND	8 (18%)	0.006	ND
	placebo	70	21 (30%)		269 (183, ND)	28 (41%)		203 (108, ND)
Pooled analysis (SCAB2003 and 2006)	lamotrigine	223	65 (29%)	0.004	ND	46 (21%)	NS	ND
	lithium	164	56 (34%)	NS	ND	18 (11%)	<0.001	ND
	placebo	188	68 (36%)		270 (138, ND)	47 (25%)		ND

Furthermore, the depressive episode incidence was 14% in the lamotrigine group, 23% in the lithium group and 30% in the placebo group in the SCAB2006 study and was of the same order of magnitude (35% to 39%) in the SCAB2003 study.
Quality of life data are not available.

3.2. Adverse events

The tolerance data described below are derived from all of the studies conducted on bipolar disorders (16 studies, including the SCAB2003 and SCAB2006 studies).

Table 4: Number (%) of patients having had at least one adverse event

In bipolar disorders	**All studies**	**Comparative studies**			**SCAB2003 and SCAB2006 studies**		
	lamotrigine N=3,894	lamotrigine N=1,192	lithium N=280	placebo N=1,034	lamotrigine N=227	lithium N=166	placebo N=190
Adverse event	2,873 (74)	907 (76)	194 (69)	767 (74)	166 (73)	130 (78)	137 (72)
Serious adverse event	290 (7)	73 (6)	22 (8)	65 (6)	25 (11)	17 (10)	26 (14)
Adverse event resulting in discontinuation of treatment	594 (15)	134 (11)	53 (19)	94 (9)	29 (13)	40 (24)	30 (16)

The most common adverse events observed with lamotrigine in all the studies conducted in the bipolar disorder indication were: headache (22%), skin rash (12%), nausea (12%) and dizziness (9%).

In the SCAB2003 and SCAB2006 studies, the most commonly reported serious adverse events were: mania, including hypomania and mixed episodes (lamotrigine: 5%, lithium: 4% and placebo: 6%) and depression (lamotrigine: 3%, lithium: 2% and placebo: 3%).

Risk of skin rash
In the studies conducted in the bipolar disorder indication, skin rashes occurred in:
- 12% of patients treated with lamotrigine in the controlled and uncontrolled studies (n=3,894)

[4] The lamotrigine 50 mg/day subgroup was excluded and the lamotrigine 200 and 400 mg groups were combined.

- 8% of patients in the lamotrigine group, 5% in the lithium group and 6% in the placebo group in the controlled studies (n=2,506).
The incidence of serious skin rash (including Stevens Johnson syndrome and Lyell's syndrome) with lamotrigine was approximately 1 in 1000.
Such rashes generally appeared during the first 8 weeks of treatment.
In order to limit the risk of serious skin rash and hypersensitivity, the dosage regimen of lamotrigine must be appropriate and the dose must be progressively increased.

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 with the bipolar disorder indication, the incidence of these events was 2.4% (29/1,212) for lamotrigine and 1.8% (19/1,054) for the placebo (non-significant difference).
In the studies conducted in various psychiatric indications, these events were more frequent during the first months of treatment in patients in the lamotrigine group. Behavioural events were more frequent in men.

In the SCAB 2003 study, the following were reported:
- 9 suicide attempts: 8 with lamotrigine (open-label phases) and 1 with placebo
- 12 cases of suicidal thoughts and behaviour: 10 with lamotrigine (9 during the open-label phase and 1 during the double-blind phase), 1 with placebo and 1 during the follow-up phase.

In the SCAB 2006 study, 2 suicide attempts with lamotrigine (1 during the double-blind phase and 1 during the open-label follow-up phase) and 3 cases of suicidal thoughts and behaviour (open-label phase) were reported.

Death/Suicide
In the SCAB 2003 study, 6 deaths, 4 of them by suicide, were observed (1 suicide in the lamotrigine group during the double-blind phase, 2 during the open-label phase with lamotrigine and 1 after a withdrawal from the study due to a hospital admission for an acute manic episode). No deaths were reported in the SCAB2006 study.

3.3. Conclusion

In the two double-blind studies, monotherapy with lamotrigine at doses between 100 and 400 mg was compared with that of placebo over a 76-week period in adults with bipolar I disorder in remission following a manic or depressive episode and who had responded in the open-label phase to treatment with lamotrigine alone or in combination with a psychotropic.

The time to intervention for mood episode relapse or recurrence (primary endpoint) was longer in the lamotrigine group than in the placebo group. The time to intervention for depressive episode relapse or recurrence (secondary endpoint) was longer in the lamotrigine group. The time to intervention for manic episode relapse or recurrence (secondary endpoint) did not differ for the 2 groups.
Furthermore, there was no formally-demonstrated reduction in the incidence of depressive episodes with lamotrigine versus placebo.

Efficacy in the acute treatment of manic or depressive episodes was not demonstrated for lamotrigine.

The most common adverse events observed with lamotrigine in all the studies conducted with the bipolar disorder indication were: headache (22%), skin rash (12%), nausea (12%) and dizziness (9%).
Serious skin rash was observed and users should comply with the precautions for use.
Suicidal thoughts and behaviour were reported. The available data do not exclude the possibility of this risk being increased with lamotrigine.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Bipolar disorders are characterised by a propensity towards recurrent episodes of altered mood. Bipolar I disorder is essentially characterised by the occurrence of one or more manic episodes or mixed episodes. Subjects also often have one or more major depressive episodes.
Bipolar disorders may cause a marked deterioration in the quality of life and can cause social disability. There main risk is suicide.

These proprietary products are indicated for prevention in terms of the time to intervention for depressive episode relapse or recurrence in adults with bipolar I disorder and predominantly depressive episodes.

The efficacy/adverse effects ratio of these products is moderate, due to their modest efficacy and cutaneous tolerance.

Public health benefit:

Bipolar I disorder can be considered at least as a substantial public health burden due to its frequency and severity.

There is a public health need, especially to prevent the recurrences that occur in bipolar patients.

Available data (efficacy versus placebo in monotherapy, insufficient comparative data) suggest that this proprietary product will not have an impact on morbidity, mortality or quality of life in the prevention of depressive episodes in adults with bipolar I disorder. In addition, there is no expected impact on the health care system.

The LAMICTAL proprietary product does not provide a response to the identified need.

Consequently, given the other, currently available treatments, LAMICTAL is not expected to provide a public health benefit in this indication.

This is a second-line therapy.

Few alternatives exist.

The actual benefit of these products is substantial.

4.2. Improvement in actual benefit (IAB)

The efficacy of LAMICTAL and LAMICSTART has only been demonstrated with respect to the time to relapse or recurrence of a depressive episode in bipolar I disorder. As a result, when used as a second-line treatment, these products do not provide an improvement in actual benefit (IAB V) in the prevention of depressive episodes in bipolar I disorder adult patients with predominantly depressive episodes. The Committee considers these products to be an additional therapeutic tool.

4.3. Therapeutic use[5]

The global management of bipolar disorder consists of a curative and preventive treatment combined with psychotherapeutic and psychosocial support.

In addition to medicinal treatment, it is essential to provide the patient and his/her family with educational and psychological support. Following certain hygienic and dietary rules contributes to a favourable course: This involves respecting regular bedtimes, avoiding periods of overwork and controlling the intake of alcohol and psychostimulants. Stressful life event management will rely on reinforced psychological support. Some patients may benefit from more structured psychotherapy.

Manic episode treatment generally involves two classes of psychotropic drugs: mood stabilisers (lithium, carbamazepine and sodium divalproate[6]) and antipsychotics. Curative treatment for major depressive bipolar episodes should favour the use of mood stabilisers with or without the addition of antidepressants (off-label).

Since bipolar disorder is characterised by the recurrence of the problems, the risk of relapse justifies the introduction of prophylactic medicinal treatment to prevent suicidal behaviour and recurrent depressive and manic states, as well as to improve residual symptoms, treatment compliance and quality of life. Currently, it is acceptable for this treatment to be started when the first manic episode occurs. In stabilised patients, it is not possible to predict whether the next episode will be depressive or manic.
First-line prophylactic treatment is based on giving a normothymic medicinal product (or mood-stabiliser): lithium, which is also indicated for the curative treatment of manic or hypomanic states.
Some antiepileptics (sodium divalproate, valpromide) are alternatives, especially when lithium is contraindicated or not tolerated.
Other treatments can be used as second-line or adjunctive treatments in compliance with their indications: lamotrigine, olanzapine, aripiprazole, carbamazepine.
The prophylactic efficacy of these treatments with respect to suicide risk remains to be determined.
Olanzapine and aripiprazole are indicated for curative treatment and for the prophylaxis of recurrences (for olanzapine) and manic episode recurrence (for aripiprazole) in patients with bipolar I disorder who responded to these treatments during manic episodes. Their efficacy has not been demonstrated in the prophylaxis of major depressive episodes (i.e., typical), which are associated with this disease. Their prolonged prescription for prophylactic purposes should consider that the efficacy/adverse event ratio of these medicinal products has not been evaluated for long-term use in this indication.

<u>Therapeutic use of lamotrigine</u>
Lamotrigine is a second-line alternative for the prevention of depressive episodes in the management of patients with bipolar I disorder experiencing predominantly depressive episodes.

4.4. Target population

The target population for LAMICTAL and LAMICSTART in this indication extension consists of adults with bipolar I disorder and predominantly depressive episodes.
The prevalence of bipolar I disorder in the general population is 0.4 to 1.6% [7], which corresponds to approximately 200,000 to 700,000 patients.
According to experts, lithium is not effective long term in 50% of patients.

[5] Guide médecin – ALD 23 « Troubles bipolaires » HAS, mai 2009
[6] Indicated in cases of contraindication or intolerance to lithium
[7] Manuel Diagnostic et Statistique des Troubles Mentaux (DSM-IV-TR).

The proportion of patients with predominantly depressive episodes is difficult to quantify and the target population for these proprietary products when used as second-line treatment in the prophylaxis of depressive episodes during bipolar I disorder remains to be determined.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of products reimbursed by National Health Insurance and on the list of medicinal products approved for use by hospitals and various public services in the indication extension and at the dosage mentioned in the MA.

Packaging: appropriate for the prescription conditions

Reimbursement rate: 65%

APPENDIX: Dosage recommendations in bipolar disorder (see SPC)

Table 1: Adults aged 18 years and over – recommended dose escalation to the total daily stabilisation dose in the treatment of bipolar disorder

Treatment regimen	Weeks 1 + 2	Weeks 3 + 4	Week 5	Target stabilisation dose (Week 6)*
Monotherapy with lamotrigine OR adjunctive treatment WITHOUT valproate and WITHOUT inducers of lamotrigine glucuronidation (see SPC):				
This dosage regimen should be used with other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation.	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day (once a day or two divided doses)	200 mg/day - usual target dosage for optimal response (once a day or two divided doses) Doses in the range 100 to 400 mg/day used in clinical trials
Adjunctive therapy WITH valproate (inhibitor of lamotrigine glucuronidation – see SPC):				
This dosage regimen should be used with valproate, regardless of any concomitant medicinal products.	12.5 mg/day (given as 25 mg on alternate days)	25 mg/day (once a day)	50 mg/day (once a day or two divided doses)	100 mg/day - usual target dose for optimal response (once a day or two divided doses) Maximum dose of 200 mg/day can be used depending on clinical response.
Adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation (see SPC):				
This dosage regimen should be used without valproate, but with: phenytoin carbamazepine phenobarbital primidone rifampicin lopinavir/ritonavir	50 mg/day (once a day)	100 mg/day (two divided doses)	200 mg/day (two divided doses)	300 mg/day in week 6, if necessary increasing to usual target dose of 400 mg/day in week 7, to achieve optimal response (two divided doses)
In patients taking medicinal products for which the pharmacokinetic interaction with lamotrigine is currently not known (see SPC), the recommended dose for Lamictal with concurrent valproate should be used.				

* The target stabilisation dose will vary depending on clinical response.

Table 2: Adults aged 18 years and over – maintenance stabilisation total daily dose following the discontinuation of concomitant medicinal products in treatment of bipolar disorder

Once the target daily maintenance stabilisation dose has been achieved, other medicinal products may be discontinued as shown below.

Treatment regimen	Current lamotrigine stabilisation dose (prior to discontinuation)	Week 1 (beginning with discontinuation)	Week 2	Week 3 and onward*
Discontinuation of valproate (inhibitor of lamotrigine glucuronidation – see SPC) depending on the initial dose of lamotrigine:				
When valproate is discontinued, double the stabilisation dose, not exceeding an increase of more than100 mg/week	100 mg/day	200 mg/day	Maintain this dose (200 mg/day) (two divided doses)	
	200 mg/day	300 mg/day	400 mg/day	Maintain this dose (400 mg/day)
Discontinuation of inducers of lamotrigine glucuronidation (see SPC) depending on the initial dose of lamotrigine:				
This dosage regimen should be used when the following are discontinued: phenytoin carbamazepine phenobarbital primidone rifampicin lopinavir/ritonavir	400 mg/day	400 mg/day	300 mg/day	200 mg/day
	300 mg/day	300 mg/day	225 mg/day	150 mg/day
	200 mg/day	200 mg/day	150 mg/day	100 mg/day
Discontinuation of medicinal products that DO NOT significantly inhibit or induce lamotrigine glucuronidation (see SPC)				
This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are discontinued.	Maintain target dose achieved in dose escalation (200 mg/day; two divided doses) (dose range 100 to 400 mg/day)			
In the patients taking medicinal products for which the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the recommended dose for Lamictal with concurrent valproate should be used.				

* Dose may be increased to 400 mg/day as needed.

Table 3: Adults aged 18 years and over – adjustment of lamotrigine daily dosing following the addition of other medicinal products in the treatment of bipolar disorder

There is no clinical experience in adjusting the daily lamotrigine dose following the addition of other medicinal products in the treatment of bipolar disorder.

However, based on studies of interactions with other medicinal products, the following recommendations can be made:

<table>
<tr><th>Treatment Regimen</th><th>Current lamotrigine stabilisation dose (prior to addition)</th><th>Week 1 (beginning with addition)</th><th>Week 2</th><th>Week 3 and onwards</th></tr>
<tr><td colspan="5">Addition of valproate (inhibitor of lamotrigine glucuronidation – see section 4.5) depending on initial dose of lamotrigine:</td></tr>
<tr><td rowspan="3">This dosage regimen should be used when valproate is added regardless of any concomitant medicinal products.</td><td>200 mg/day</td><td>100 mg/day</td><td colspan="2">Maintain the dose (100 mg/day)</td></tr>
<tr><td>300 mg/day</td><td>150 mg/day</td><td colspan="2">Maintain the dose (150 mg/day)</td></tr>
<tr><td>400 mg/day</td><td>200 mg/day</td><td colspan="2">Maintain the dose (200 mg/day)</td></tr>
<tr><td colspan="5">Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate (see SPC), depending on initial dose of lamotrigine:</td></tr>
<tr><td rowspan="3">This dosage should be used when the following are added without valproate:

phenytoin
carbamazepine
phenobarbital
primidone
rifampicin
lopinavir/ritonavir</td><td>200 mg/day</td><td>200 mg/day</td><td>300 mg/day</td><td>400 mg/day</td></tr>
<tr><td>150 mg/day</td><td>150 mg/day</td><td>225 mg/day</td><td>300 mg/day</td></tr>
<tr><td>100 mg/day</td><td>100 mg/day</td><td>150 mg/day</td><td>200 mg/day</td></tr>
<tr><td colspan="5">Addition of medicinal products that DO NOT significantly inhibit or induce lamotrigine glucuronidation (see SPC):</td></tr>
<tr><td>This dosage regimen should be used when other medicinal products that do not significantly inhibit or induce lamotrigine glucuronidation are added</td><td colspan="4">Maintain target dose achieved in dose escalation (200 mg/day; dose range 100 to 400 mg/day)</td></tr>
<tr><td colspan="5">In patients taking medicinal products for which the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the recommended dose for Lamictal with concurrent valproate should be used.</td></tr>
</table>

Discontinuation Lamictal in patients with bipolar disorder

In clinical trials, there was no increase in the incidence or severity and no change in the type of adverse effects following abrupt discontinuation of lamotrigine versus placebo. Therefore, patients may discontinue Lamictal without tapering down the dose.

Children and adolescents under the age of 18 years:

Lamictal is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy (see section 4.4)"