LAMICTAL
Lamotrigine

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tablets:
Each tablet contains 50 mg of lamotrigine.
Pale yellowish brown, multifaceted, superelliptical unscored tablet, branded 'GSEE1' on one side, with '50' on the reverse.

Each tablet contains 100 mg of lamotrigine.
Pale yellowish brown, multifaceted, superelliptical, unscored tablets, branded 'GSEE5' on one side, with '100' on the reverse.

Dispersible/Chewable Tablets:
Each tablet contains 5 mg of lamotrigine.
White to off-white tablet with odour of blackcurrant. Elongated, biconvex, unscored tablets branded "GSCL2" on one side and "5" on the other. The tablets may be slightly mottled.

Each tablet contains 25 mg of lamotrigine.
White to off-white multi-faceted, superelliptical, unscored tablet with odour of blackcurrant. Branded with a "GSCL5" coding on one side and "25" on the other. The tablets may be slightly mottled.

2. CLINICAL INFORMATION
2.1 Indications
Epilepsy
- **Adults and adolescents (over 12 years of age)**

LAMICTAL is indicated for use as adjunctive or monotherapy in the treatment of epilepsy, for partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.

- **Children (2 to 12 years of age)**

LAMICTAL is indicated as adjunctive therapy in the treatment of epilepsy, for partial seizures and generalised seizures including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome. Initial monotherapy treatment in newly diagnosed paediatric patient is not recommended.

After epileptic control has been achieved during adjunctive therapy, concomitant antiepileptic drugs (AEDs) may be withdrawn and patients continued on *LAMICTAL* monotherapy.

If *LAMICTAL* 2 mg dispersible/chewable tablet is not available and the calculated dose in children is less than 2.5 mg daily, then *LAMICTAL* cannot be used. DO NOT attempt to administer partial quantities of the dispersible/chewable tablets.

Bipolar Disorder
- **Adults (18 years of age and over)**

LAMICTAL is indicated for the prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes.

2.2 Dosage and Administration
Pharmaceutical form: Tablets and Dispersible/Chewable tablets.

LAMICTAL tablets should be swallowed whole and should not be chewed or crushed.

LAMICTAL dispersible/chewable tablets may be chewed, dispersed in a small volume of water (at least enough to cover the whole tablet) or swallowed whole with a little water.

DO NOT attempt to administer partial quantities of the dispersible/chewable tablets.

If a calculated dose of *LAMICTAL,* e.g. for use in children (epilepsy only) or patients with hepatic impairment, cannot be divided into multiple lower strength tablets, the dose to be administered is that equal to the nearest lower strength of whole tablets.

Restarting Therapy
Prescribers should assess the need for escalation to maintenance dose when restarting *LAMICTAL* in patients who have discontinued *LAMICTAL* for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for *LAMICTAL (see Warnings and Precautions)*. The greater the interval of time since the previous dose, the more consideration should be given to escalation to the maintenance dose. When the interval since discontinuing *LAMICTAL* exceeds five half-lives *(see Pharmacokinetics), LAMICTAL* should generally be escalated to the maintenance dose according to the appropriate schedule.

It is recommended that *LAMICTAL* not be restarted in patients who have discontinued due to rash associated with prior treatment with *LAMICTAL* unless the potential benefit clearly outweighs the risk.

Epilepsy
When concomitant antiepileptic drugs are withdrawn to achieve *LAMICTAL* monotherapy or other AEDs are added-on to treatment regimes containing lamotrigine, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (*see Interactions*).

- **Dosage in epilepsy monotherapy**

Adults and adolescents (over 12 years of age) (*see Table 1*)
The initial *LAMICTAL* dose in monotherapy is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of *LAMICTAL* to achieve the desired response.

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

- **Dosage in epilepsy add-on therapy**

Adults and adolescents (over 12 years of age) (*see Table 1*)
In patients taking valproate with/without any other AED, the initial *LAMICTAL* dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 25 to 50 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 to 200 mg/day given once a day or in two divided doses.

In those patients taking concomitant AEDs or other medications (*see Interactions*) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial *LAMICTAL* dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks.

Thereafter, the dose should be increased by a maximum of 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200 to 400 mg/day given in two divided doses.

Some patients have required 700 mg/day of *LAMICTAL* to achieve the desired response.

In those patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (*see Interactions*), the initial *LAMICTAL* dose is 25 mg once a day for two weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 to 100 mg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve an optimal response is 100 to 200 mg/day given once a day or as two divided doses.

Table 1: Recommended treatment regimen in EPILEPSY for adults and adolescents over 12 years of age

Treatment Regimen		Weeks 1-2	Weeks 3-4	Maintenance Dose
Monotherapy		25 mg (once a day)	50 mg (once a day)	100 - 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 - 100 mg every one to two weeks
Add-on therapy with valproate regardless of any concomitant medications		12.5 mg (given 25 mg alternate days)	25 mg (once a day)	100 - 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 25 - 50 mg every one to two weeks
Add-on therapy without valproate	This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone or with other inducers of lamotrigine glucuronidation (*see Interactions*)	50 mg (once a day)	100 mg (two divided doses)	200 - 400 mg (two divided doses) To achieve maintenance, doses may be increased by 100 mg every one to two weeks
	This dosage regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (*see Interactions*)	25 mg (once a day)	50 mg (once a day)	100 - 200 mg (once a day or two divided doses) To achieve maintenance, doses may be increased by 50 - 100 mg every one to two weeks
In patients taking AEDs where the pharmacokinetic interaction with *LAMICTAL* is currently not known (*see Interactions*), the treatment regimen as recommended for *LAMICTAL* with concurrent valproate should be used.				

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

Children (2 to 12 years of age) (*see Table 2*)
In patients taking valproate with/without any other AED, the initial *LAMICTAL* dose is 0.15 mg/kg bodyweight/day given once a day for two weeks, followed by 0.3 mg/kg/day once a day for two weeks. Thereafter, the dose should be increased by a maximum of 0.3 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 5 mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

In those patients taking concomitant AEDs or other medications (*see Interactions*) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial *LAMICTAL* dose is 0.6 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2 mg/kg/day given in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 1.2 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance

dose to achieve optimal response is 5 to 15 mg/kg/day given in two divided doses, with a maximum of 400 mg/day.

In patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (*see Interactions*), the initial *LAMICTAL* dose is 0.3 mg/kg bodyweight/day given once a day or in two divided doses for two weeks, followed by 0.6 mg/kg/day given once a day or in two divided doses for two weeks. Thereafter, the dose should be increased by a maximum of 0.6 mg/kg every one to two weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 to 10 mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur.

Table 2: Recommended treatment regimen in EPILEPSY for children aged 2-12 years (total daily dose in mg/kg bodyweight/day) on combined drug therapy**

Treatment Regimen		Weeks 1-2	Weeks 3-4	Maintenance Dose
Add-on therapy with valproate regardless of any other concomitant medication		0.15 mg/kg* (once a day)	0.3 mg/kg (once a day)	0.3 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 - 5 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day
Add-on therapy without valproate	This dosage regimen should be used with: Phenytoin Carbamazepine Phenobarbitone Primidone or with other inducers of lamotrigine glucuronidation (*see Interactions*)	0.6 mg/kg (two divided doses)	1.2 mg/kg (two divided doses)	1.2 mg/kg increments every one to two weeks to achieve a maintenance dose of 5 - 15 mg/kg (once a day or two divided doses) to a maximum of 400 mg/day
	This dosage regimen should be used with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (*see Interactions*)	0.3 mg/kg (one or two divided doses)	0.6 mg/kg (one or two divided doses)	0.6 mg/kg increments every one to two weeks to achieve a maintenance dose of 1 - 10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day

In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (*see Interactions*), the treatment regimen as recommended for lamotrigine with concurrent valproate should be used.

*(Where 2 mg tablets are the lowest strength available) if the calculated daily dose in patients taking valproate is between 1 to 2 mg, then 2 mg may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 1 mg, then *LAMICTAL* should not be administered. DO NOT attempt to give partial quantities of the dispersible/chewable tablets.

*(Where 5 mg tablets are the lowest strength available) if the calculated daily dose in patients taking valproate is between 2.5 to 5 mg, then 5 mg may be taken on alternate days for the first two weeks. If the calculated daily dose in patients taking valproate is less than 2.5 mg, then *LAMICTAL* should not be used. DO NOT attempt to administer partial quantities of the dispersible/chewable tablets.

**If the calculated dose of *LAMICTAL* cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet.

Because of a risk of rash, the initial dose and subsequent dose escalation should not be exceeded (*see Warnings and Precautions*). It is likely that patients aged two to six years will require a maintenance dose at the higher end of the recommended range.

Children aged less than 2 years
There is insufficient information on the use of *LAMICTAL* in children aged less than two years.

Bipolar Disorder

- **Adults (18 years of age and over)**

Because of the risk of rash, the initial dose and subsequent dose escalation should not be exceeded (*see Warnings and Precautions*).

LAMICTAL is recommended for use in bipolar patients at risk for a future depressive episode.

The following transition regimen should be followed to prevent recurrence of depressive episodes. The transition regimen involves escalating the dose of *LAMICTAL* to a maintenance stabilisation dose over six weeks (*see Table 3*) after which other psychotropic and/or antiepileptic drugs can be withdrawn, if clinically indicated (*see Table 4*).

Adjunctive therapy should be considered for the prevention of manic episodes, as efficacy with *LAMICTAL* in mania has not been conclusively established.

Table 3: Recommended dose escalation to the maintenance total daily stabilisation dose for adults (18 years of age and over) treated for BIPOLAR DISORDER

Treatment Regimen	Weeks 1-2	Weeks 3-4	Week 5	Target Stabilisation Dose (Week 6)**
a) Adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. valproate	12.5 mg (given 25 mg alternate days)	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses) (maximum daily dose of 200 mg)
b) Adjunct therapy with inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate. **This dosage regimen should be used with:** **Phenytoin** **Carbamazepine** **Phenobarbitone** **Primidone** **or with other inducers of lamotrigine glucuronidation (*see Interactions*)**	50 mg (once a day)	100 mg (two divided doses)	200 mg (two divided doses)	300 mg in week 6, increasing to 400 mg/day if necessary in week 7 (two divided doses)
c) Monotherapy with *LAMICTAL* **OR** **adjunctive therapy in patients taking other medications that do not significantly inhibit or induce lamotrigine glucuronidation (*see Interactions*)**	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses)	200 mg (range 100 - 400 mg) (once a day or two divided doses)
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation as recommended for *LAMICTAL* with concurrent valproate, should be used.				

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

a) Adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. valproate
In patients taking glucuronidation inhibiting concomitant drugs such as valproate, the initial *LAMICTAL* dose is 25 mg every alternate day for two weeks, followed by 25 mg once a day for two weeks. The dose should be increased to 50 mg once a day (or in two divided doses) in week 5. The usual target dose to achieve optimal response is 100 mg/day given once a day or in two divided doses. However, the dose can be increased to a maximum daily dose of 200 mg, depending on clinical response.

b) Adjunct therapy with inducers of lamotrigine glucuronidation in patients NOT taking inhibitors such as valproate. This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone and other drugs known to induce lamotrigine glucuronidation (*see Interactions*)
In those patients currently taking drugs that induce lamotrigine glucuronidation and NOT taking valproate, the initial *LAMICTAL* dose is 50 mg once a day for two weeks, followed by 100 mg/day given in two divided doses for two weeks. The dose should be increased to 200 mg/day given as two divided doses in week 5. The dose may be increased in week 6 to 300 mg/day. However, the usual target dose to achieve optimal response is 400 mg/day given in two divided doses which may be given from week 7.

c) Monotherapy with *LAMICTAL* OR adjunctive therapy in patients taking other medications that do not significantly induce or inhibit lamotrigine glucuronidation (*see Interactions*)
The initial *LAMICTAL* dose is 25 mg once a day for two weeks, followed by 50 mg once a day (or in two divided doses) for two weeks. The dose should be increased to 100 mg/day in week 5. The usual target dose to achieve optimal response is 200 mg/day given once a day or as two divided doses. However, a range of 100 to 400 mg was used in clinical trials.

Once the target daily maintenance stabilisation dose has been achieved, other psychotropic medications may be withdrawn as laid out in the dosage schedule below (*see Table 4*).

Table 4: Maintenance stabilisation total daily dose in adults (18 years of age and over) with BIPOLAR DISORDER following withdrawal of concomitant psychotropic or antiepileptic drugs

<table>
<tr><th>Treatment Regimen</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards*</th></tr>
<tr><td>(a) Following withdrawal of inhibitors of lamotrigine glucuronidation e.g. valproate</td><td>Double the stabilisation dose, not exceeding 100 mg/week

i.e. 100 mg/day target stabilisation dose will be increased in week 1 to 200 mg/day</td><td colspan="2">Maintain this dose (200 mg/day)

(two divided doses)</td></tr>
<tr><td rowspan="3">(b) Following withdrawal of inducers of lamotrigine glucuronidation depending on original dose.

This dosage regimen should be used with:
Phenytoin
Carbamazepine
Phenobarbitone
Primidone

or with other inducers of lamotrigine glucuronidation (see Interactions)</td><td>400 mg</td><td>300 mg</td><td>200 mg</td></tr>
<tr><td>300 mg</td><td>225 mg</td><td>150 mg</td></tr>
<tr><td>200 mg</td><td>150 mg</td><td>100 mg</td></tr>
<tr><td>(c) Following withdrawal of other medications that do not significantly inhibit or induce lamotrigine glucuronidation (see Interactions)</td><td colspan="3">Maintain target dose achieved in dose escalation (200 mg/day)

(two divided doses)

(range 100 - 400 mg)</td></tr>
<tr><td colspan="4">NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the treatment regimen recommended for LAMICTAL is to initially maintain the current dose and adjust the LAMICTAL treatment based on clinical response.</td></tr>
</table>

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

(a) Following withdrawal of adjunct therapy with inhibitors of lamotrigine glucuronidation e.g. valproate
The dose of *LAMICTAL* should be increased to double the original target stabilisation dose and maintained at this, once valproate has been terminated.

(b) Following withdrawal of adjunct therapy with inducers of lamotrigine glucuronidation depending on original maintenance dose. This regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone or other drugs known to induce *LAMICTAL* glucuronidation (*see Interactions*)
The dose of *LAMICTAL* should be gradually reduced over three weeks as the glucuronidation inducer is withdrawn.

(c) Following withdrawal of adjunct therapy with other medications that do not significantly inhibit or induce lamotrigine glucuronidation (*see Interactions*)

The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medication.

Adjustment of LAMICTAL daily dosing in patients with BIPOLAR DISORDER following addition of other medications

There is no clinical experience in adjusting the *LAMICTAL* daily dose following the addition of other medications. However, based on drug interaction studies, the following recommendations can be made (*see Table 5*, below):

Table 5: Adjustment of *LAMICTAL* daily dosing in adults (18 years of age and over) with BIPOLAR DISORDER following the addition of other medications

Treatment Regimen	Current *LAMICTAL* Stabilisation dose (mg/day)	Week 1	Week 2	Week 3 onwards
(a) Addition of inhibitors of lamotrigine glucuronidation e.g. valproate, depending on original dose of *LAMICTAL*	200 mg	100 mg	Maintain this dose (100 mg/day)	
	300 mg	150 mg	Maintain this dose (150 mg/day)	
	400 mg	200 mg	Maintain this dose (200 mg/day)	
(b) Addition of inducers of lamotrigine glucuronidation in patients NOT taking valproate and depending on original dose of *LAMICTAL* **This dosage regimen should be used with:** **Phenytoin** **Carbamazepine** **Phenobarbitone** **Primidone** **or with other inducers of lamotrigine glucuronidation (*see Interactions*)**	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg
	100 mg	100 mg	150 mg	200 mg
(c) Addition of other medications that do not significantly inhibit or induce lamotrigine glucuronidation (*see Interactions*)	Maintain target dose achieved in dose escalation (200 mg/day) (range 100 - 400 mg)			
NOTE: In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known, the treatment regimen as recommended for *LAMICTAL* with concurrent valproate, should be used.				

Discontinuation of LAMICTAL in adult patients with Bipolar Disorder

In clinical trials, there was no increase in the incidence, severity or type of adverse experiences following abrupt termination of *LAMICTAL* versus placebo. Therefore, patients may terminate *LAMICTAL* without a stepwise reduction of dose.

- **Children and adolescents (less than 18 years of age)**

LAMICTAL is not indicated for use in bipolar disorder in children and adolescents aged less than 18 years (*see Warnings and Precautions*). Safety and efficacy of *LAMICTAL* in bipolar disorder has not been established in this age group. Therefore, a dosage recommendation cannot be made.

GENERAL DOSING RECOMMENDATIONS FOR *LAMICTAL* IN SPECIAL PATIENT POPULATIONS

- **Women taking hormonal contraceptives**

(a) Starting *LAMICTAL* in patients already taking hormonal contraceptives:
Although an oral contraceptive has been shown to increase the clearance of lamotrigine (*see Warnings and Precautions and Interactions*), no adjustments to the recommended dose escalation guidelines for *LAMICTAL* should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether lamotrigine is added to valproate (an inhibitor of lamotrigine glucuronidation), or to an inducer of lamotrigine glucuronidation, or whether *LAMICTAL* is added in the absence of valproate or an inducer of lamotrigine glucuronidation (*see Table 1* for epilepsy and *Table 3* for bipolar disorder patients).

(b) Starting hormonal contraceptives in patients already taking maintenance doses of *LAMICTAL* and NOT taking inducers of lamotrigine glucuronidation:
The maintenance dose of *LAMICTAL* will in most cases need to be increased by as much as two-fold (*see Warnings and Precautions and Interactions*).

(c) Stopping hormonal contraceptives in patients already taking maintenance doses of *LAMICTAL* and NOT taking inducers of lamotrigine glucuronidation:
The maintenance dose of *LAMICTAL* will in most cases need to be decreased by as much as 50% (*see Warnings and Precautions & Interactions*).

- **Use with atazanavir/ritonavir**

Although atazanavir/ritonavir has been shown to reduce lamotrigine plasma concentrations (*see Interactions*), no adjustments to the recommended dose escalation guidelines for *LAMICTAL* should be necessary solely based on the use of atazanavir/ritonavir. Dose escalation should follow the recommended guidelines based on whether *LAMICTAL* is added to valproate (an inhibitor of lamotrigine glucuronidation), or to an inducer of lamotrigine glucuronidation, or whether *LAMICTAL* is added in the absence of valproate or an inducer of lamotrigine glucuronidation.

In patients already taking maintenance doses of *LAMICTAL* and not taking glucuronidation inducers, the *LAMICTAL* dose may need to be increased if atazanavir/ritonavir is added or decreased if atazanavir/ritonavir is discontinued.

- **Use with other oestrogen-containing products**

Other oestrogen-containing therapies, such as hormone replacement therapies (HRTs), may interfere with LAMICTAL. Therefore, close clinical monitoring on effectiveness of LAMICTAL with dose adjustment may be necessary (see Warnings and Precautions).

- **Elderly (over 65 years of age)**

No dosage adjustment from recommended schedule is required. The pharmacokinetics of *LAMICTAL* in this age group do not differ significantly from a non-elderly adult population.

- **Hepatic impairment**

Initial, escalation and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh grade B) and 75% in severe (Child-Pugh grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response (*see Pharmacokinetics*).

- **Renal impairment**

Caution should be exercised when administering *LAMICTAL* to patients with renal failure. For patients with end-stage renal failure, initial doses of *LAMICTAL* should be based on patient's AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment (*see Warnings and Precautions*). For more detailed pharmacokinetic information (*see Pharmacokinetics*).

2.3 Contraindications
LAMICTAL tablets and dispersible/chewable tablets are contraindicated in individuals with known hypersensitivity to, lamotrigine or any other ingredient of the preparation.

2.4 Warnings and Precautions
Skin Rash
There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiation of *LAMICTAL* treatment. The majority of rashes are mild and self limiting, however serious rashes requiring hospitalisation and discontinuation of *LAMICTAL* have also been

reported. These have included potentially life-threatening rashes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (*see Adverse Reactions*).

In adults enrolled in studies utilising the current *LAMICTAL* dosing recommendations, the incidence of serious skin rashes is approximately 1 in 500 in epilepsy patients. Approximately half of these cases have been reported as SJS (1 in 1,000).

In clinical trials in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1,000.

The risk of serious skin rashes in children is higher than in adults.

Available data from a number of studies suggest the incidence of rashes associated with hospitalisation in children is from 1 in 300 to 1 in 100.

In children, the initial presentation of a rash can be mistaken for an infection. Physicians should consider the possibility of a drug reaction in children that develop symptoms of rash and fever during the first eight weeks of therapy.

Additionally, the overall risk of rash appears to be strongly associated with:
- high initial doses of *LAMICTAL* and exceeding the recommended dose escalation of *LAMICTAL* therapy (*see Dosage and Administration*)
- concomitant use of valproate (*see Dosage and Administration*).

Caution is also required when treating patients with a history of allergy or rash to other antiepileptic drugs as the frequency of non-serious rash after treatment with *LAMICTAL* was approximately three times higher in these patients than in those without such history.

Limited data suggest that human leukocyte antigen (HLA) B*1502 allele in individuals of Asian primarily Han Chinese and Thai) origin is associated with the risk of developing SJS/TEN when treated with *LAMICTAL*. However, there are patients who are positive for HLA B*1502 who do not go on to develop SJS/TEN, and SJS/TEN may still occur in patients taking *LAMICTAL* who are found to be negative for HLA B*1502. If patients are known to be carrying this genetic variant, the benefits of treatment with *LAMICTAL* should be carefully weighed against the risk of developing SJS/TEN.

All patients (adults and children) who develop a rash should be promptly evaluated and *LAMICTAL* withdrawn immediately unless the rash is clearly not drug related. It is recommended that *LAMICTAL* not be restarted in patients who have discontinued due to rash associated with prior treatment with *LAMICTAL* unless the potential benefit clearly outweighs the risk.

Rash has also been reported as part of drug reaction with eosinophilia and systemic symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver and kidney and aseptic meningitis (*see Adverse Reactions*). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and *LAMICTAL* discontinued if an alternative aetiology cannot be established.

Aseptic meningitis was reversible on withdrawal of the drug in most cases but recurred in a number of cases on re-exposure to lamotrigine. Re-exposure resulted in a rapid return of symptoms that were frequently more severe. Lamotrigine should not be restarted in patients who have discontinued due to aseptic meningitis associated with prior treatment of lamotrigine.

Haemophagocytic Lymphohistiocytosis (HLH)
HLH has occurred in patients taking *LAMICTAL* (*see Adverse Reactions*). HLH is a syndrome of pathological immune activation, which can be life threatening, characterised by clinical signs and symptoms such as fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, high serum ferritin, hypertriglyceridaemia and abnormalities of liver function and coagulation. Symptoms occur generally within 4 weeks of treatment initiation.

Immediately evaluate patients who develop these signs and symptoms and consider a diagnosis of HLH. *LAMICTAL* should be discontinued unless an alternative aetiology can be established.

Suicide Risk
Symptoms of depression and/or bipolar disorder may occur in patients with epilepsy, and there is evidence that patients with epilepsy and bipolar disorder have an elevated risk for suicidality.

Twenty-five to fifty percents of patients with bipolar disorder attempt suicide at least once and may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking medications for bipolar disorder, including *LAMICTAL*.

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications, including epilepsy and bipolar disorder. A meta-analysis of randomised placebo-controlled trials of AEDs (including lamotrigine) has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for lamotrigine. Therefore, patients should be monitored for signs of suicidal ideation and behaviours.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Clinical Worsening in Bipolar Disorder
Patients receiving *LAMICTAL* for bipolar disorder should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. Certain patients, such as those with a history of suicidal behaviour or thoughts, young adults, and those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behaviour, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Effects of Oestrogen-containing Products Including Hormonal Contraceptives on *LAMICTAL* Efficacy
An ethinylestradiol/levonorgestrel (30 micrograms/150 micrograms) combination has been demonstrated to increase the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (*see Interactions*). Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) will be needed in most cases to attain a maximal therapeutic response. In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive medication (e.g. "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive medication. These increases will be greater when lamotrigine dose increases are made in the days before or during the week of inactive medication. For dosing instructions see "*General Dosing Recommendations for LAMICTAL in Special Patient Populations, Dosage and Administration*".

Clinicians should exercise appropriate clinical management of women starting or stopping hormonal contraceptives during *LAMICTAL* therapy and lamotrigine dosing adjustments will be needed in most cases.

Other oral contraceptive and other oestrogen-containing therapies (such as HRT) have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of *LAMICTAL* on Hormonal Contraceptive Efficacy
An interaction study in 16 healthy volunteers has shown that when lamotrigine and a hormonal contraceptive (ethinylestradiol/levonorgestrel combination) are administered in combination, there is a modest increase in levonorgestrel clearance and changes in serum FSH and LH (*see Interactions*). The impact of these changes on ovarian ovulatory activity is unknown. However, the possibility of these changes resulting in decreased contraceptive efficacy in some patients taking hormonal

preparations with *LAMICTAL* cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Effect of Lamotrigine on Organic Cationic Transporter 2 (OCT2) Substrates
Lamotrigine is an inhibitor of renal tubular secretion via OCT2 proteins (*see Interactions*). This may result in increased plasma levels of certain drugs that are substantially excreted via this route. Co-administration of *LAMICTAL* with OCT2 substrates with a narrow therapeutic index e.g. dofetilide is not recommended.

Dihydrofolate Reductase
Lamotrigine is a weak inhibitor of dihydrofolate reductase, hence there is a possibility of interference with folate metabolism during long-term therapy. However, during prolonged human dosing, *LAMICTAL* did not induce significant changes in the haemoglobin concentration, mean corpuscular volume, or serum or red blood cell folate concentrations up to 1 year or red blood cell folate concentrations for up to 5 years.

Renal Failure
In single dose studies in subjects with end-stage renal failure, plasma concentrations of lamotrigine were not significantly altered. However, accumulation of the glucuronide metabolite is to be expected; caution should therefore be exercised in treating patients with renal failure.

Patients Taking Other Preparations Containing Lamotrigine
LAMICTAL tablets and dispersible/chewable tablets should not be administered to patients currently being treated with any other preparation containing lamotrigine without consulting a doctor.

Brugada-type ECG
A very rare association with Brugada-type ECG has been observed, although a causal relationship has not been established. Therefore, careful consideration should be given before using LAMICTAL in patients with Brugada syndrome (*see Pharmacodynamics*).

Cardiac Rhythm and Conduction Abnormalities
In vitro testing showed that *LAMICTAL* exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. Based on these *in vitro* findings, *LAMICTAL* could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia in patients with clinically important structural or functional heart disease. Therefore, any expected or observed benefit of *LAMICTAL* for those patients must be carefully weighed against the potential risks for serious or fatal cardiac events. Concomitant use of other sodium channel blockers may further increase the risk of proarrhythmia (*see Pharmacodynamics*).

Epilepsy
As with other AEDs, abrupt withdrawal of *LAMICTAL* may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of *LAMICTAL* should be gradually decreased over a period of two weeks.

There are reports in the literature that severe convulsive seizures including status epilepticus may lead to rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation, sometimes with fatal outcome. Similar cases have occurred in association with the use of *LAMICTAL*.

Bipolar Disorder
- **Children and adolescents (less than 18 years of age)**

Treatment with antidepressants is associated with an increased risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder and other psychiatric disorders.

2.5 Interactions
Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs that induce or inhibit glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGTs, may also enhance the metabolism of lamotrigine. There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes. Lamotrigine may induce its own metabolism but the effect is modest and unlikely to have significant clinical consequences.

Those drugs that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in *Table 6*. Specific dosing guidance for these drugs is provided in *Dosage and Administration.* In addition, this table lists those drugs which have been shown to have little or no effect on the concentration of lamotrigine. Co-administration of such drugs would generally not be expected to result in any clinical impact. However, consideration should be given to patients whose epilepsy is especially sensitive to fluctuations in concentrations of lamotrigine.

Table 6: Effects of drugs on the concentration of lamotrigine

Drugs that increase the concentration of lamotrigine	Drugs that decrease the concentration of lamotrigine	Drugs that have little or no effect on the concentration of lamotrigine
Valproate	Atazanavir/ritonavir Carbamazepine Ethinylestradiol/levonorgestrel combination Lopinavir/ritonavir Phenobarbitone Phenytoin Primidone Rifampicin	Aripiprazole Bupropion Felbamate Gabapentin Lacosamide Levetiracetam Lithium Olanzapine Oxcarbazepine Paracetamol Perampanel Pregabalin Topiramate Zonisamide

For dosing guidance, *see Dosage and Administration - General Dosing Recommendations for LAMICTAL in Special Patient Populations, plus for women taking hormonal contraceptives also see Warnings and Precautions – Effects of Oestrogen-containing Products Including Hormonal Contraceptives on LAMICTAL Efficacy and Effects of LAMICTAL on Hormonal Contraceptive Efficacy.*

Interactions Involving AEDs (*see Dosage and Administration*)
Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold.

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, enhance the metabolism of lamotrigine.

There have been reports of central nervous system events including dizziness, ataxia, diplopia, blurred vision and nausea in patients taking carbamazepine following the introduction of *LAMICTAL*. These events usually resolve when the dose of carbamazepine is reduced. A similar effect was seen during a study of lamotrigine and oxcarbazepine in healthy adult volunteers, but dose reduction was not investigated.

In a study in healthy adult volunteers using doses of 200 mg lamotrigine and 1,200 mg oxcarbazepine, oxcarbazepine did not alter the metabolism of lamotrigine and lamotrigine did not alter the metabolism of oxcarbazepine.

In a study of healthy volunteers, co-administration of felbamate (1,200 mg twice daily) with *LAMICTAL* (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

Based on a retrospective analysis of plasma levels in patients who received *LAMICTAL* both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Potential drug interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

Steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic interactions between lamotrigine and pregabalin.

Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of *LAMICTAL* resulted in a 15% increase in topiramate concentrations.

In a study of patients with epilepsy, co-administration of zonisamide (200 to 400 mg/day) with *LAMICTAL* (150 to 500 mg/day) for 35 days had no significant effect on the pharmacokinetics of lamotrigine.

Plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200, 400, or 600 mg/day) in placebo-controlled clinical trials in patients with partial-onset seizures.

In a pooled analysis of data from three placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and primary generalised tonic-clonic seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by less than 10%.

Although changes in the plasma concentrations of other antiepileptic drugs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of concomitant antiepileptic drugs. Evidence from *in vitro* studies indicates that lamotrigine does not displace other antiepileptic drugs from protein binding sites.

Interactions Involving Other Psychoactive Agents (*see Dosage and Administration*)
The pharmacokinetics of lithium after 2 g of anhydrous lithium gluconate given twice daily for six days to 20 healthy subjects were not altered by co-administration of 100 mg/day *LAMICTAL*.

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of *LAMICTAL* in 12 subjects and had only a slight increase in the AUC of lamotrigine glucuronide.

In a study in healthy adult volunteers, 15 mg olanzapine reduced the AUC and C_{max} of lamotrigine by an average of 24% and 20%, respectively. Lamotrigine at 200 mg did not affect the pharmacokinetics of olanzapine.

Multiple oral doses of *LAMICTAL* 400 mg daily had no clinically significant effect on the single dose pharmacokinetics of 2 mg risperidone in 14 healthy adult volunteers. Following the co-administration of risperidone 2 mg with lamotrigine, 12 out of the 14 volunteers reported somnolence compared to 1 out of 20 when risperidone was given alone, and none when *LAMICTAL* was administered alone.

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (>/=100 mg/day), doses of aripiprazole were increased from 10 mg/day to a target of 30 mg/day over a 7 day period and continued once daily for a further 7 days. An average reduction of approximately 10% in C_{max} and AUC of lamotrigine was observed.

In vitro inhibition experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally affected by co-incubation with amitriptyline, bupropion, clonazepam, fluoxetine, haloperidol, or lorazepam. Bufuralol metabolism data from human liver microsome suggested that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6. Results of *in vitro* experiments also suggest that clearance of lamotrigine is unlikely to be affected by clozapine, phenelzine, risperidone, sertraline or trazodone.

Interactions Involving Hormonal Contraceptives
- **Effect of hormonal contraceptives on lamotrigine pharmacokinetics**

In a study of 16 female volunteers, 30 micrograms ethinylestradiol/150 micrograms levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in an average 52% and 39% reduction in lamotrigine AUC and C_{max}, respectively. Serum lamotrigine concentrations gradually increased during the course of the week of inactive medication (e.g. "pill-free" week), with pre-dose concentrations at the end of the week of inactive medication being, on average, approximately two-fold higher than during co-therapy - *see Dosage and Administration - General Dosing Recommendations for LAMICTAL in Special Patient Populations* (for dosing instructions for women taking oestrogen-containing products including hormonal contraceptives) and *Warnings and Precautions - Effects of Oestrogen-containing Products*

Including Hormonal Contraceptives on LAMICTAL Efficacy and Effects of LAMICTAL on Hormonal Contraceptive Efficacy.

- **Effect of lamotrigine on hormonal contraceptive pharmacokinetics**

In a study of 16 female volunteers, a steady state dose of 300 mg lamotrigine had no effect on the pharmacokinetics of the ethinylestradiol component of a combined oral contraceptive pill. A modest increase in oral clearance of the levonorgestrel component was observed, resulting in an average 19% and 12% reduction in levonorgestrel AUC and C_{max}, respectively. Measurement of serum FSH, LH and estradiol during the study indicated some loss of suppression of ovarian hormonal activity in some women, although measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 subjects. The impact of the modest increase in levonorgestrel clearance, and the changes in serum FSH and LH, on ovarian ovulatory activity is unknown (*see Warnings and Precautions*). The effects of doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations (including progesterone/progesterone-containing HRT) have not been conducted.

Interactions Involving Other Medications

In a study in 10 male volunteers, rifampicin increased lamotrigine clearance and decreased lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. In patients receiving concomitant therapy with rifampicin, the treatment regimen recommended for lamotrigine and concurrent glucuronidation inducers should be used (*see Dosage and Administration*).

In a study in healthy volunteers, lopinavir/ritonavir approximately halved the plasma concentrations of lamotrigine, probably by induction of glucuronidation. In patients receiving concomitant therapy with lopinavir/ritonavir, the treatment regimen recommended for lamotrigine and concurrent glucuronidation inducers should be used (*see Dosage and Administration*).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and C_{max} of lamotrigine (single 100 mg dose) by an average of 32% and 6%, respectively (*see Dosage and Administration - General Dosing Recommendations for LAMICTAL in Special Patient Populations*).

In a study in healthy adult volunteers, paracetamol 1 g (four times daily) reduced the plasma AUC and C_{min} of lamotrigine by an average of 20% and 25%, respectively.

Data from *in vitro* assessment of the effect of lamotrigine at OCT2 demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT2 at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT2, with an IC_{50} value of 53.8 µM (*see Warnings and Precautions*).

Interactions Involving Laboratory Tests

LAMICTAL has been reported to interfere with the assay used in some rapid urine drug screens, which can result in false positive readings, particularly for phencyclidine (PCP). A more specific alternative chemical method should be used to confirm a positive result.

2.6 Pregnancy and Lactation

Fertility

Administration of lamotrigine did not impair fertility in animal reproductive studies.

There is no experience of the effect of *LAMICTAL* on human fertility.

Pregnancy

Post-marketing data from several prospective pregnancy registries have documented outcomes in over 8,700 women exposed to *LAMICTAL* monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations. Although data from a limited number of registries have reported an increase in the risk of isolated oral cleft malformations, a completed case control study did not demonstrate an

increased risk of oral clefts compared to other major congenital malformations following exposure to lamotrigine *(see Non-Clinical Information)*.

The data on use of *LAMICTAL* in polytherapy combinations are insufficient to assess whether the risk of malformation associated with other agents is affected by concomitant *LAMICTAL* use.

As with other medicines, *LAMICTAL* should only be used during pregnancy if the expected benefits outweigh the potential risks.

Physiological changes during pregnancy may affect lamotrigine levels and/or therapeutic effect. There have been reports of decreased lamotrigine levels during pregnancy. Appropriate clinical management of pregnant women during *LAMICTAL* therapy should be ensured.

Lactation
Lamotrigine has been reported to pass into breast milk in highly variable concentrations, resulting in total lamotrigine levels in infants of up to approximately 50% of the mother's. Therefore, in some breast-fed infants, serum concentrations of lamotrigine may reach levels at which pharmacological effects occur.

The potential benefits of breastfeeding should be weighed against the potential risk of adverse effects occurring in the infant.

2.7 Effects on Ability to Drive and Use Machines
Two volunteer studies have demonstrated that the effect of *LAMICTAL* on fine visual motor coordination, eye movements, body sway and subjective sedative effects did not differ from placebo. In clinical trials with *LAMICTAL,* adverse events of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how *LAMICTAL* therapy affects them before driving or operating machinery.

Epilepsy
As there is individual variation in response to all antiepileptic drug therapy, patients should consult their physician on the specific issues of driving and epilepsy.

2.8 Adverse Reactions
The adverse reactions identified from epilepsy or bipolar disorder clinical trial data have been divided into indication specific sections. Additional adverse reactions identified through post-marketing surveillance for both indications are included in the post-marketing section. All three sections should be consulted when considering the overall safety profile of *LAMICTAL*.

The following convention has been utilised for the classification of undesirable effects: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Clinical Trial Data
Epilepsy
The following adverse reactions were identified during epilepsy clinical trials and should be considered alongside those seen in the bipolar disorder clinical trials and post-marketing sections for an overall safety profile of *LAMICTAL*.

Skin and subcutaneous tissue disorders

Very common:	Skin rash
Rare:	Erythema multiforme, Stevens-Johnson syndrome
Very rare:	Toxic epidermal necrolysis

In double-blind, add-on clinical trials in adults, skin rashes occurred in up to 10% of patients taking *LAMICTAL* and in 5% of patients taking placebo. The skin rashes led to the withdrawal of *LAMICTAL* treatment in 2% of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of *LAMICTAL* (*see Warnings and Precautions*).

Rarely, serious potentially life-threatening skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been reported. Although the majority recover on

drug withdrawal, some patients experience irreversible scarring and there have been rare cases of associated death (*see Warnings and Precautions*).

The overall risk of rash appears to be strongly associated with:
- high initial doses of *LAMICTAL* and exceeding the recommended dose escalation of *LAMICTAL* therapy (*see Dosage and Administration*).
- concomitant use of valproate (*see Dosage and Administration*).

Rash has also been reported as part of drug reaction with eosinophilia and systemic symptoms (DRESS); also known as hypersensitivity syndrome. This condition is associated with a variable pattern of systemic symptoms (*see Warnings and Precautions and Immune system disorders***).

Blood and lymphatic system disorders

Very rare:	Haematological abnormalities (including, neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis), lymphadenopathy

Haematological abnormalities and lymphadenopathy may or may not be associated with DRESS/hypersensitivity syndrome (*see Warning and Precautions and Immune system disorders***).

Immune system disorders

Very rare:	DRESS/hypersensitivity syndrome** including such symptoms as, fever, lymphadenopathy, facial oedema, abnormalities of the blood, liver and kidney.

**Rash has also been reported as part of this syndrome which shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation (DIC) and multiorgan failure. It is important to note that early manifestations of hypersensitivity (e.g. fever, lymphadenopathy) may be present even though rash is not evident. If such signs and symptoms are present, the patient should be evaluated immediately and *LAMICTAL* discontinued if an alternative aetiology cannot be established.

Psychiatric disorders

Common:	Aggression, irritability
Very rare:	Tics, hallucinations, confusion

Nervous system disorders

Very common:	Headache
Common:	Somnolence, insomnia, dizziness, tremor
Uncommon:	Ataxia
Rare:	Nystagmus

Eye disorders

Uncommon:	Diplopia, blurred vision

Gastrointestinal disorders

Common:	Nausea, vomiting, diarrhoea

Hepatobiliary disorders

Very rare:	Increased liver function tests, hepatic dysfunction, hepatic failure

Hepatic dysfunction usually occurs in association with hypersensitivity reactions but isolated cases have been reported without overt signs of hypersensitivity.

Musculoskeletal and connective tissue disorders

Very rare:	Lupus-like reactions

General disorders and administration site conditions

Common:	Tiredness

Bipolar disorder
The following adverse reactions were identified during bipolar disorder clinical trials and should be considered alongside those seen in the epilepsy clinical trials and post-marketing sections for an overall safety profile of *LAMICTAL*.

Skin and subcutaneous tissue disorders
Very Common: Skin rash
Rare: Erythema multiforme, Stevens-Johnson syndrome

When all bipolar disorder studies (controlled and uncontrolled) conducted with *LAMICTAL* are considered, skin rashes occurred in 12% of patients on *LAMICTAL*. Whereas, in controlled clinical trials with bipolar disorder patients, skin rashes occurred in 8% of patients taking *LAMICTAL* and in 6% of patients taking placebo.

Nervous system disorders
Very Common: Headache
Common: Agitation, somnolence, dizziness

Musculoskeletal and connective tissue disorders
Common: Arthralgia

General disorders and administration site conditions
Common: Pain, back pain

Post-marketing Data
This section includes adverse reactions identified through post-marketing surveillance for both indications. These adverse reactions should be considered alongside those seen in the epilepsy and bipolar disorder clinical trials sections for an overall safety profile of *LAMICTAL*.

Blood and lymphatic system disorders
Very rare: Haemophagocytic lymphohistiocytosis (*see Warnings and Precautions*), pseudolymphoma

Immune system disorders
Very rare: Hypogammaglobulinaemia

Psychiatric disorders
Very rare: Nightmares

Nervous system disorders
Very common: Somnolence, ataxia, headache, dizziness
Common: Nystagmus, tremor, insomnia
Rare: Aseptic meningitis (*see Warnings and Precautions*)

Very rare: Agitation, unsteadiness, movement disorders, worsening of Parkinson's disease, extrapyramidal effects, choreoathetosis

There have been reports that *LAMICTAL* may worsen parkinsonian symptoms in patients with pre-existing Parkinson’s disease, and isolated reports of extrapyramidal effects and choreoathetosis in patients without this underlying condition.

Eye disorders
Very common: Diplopia, blurred vision
Rare: Conjunctivitis

Gastrointestinal disorders
Very common: Nausea, vomiting
Common: Diarrhoea

Skin and subcutaneous tissue disorders
Uncommon: Photosensitivity reaction
Rare: Alopecia

Renal and urinary disorders
Very rare: Tubulointerstitial nephritis*

*may occur in association with uveitis

Epilepsy only
Nervous system disorders
Very rare: Increase in seizure frequency

Adverse events should be reported to GSK Indonesia via website https://gsk.public.reportum.com and Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan.
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

2.9 Overdose
Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose, have been reported, including fatal cases. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness, grand mal convulsion and coma. QRS broadening (intraventricular conduction delay) has also been observed in overdose patients.

In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy as clinically indicated or as recommended by the national poisons centre, where available.

3. PHARMACOLOGICAL PROPERTIES

3.1 Pharmacodynamics
ATC Code: N 03 AX 09

Mechanism of Action
The results of pharmacological studies suggest that lamotrigine is a use-dependent blocker of voltage-gated sodium channels. It produces a use- and voltage-dependent block of sustained repetitive firing in cultured neurones and inhibits pathological release of glutamate (the amino acid which plays a key role in the generation of epileptic seizures), as well as inhibiting glutamate-evoked bursts of action potentials.

Pharmacodynamic Effects
In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. At therapeutic doses, lamotrigine did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, in patients with clinically important structural or functional heart disease lamotrigine could potentially slow ventricular conduction (widen QRS) and induce proarrhythmia.

In tests designed to evaluate the central nervous system effects of drugs, the results obtained using doses of 240 mg lamotrigine administered to healthy volunteers did not differ from placebo, whereas both 1,000 mg phenytoin and 10 mg diazepam each significantly impaired fine visual motor coordination and eye movements, increased body sway and produced subjective sedative effects.

In another study, single oral doses of 600 mg carbamazepine significantly impaired fine visual motor coordination and eye movements, while increasing both body sway and heart rate, whereas results with lamotrigine at doses of 150 mg and 300 mg did not differ from placebo.

3.2 Pharmacokinetics
Absorption
Lamotrigine is rapidly and completely absorbed from the gut with no significant first pass metabolism. Peak plasma concentrations occur approximately 2.5 hours after oral drug administration. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. The pharmacokinetics are linear up to 450 mg, the highest single dose tested. There is considerable inter-individual variation in steady state maximum concentrations but within an individual concentrations rarely vary.

Distribution
Binding to plasma proteins is about 55%; it is very unlikely that displacement from plasma proteins would result in toxicity.

The volume of distribution is 0.92 to 1.22 L/kg.

Metabolism
UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine.

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and drugs metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination
The mean steady state clearance in healthy adults is 39 ± 14 mL/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of drug-related material is excreted in faeces. Clearance and half-life are independent of dose. The mean elimination half-life in healthy adults is 24 to 35 hours. In a study of subjects with Gilbert's syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

The half-life of lamotrigine is greatly affected by concomitant medication. Mean half-life is reduced to approximately 14 hours when given with glucuronidation-inducing drugs such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone (*see Dosage and Administration and Interactions*).

Special Patient Populations
- **Children**

Clearance adjusted for bodyweight is higher in children than in adults with the highest values in children under five years. The half-life of lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when given with enzyme-inducing drugs such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with valproate alone (s*ee Dosage and Administration*).

- **Elderly**

Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35 mL/min at age 20 to 31 mL/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37 mL/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0.39 mL/min/kg) lies within the range of the mean clearance values (0.31 to 0.65 mL/min/kg) obtained in 9 studies with non-elderly adults after single doses of 30 to 450 mg.

- **Renal impairment**

Twelve volunteers with chronic renal failure, and another 6 individuals undergoing haemodialysis were each given a single 100 mg dose of lamotrigine. Mean CL/F were 0.42 mL/min/kg (chronic renal failure), 0.33 mL/min/kg (between haemodialysis), and 1.57 mL/min/kg (during haemodialysis) compared to 0.58 mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9 hours (chronic renal failure), 57.4 hours (between haemodialysis) and 13.0 hours (during haemodialysis), compared to 26.2 hours in healthy volunteers. On average, approximately 20% (range= 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4 hours haemodialysis session. For this patient population, initial doses of *LAMICTAL* should be based on patient's AED regimen; reduced maintenance doses may be effective for patients with significant renal functional impairment.

- **Hepatic impairment**

A single-dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24 or 0.10 mL/min/kg in patients with Grade A, B, or C (Child-Pugh Classification) hepatic impairment, respectively, compared to 0.34 mL/min/kg in the healthy controls. Initial, escalation, and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh Grade B) and 75% in patients with severe (Child-Pugh Grade C) hepatic impairment. Escalation and maintenance doses should be adjusted according to clinical response.

3.3 Clinical Studies

Clinical Efficacy in The Prevention of Depressive Episodes in Patients With Bipolar Disorder:

- **Adults (18 years of age and over)**

Two pivotal studies have demonstrated efficacy in the prevention of depressive episodes in patients with bipolar I disorder.

Clinical study SCAB20003 was a multicentre, double-blind, double dummy, placebo and lithium-controlled, randomised fixed dose evaluation of the long-term prevention of relapse and recurrence of depression and/or mania in patients with bipolar I disorder who had recently or were currently experiencing a major depressive episode. Once stabilised using *LAMICTAL* monotherapy or *LAMICTAL* plus psychotropic medication, patients were randomly assigned into one of five treatment groups: *LAMICTAL* (50, 200, 400 mg/day), lithium (serum levels of 0.8 to 1.1 mMol/L) or placebo for a maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was "Time to Intervention for a Mood Episode (TIME)", where the interventions were either additional pharmacotherapy or ECT. This endpoint was analysed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0.003 to 0.029. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the *LAMICTAL* patients had longer times to first depressive episode than placebo patients (p=0.047), and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

Clinical study SCAB2006 was a multicentre, double-blind, double dummy, placebo and lithium-controlled, randomised, flexible dose evaluation of *LAMICTAL* in the long-term prevention of relapse and recurrence of mania and/or depression in patients with bipolar I disorder who had recently or were currently experiencing a manic or hypomanic episode. Once stabilised using *LAMICTAL* monotherapy or *LAMICTAL* plus psychotropic medication, patients were randomly assigned into one of three treatment groups: *LAMICTAL* (100 to 400 mg/day), lithium (serum levels of 0.8 to 1.1 mMol/L) or placebo for a maximum of 76 weeks (18 months). Treatment regimens were maintained until an emerging mood episode (depressive or manic) deemed it necessary to intervene with additional pharmacotherapy or electroconvulsive therapy (ECT).

The primary endpoint was "Time to Intervention for a Mood Episode (TIME)", where the interventions were either additional pharmacotherapy or ECT. This endpoint was analysed using three methods of handling data from patients who were withdrawn prior to having an intervention. The p-values for these analyses ranged from 0.003 to 0.023. In supportive analyses of time to first depressive episode and time to first manic/hypomanic or mixed episode, the *LAMICTAL* patients had longer times to first depressive episode than placebo patients (p=0.015), and the treatment difference with respect to time to manic/hypomanic or mixed episodes was not statistically significant.

In clinical trials, propensity to induce destabilisation, mania or hypomania whilst on *LAMICTAL* therapy was not significantly different to placebo.

3.4 Non-Clinical Information

Reproductive toxicology studies with lamotrigine in animals at doses less than the human dose of 400 mg/day [on a body surface area (mg/m^2) basis] showed developmental toxicity (increased mortality, decreased body weight, increased structural variations, neurobehavioral abnormalities), but no teratogenic effects. However, as lamotrigine is a weak inhibitor of dihydrofolate reductase, there is a theoretical risk of human foetal malformations when the mother is treated with a folate inhibitor during pregnancy.

The results of a wide range of mutagenicity tests indicate that lamotrigine does not present a genetic risk to man.

Lamotrigine was not carcinogenic in long-term studies in the rat and the mouse.

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Tablets:

Lactose, microcrystalline cellulose, povidone, sodium starch glycollate, iron oxide yellow (E172), magnesium stearate.

Dispersible/Chewable Tablets:
Calcium carbonate, low substituted hydroxypropyl cellulose, aluminium magnesium silicate, sodium starch glycollate, povidone, saccharin sodium, blackcurrant flavour, magnesium stearate.

4.2 Shelf Life
The expiry date is indicated on the packaging.

4.3 Storage
The storage conditions are detailed on the packaging.

Keep dry.

Protect dispersible/chewable tablets from light.

4.4 Nature and Contents of Container
Tablets
LAMICTAL 50 mg and 100 mg are available in child resistant PVC/PE/PVDC-aluminium/paper blister.

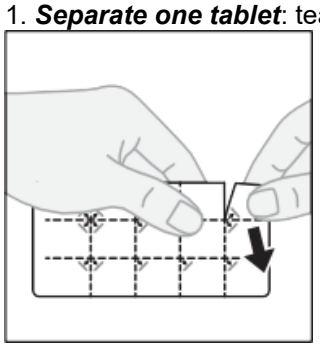
Dispersible/chewable tablets
LAMICTAL 5 mg is available in HDPE bottles with child resistant closure.

LAMICTAL 25 mg is available in PVC/PVdC/aluminium foil blister and child resistant PVC/PVdC – peel-push lidding foil blisters.

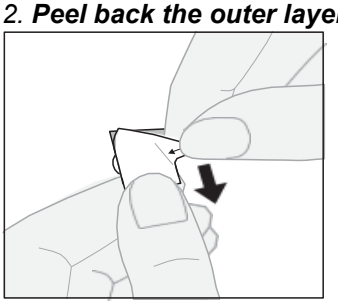
4.5 Incompatibilities
None reported.

4.6 Use and Handling
The 25 mg dispersible tablets may be supplied with a peel-push child resistant opening feature.

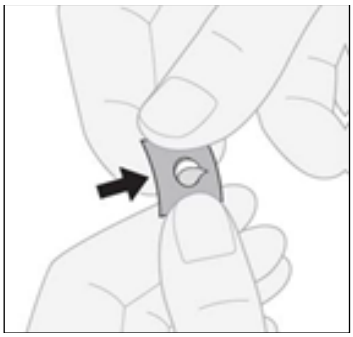
1. ***Separate one tablet***: tear along the cutting lines to separate one “pocket” from the blister.



2. ***Peel back the outer layer***: starting at the corner, lift and peel over the pocket.



3. ***Push out the tablet***: gently push one end of the tablet through the foil layer.



4.7 Package Quantities and Registration Number

Lamictal Dispersible Tablet 5 mg, Box, Bottle @ 30 tablets	Reg. No. DKI1433900281A2
Lamictal Dispersible Tablet 25 mg, Box, 3 Blisters @ 10 tablets	Reg. No. DKI1433900281B1
Lamictal Dispersible Tablet 25 mg, Box, 2 Blisters @ 15 tablets	Reg. No. DKI1433900281B1
Lamictal Tablet 50 mg, Box, 2 Blisters @ 15 tablets	Reg. No. DKI1833900510A1
Lamictal Tablet 100 mg, Box, 2 Blisters @ 15 tablets	Reg. No. DKI1833900510B1

OBAT KERAS - HARUS DENGAN RESEP DOKTER

Manufactured by
Delpharm Poznań Spółka Akcyjna
Poznań, Poland

Imported by
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia

Version number	: 04
Reference	: GDS54/IPI32
Date of local revision	: 10 March 2025

INFORMASI UNTUK PASIEN

Lamictal Tablet & Tablet Dispersibel

Lamotrigine

Baca keseluruhan brosur ini secara teliti sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting untuk Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, perawat atau apoteker.
- Obat ini hanya diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dapat membahayakan mereka, meskipun gejala penyakit mereka sama dengan gejala Anda.

Jika Anda merasakan efek samping, konsultasikan dengan dokter, perawat atau apoteker. Hal ini termasuk kemungkinan efek samping lain yang tidak tertulis dalam brosur ini. *Lihat bagian 4.*

Apa saja yang ada dalam brosur ini:

1. Apa itu LAMICTAL dan digunakan untuk apa

LAMICTAL termasuk ke dalam kelompok obat anti epilepsi. Digunakan untuk pengobatan dua kondisi yaitu, epilepsi dan gangguan bipolar.

LAMICTAL mengobati epilepsi dengan memblokir sinyal di otak yang memicu serangan epilepsi.

- Untuk orang dewasa dan anak berusia 13 tahun ke atas, LAMICTAL dapat digunakan secara tunggal atau dengan obat lain untuk mengobati epilepsi. LAMICTAL juga dapat digunakan dengan obat lain untuk mengobati kejang yang terjadi pada kondisi yang disebut *Lennox-Gastaut syndrome.*
- Untuk anak- anak berusia antara 2 dan 12 tahun, LAMICTAL dapat digunakan dengan obat lain.

LAMICTAL untuk mengobati gangguan bipolar

Orang dengan gangguan bipolar (kadang-kadang disebut depresi manik) mengalami perubahan suasana hati yang ekstrem, dengan periode mania (kegembiraan atau euforia) yang bergantian dengan periode depresi (kesedihan atau keputusasaan yang mendalam). Untuk pasien dewasa berusia 18 tahun ke atas, LAMICTAL dapat digunakan secara tunggal atau dengan obat lain, untuk mencegah periode depresi yang terjadi pada gangguan bipolar. Belum diketahui bagaimana LAMICTAL bekerja di otak untuk memiliki efek ini.

2. Apa yang perlu Anda ketahui sebelum menggunakan LAMICTAL

Jangan gunakan LAMICTAL jika Anda alergi (hipersensitif) terhadap lamotrigine atau salah satu bahan lain dari obat ini (*Lihat bagian 6*). **Jika ini terjadi pada Anda, beritahu dokter Anda** dan jangan gunakan LAMICTAL.

Perhatian dalam menggunakan LAMICTAL

Konsultasikan dengan dokter atau apoteker Anda sebelum menggunakan LAMICTAL.

- **Jika Anda memiliki masalah ginjal**.
- **Jika Anda pernah mengalami ruam** setelah minum lamotrigine atau obat lain untuk gangguan bipolar atau epilepsi.
- **Jika Anda pernah mengalami meningitis setelah minum lamotrigine** (*Lihat bagian 4* – Efek samping yang jarang terjadi).
- **Jika Anda sudah menggunakan obat yang mengandung lamotrigine**.

- **Jika Anda memiliki kondisi *Brugada syndrome***. *Brugada syndrome* adalah penyakit genetik yang menyebabkan adanya aktivitas listrik abnormal di dalam jantung. Kelainan EKG yang dapat menyebabkan aritmia (ritme jantung abnormal) dapat dipicu oleh lamotrigine.
- **Jika Anda memiliki kelainan ritme jantung dan konduksi jantung**.

Jika ini terjadi pada Anda, beritahu dokter Anda, yang mungkin akan menurunkan dosis atau LAMICTAL tidak cocok untuk Anda.

Informasi penting tentang reaksi yang berpotensi mengancam jiwa
Sebagian kecil orang yang menggunakan LAMICTAL mengalami reaksi alergi atau kulit yang berpotensi mengancam jiwa, reaksi yang dapat berkembang menjadi masalah yang lebih serius jika tidak ditangani. Termasuk *Stevens-Johnson syndrome* (SJS), *toxic epidermal necrolysis* (TEN) dan *drug reaction with eosinophilia and systemic symptoms* (DRESS). Anda perlu mengetahui gejala yang harus diwaspadai saat Anda menggunakan LAMICTAL.

Bacalah penjelasan gejala ini di bagian 4 pada brosur ini – Reaksi yang berpotensi mengancam jiwa. Segera dapatkan bantuan dokter.

Risiko reaksi kulit yang serius mungkin ada kaitannya dengan varian gen yang disebut HLA B*1502 pada orang-orang yang berasal dari Asia (terutama suku Han Cina dan Thailand). Jika Anda telah menjalani tes sebelumnya dan tahu bahwa Anda membawa varian genetik ini, bicarakan hal ini dengan dokter Anda sebelum menggunakan LAMICTAL.

Haemophagocytic lymphohistiocytosis **(HLH)**
Terdapat laporan terhadap reaksi sistem kekebalan tubuh yang jarang tetapi sangat serius pada pasien yang menggunakan lamotrigine.

Hubungi dokter atau apoteker Anda segera jika Anda mengalami gejala-gejala berikut ini saat menggunakan lamotrigine: demam, ruam, gejala neurologis (misalnya gemetar atau tremor, bingung, gangguan fungsi otak).

Pikiran untuk menyakiti diri sendiri atau bunuh diri
Obat anti epilepsi digunakan untuk mengobati beberapa kondisi, termasuk epilepsi dan gangguan bipolar. Orang-orang penderita bipolar terkadang memiliki pikiran untuk melukai diri sendiri atau melakukan bunuh diri. Jika Anda menderita gangguan bipolar, Anda mungkin berpikir seperti ini:
- Saat Anda pertama kali memulai pengobatan.
- Jika sebelumnya Anda pernah berpikir tentang melukai diri sendiri atau tentang bunuh diri.
- Jika Anda berusia di bawah 25 tahun.

Jika Anda memiliki pikiran atau pengalaman yang membuat stres, atau jika Anda menyadari bahwa Anda merasa lebih buruk atau terjadi gejala baru saat Anda menggunakan LAMICTAL:
Temui dokter sesegera mungkin atau ke rumah sakit terdekat untuk mendapatkan bantuan.

Anda mungkin merasa terbantu dengan memberi tahu anggota keluarga, pengasuh, teman dekat bahwa Anda dapat mengalami depresi atau mengalami perubahan suasana hati yang signifikan, dan meminta mereka untuk membaca brosur ini. Anda dapat meminta mereka untuk memberi tahu Anda jika mereka khawatir tentang depresi Anda atau perubahan lain dalam perilaku Anda.

Sebagian kecil orang yang dirawat dengan anti epilepsi seperti LAMICTAL juga memiliki pemikiran untuk menyakiti diri atau bunuh diri. Jika suatu saat Anda memiliki pemikiran ini, segera hubungi dokter Anda.

Jika Anda menggunakan LAMICTAL untuk pengobatan epilepsi
Kejang pada beberapa jenis epilepsi terkadang menjadi lebih buruk atau lebih sering terjadi saat Anda menggunakan LAMICTAL. Beberapa pasien mungkin mengalami kejang yang parah, yang dapat menyebabkan masalah kesehatan yang serius. Jika kejang Anda terjadi lebih sering atau jika Anda mengalami kejang parah saat Anda menggunakan LAMICTAL, **temui dokter sesegera mungkin.**

LAMICTAL tidak boleh diberikan kepada orang yang berusia di bawah 18 tahun untuk mengobati gangguan bipolar. Obat untuk merawat depresi dan masalah kesehatan mental lainnya dapat meningkatkan risiko pikiran dan perilaku bunuh diri pada anak-anak dan remaja berusia di bawah 18 tahun.

Obat-obatan lain dan LAMICTAL
Beritahu dokter atau apoteker jika Anda sedang menggunakan, telah menggunakan, atau mungkin menggunakan obat lain termasuk obat herbal atau obat lain yang dibeli tanpa resep dokter.

Dokter Anda perlu mengetahui apakah Anda sedang menggunakan obat lain untuk mengobati epilepsi atau masalah kesehatan mental. Hal ini untuk memastikan Anda menggunakan dosis LAMICTAL yang benar. Obat-obatan ini yaitu:
- **Oxcarbazepine, felbamate, gabapentin, levetiracetam, pregabalin, topiramate atau zonisamide, perampanel** digunakan untuk mengobati **epilepsi**.
- **Lithium, olanzapine atau aripiprazole** digunakan untuk mengobati **gangguan kesehatan mental**.
- **Bupropion** digunakan untuk mengobati **gangguan kesehatan mental** atau **berhenti merokok**.
- **Parasetamol** digunakan untuk mengobati **rasa nyeri** dan **demam**.
- **Obat-obatan untuk kelainan ritme dan konduksi jantung (golongan *sodium channel blockers)*.**

Beritahu dokter Anda jika Anda menggunakan obat tersebut.

Beberapa obat berinteraksi dengan LAMICTAL atau membuat orang lebih mungkin mengalami efek samping, yaitu sebagai berikut:
- **Valproate,** digunakan untuk mengobati **epilepsi** dan **gangguan kesehatan mental**.
- **Carbamazepine,** digunakan untuk mengobati **epilepsi** dan **gangguan kesehatan mental**.
- **Phenytoin, primidone** atau **phenobarbitone** digunakan untuk mengobati **epilepsi**.
- **Risperidone**, digunakan untuk mengobati **gangguan kesehatan mental**.
- **Rifampisin**, yaitu **antibiotik**.
- **Obat** yang digunakan untuk mengobati ***Human Immunodeficiency Virus*** **(HIV)** (kombinasi lopinavir dan ritonavir atau atazanavir dan ritonavir).
- **Obat yang mengandung estrogen** seperti terapi penggantian hormon.
- **Kontrasepsi hormonal**, seperti **pil KB** (*lihat bagian bawah*).

Beritahu dokter Anda jika Anda menggunakan, mulai menggunakan atau berhenti menggunakan obat tersebut.

Kontrasepsi hormonal (seperti pil KB) dapat mempengaruhi cara kerja LAMICTAL
Dokter Anda mungkin menyarankan agar Anda menggunakan jenis kontrasepsi hormonal tertentu atau metode kontrasepsi lainnya, seperti kondom, IUD. Jika Anda menggunakan kontrasepsi hormonal seperti pil KB, dokter Anda mungkin akan mengambil sampel darah Anda untuk memeriksa kadar LAMICTAL. Jika Anda menggunakan kontrasepsi hormonal atau jika Anda berencana untuk menggunakannya, **beritahu dokter Anda** yang akan mendiskusikan metode kontrasepsi yang sesuai dengan Anda.

LAMICTAL juga dapat mempengaruhi cara kerja kontrasepsi hormonal, meskipun kemungkinan tidak membuat efektivitasnya berkurang. Jika Anda menggunakan kontrasepsi hormonal dan Anda melihat ada perubahan pada pola menstruasi Anda seperti pendarahan atau bercak antara periode, **beritahu dokter Anda**. Hal ini mungkin pertanda bahwa LAMICTAL mempengaruhi cara kerja kontrasepsi Anda.

Kehamilan dan menyusui
Jika Anda sedang hamil, mengira Anda mungkin hamil atau berencana untuk memiliki bayi, tanyakan kepada dokter atau apoteker Anda sebelum menggunakan obat ini.
- **Anda tidak boleh menghentikan pengobatan tanpa membicarakan hal ini dengan dokter Anda**. Khususnya jika Anda menderita epilepsi.
- Kehamilan dapat mengubah efektivitas LAMICTAL, mungkin Anda memerlukan tes darah dan dosis LAMICTAL Anda dapat disesuaikan.
- Mungkin ada sedikit peningkatan risiko cacat lahir, termasuk bibir sumbing atau celah pada langit-langit mulut, jika LAMICTAL digunakan selama 3 bulan pertama kehamilan.

- Dokter Anda mungkin menyarankan Anda untuk meminum **asam folat** lebih banyak jika Anda berencana untuk hamil dan saat Anda hamil.

Jika Anda menyusui atau berencana untuk menyusui tanyakan kepada dokter atau apoteker Anda sebelum menggunakan obat ini. Bahan aktif LAMICTAL masuk ke dalam ASI dan dapat mempengaruhi bayi Anda. Dokter Anda akan mendiskusikan risiko dan manfaat menyusui saat Anda menggunakan LAMICTAL dan akan memeriksa bayi Anda dari waktu ke waktu, apakah mengantuk, ruam atau berat badan yang buruk terjadi. Jika Anda memutuskan untuk menyusui, beritahu dokter Anda jika Anda mengamati gejala-gejala tersebut pada bayi Anda.

Mengemudi dan menggunakan mesin
LAMICTAL bisa menyebabkan pusing dan penglihatan ganda. **Jangan mengemudi atau menggunakan mesin kecuali Anda yakin Anda tidak terpengaruh.**

Jika Anda menderita epilepsi, bicarakan dengan dokter Anda tentang mengemudi dan menggunakan mesin.

Informasi penting tentang bahan LAMICTAL
Tablet LAMICTAL mengandung sedikit gula yang disebut laktosa. Jika Anda memiliki intoleransi terhadap laktosa atau terhadap gula lainnya, beritahu dokter Anda dan jangan menggunakan LAMICTAL.

Tablet dan tablet kunyah/dispersibel LAMICTAL mengandung kurang dari 1 mmol natrium (23 mg) per tablet, yang dapat dikatakan pada dasarnya ‘bebas natrium’.

3. Cara menggunakan LAMICTAL

Selalu gunakan obat ini sesuai saran dokter atau perawat atau apoteker pada Anda. Konsultasikan dengan dokter, perawat atau apoteker jika Anda tidak yakin.

Berapa LAMICTAL yang harus digunakan
Perlu beberapa waktu untuk dapat menemukan dosis LAMICTAL yang terbaik untuk Anda. Dosis yang Anda gunakan tergantung pada:
- Usia Anda.
- Apakah Anda menggunakan LAMICTAL dengan obat lain.
- Apakah Anda memiliki masalah ginjal atau hati.

Dokter Anda akan memberikan dosis yang rendah untuk memulai dan secara bertahap akan meningkatkan dosis selama beberapa minggu sampai Anda mencapai dosis yang sesuai untuk Anda (disebut sebagai dosis efektif). **Jangan pernah menggunakan LAMICTAL lebih banyak dari yang disarankan oleh dokter Anda.**

Dosis efektif LAMICTAL yang biasa digunakan untuk orang dewasa dan anak-anak berusia 13 tahun atau lebih adalah antara 100 mg – 400 mg setiap hari.

Untuk anak-anak berusia 2 – 12 tahun, dosis efektif bergantung pada berat badan mereka. Biasanya antara 1 – 15 mg untuk setiap kilogram berat badan anak, sehingga dosis pemeliharaan maksimum 200 mg setiap hari.

LAMICTAL tidak dianjurkan untuk anak di bawah 2 tahun.

Bagaimana cara menggunakan dosis LAMICTAL
Anda dapat menggunakan dosis LAMICTAL sekali atau dua kali sehari, seperti yang disarankan dokter Anda. LAMICTAL dapat dikonsumsi dengan atau tanpa makanan.

Selalu minum keseluruhan dosis yang telah diresepkan dokter Anda. Jangan hanya mengambil sebagian dari tablet.

Dokter Anda mungkin juga menyarankan Anda untuk mulai atau berhenti meminum obat lain, tergantung pada kondisi Anda dirawat dan cara Anda menanggapi pengobatan.

Tablet kunyah/dispersibel LAMICTAL dapat ditelan utuh dengan sedikit air, dikunyah atau dicampur dengan air untuk membuat obat cair.

Untuk mengunyah tablet:
Anda mungkin perlu meminum sedikit air secara bersamaan untuk membantu tablet larut di dalam mulut, lalu minum sedikit air lagi untuk memastikan semua obat telah tertelan.

Untuk membuat obat cair:
- Letakkan tablet di dalam gelas dengan cukup air untuk menutupi seluruh tablet.
- Aduk hingga larut atau tunggu hingga tablet larut sepenuhnya.
- Minum semua cairannya.
- Tambahkan kembali air ke gelas dan minum untuk memastikan tidak ada obat yang tertinggal di gelas.

Apabila Anda menggunakan LAMICTAL lebih dari yang seharusnya
Segera hubungi dokter atau bagian gawat darurat rumah sakit terdekat. Jika memungkinkan, tunjukkan kemasan LAMICTAL ini.

Jika Anda menggunakan terlalu banyak LAMICTAL, mungkin Anda lebih cenderung memiliki efek samping serius yang mungkin berakibat fatal.

Gejala-gejala yang mungkin terjadi jika menggunakan terlalu banyak LAMICTAL yaitu:
- Gerakan mata yang cepat dan tidak terkendali (nistagmus).
- Kecanggungan dan kurang koordinasi, mempengaruhi keseimbangan (ataksia).
- Perubahan ritme jantung (biasanya terdeteksi pada EKG).
- Kehilangan kesadaran, kejang-kejang atau koma.

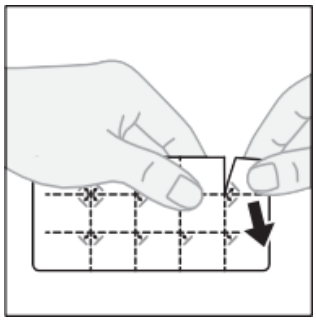
Apabila Anda lupa menggunakan LAMICTAL
- **Jangan menggunakan LAMICTAL berlebih untuk menggantikan dosis yang terlewatkan. Ambil dosis Anda berikutnya pada waktu yang biasanya**.
- **Jika Anda lupa untuk menggunakan beberapa dosis LAMICTAL, mintalah saran dokter tentang bagaimana memulainya lagi.** Penting bagi Anda untuk melakukan ini.

Jangan berhenti menggunakan LAMICTAL tanpa saran dari dokter Anda
LAMICTAL harus diminum selama dokter Anda merekomendasikannya. Jangan berhenti kecuali dokter Anda menyarankan untuk berhenti.

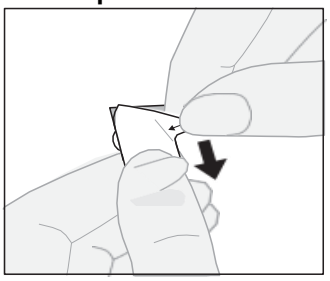
Jika Anda menggunakan LAMICTAL untuk epilepsi
Untuk berhenti menggunakan LAMICTAL, kurangi dosis secara bertahap selama sekitar 2 minggu. Jika Anda tiba-tiba berhenti menggunakan LAMICTAL, epilepsi Anda mungkin akan kembali atau menjadi lebih buruk.

Jika Anda menggunakan LAMICTAL untuk gangguan bipolar
LAMICTAL mungkin membutuhkan waktu untuk bekerja, sehingga mungkin Anda tidak langsung merasa lebih baik. Jika Anda berhenti menggunakan LAMICTAL, dosis Anda tidak perlu dikurangi secara bertahap. Tetapi Anda tetap harus konsultasikan dengan dokter Anda sebelum berhenti menggunakan LAMICTAL.

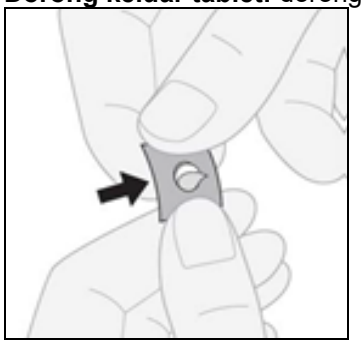
Hanya untuk tablet dispersibel
Tablet dispersibel 25 mg dikemas dalam kemasan khusus agar tidak mudah dibuka oleh anak-anak. Petunjuk untuk membuka kemasan ini dapat dilihat sebagai berikut:
- **Pisahkan satu tablet:** sobek sepanjang garis potong untuk memisahkan satu “kantong” dari blister.



- **Buka lapisan luar:** mulai dari sudut, angkat dan buka di atas kantong.



- **Dorong keluar tablet:** dorong perlahan salah satu ujung tablet melalui lapisan foil.



4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, LAMICTAL dapat menyebabkan efek samping, tetapi tidak semua orang mengalaminya.

Reaksi yang berpotensi mengancam jiwa: segera dapatkan bantuan dokter
Sejumlah kecil orang yang menggunakan LAMICTAL mengalami reaksi alergi atau kulit yang berpotensi mengancam nyawa, reaksi yang dapat berkembang menjadi masalah yang lebih serius jika tidak ditangani.

Gejala ini lebih mungkin terjadi selama beberapa bulan pertama pengobatan dengan LAMICTAL, khususnya jika dosis awal terlalu tinggi atau jika dosis dinaikkan terlalu cepat atau jika LAMICTAL digunakan dengan obat lain yang disebut valproate. Beberapa gejala lebih sering terjadi pada anak-anak, sehingga orang tua harus sangat berhati-hati dalam mengawasi.

Gejala reaksi ini meliputi:
- Ruam kulit atau kemerahan, yang dapat berkembang menjadi reaksi kulit yang dapat mengancam jiwa termasuk ruam yang melepuh dan kulit mengelupas, terutama terjadi di sekitar mulut, hidung, mata dan alat kelamin (*Stevens-Johnson syndrome*), pengelupasan kulit yang luas (lebih dari 30% permukaan tubuh – *toxic epidermal necrolysis*) atau ruam berkepanjangan yang melibatkan hati, darah dan organ tubuh lainnya (reaksi obat dengan eosinofil dan gejala sistemik yang juga dikenal sebagai DRESS *hypersensitivity syndrome*).
- Luka di mulut, tenggorokan, hidung atau alat kelamin.
- Rasa tidak nyaman di mulut atau mata merah atau bengkak (konjungtivitis).
- Suhu tinggi (demam), gejala seperti flu atau mengantuk.

- Bengkak di sekitar wajah Anda atau kelenjar bengkak di leher, ketiak atau selangkangan.
- Pendarahan atau memar yang tidak terduga, atau jari membiru.
- Sakit tenggorokan atau lebih banyak infeksi (seperti flu) dari biasanya.
- Peningkatan kadar enzim hati yang terlihat pada tes darah.
- Peningkatan jumlah sel darah putih (eosinofil).
- Kelenjar getah bening membesar.
- Gangguan pada organ tubuh termasuk hati dan ginjal.

Pada banyak kasus, gejala-gejala ini merupakan tanda-tanda efek samping yang tidak terlalu serius, **tetapi Anda harus waspada karena berpotensi mengancam jiwa dan dapat berkembang menjadi masalah yang lebih serius,** seperti kegagalan organ, jika tidak dirawat.

Jika Anda melihat salah satu dari gejala ini: **segera hubungi dokter.** Dokter Anda mungkin akan memutuskan untuk melakukan tes pada hati, ginjal atau darah dan mungkin akan memberitahu Anda untuk berhenti menggunakan LAMICTAL. Jika telah terjadi *Stevens-Johnson syndrome* atau *toxic epidermal necrolysis,* dokter Anda akan memberitahu Anda untuk tidak menggunakan lamotrigine lagi.

Haemophagocytic lymphohistiocytosis **(HLH)** (*lihat bagian 2*: Apa yang perlu Anda ketahui sebelum menggunakan LAMICTAL).

Berikut efek samping yang mungkin terjadi dengan obat ini:
Sangat umum (terjadi hingga lebih dari 1 dari 10 orang)
- Sakit kepala.
- Ruam kulit.

Umum (terjadi pada hingga 1 dari 10 orang)
- Agresif atau mudah tersinggung.
- Merasa mengantuk atau mengantuk.
- Merasa pusing.
- Gemetar atau tremor.
- Kesulitan tidur (insomnia).
- Merasa gelisah.
- Diare.
- Mulut kering.
- Merasa sakit (mual) atau sedang sakit (muntah).
- Merasa lelah.
- Nyeri di punggung atau persendian atau di tempat lain.

Tidak umum (terjadi pada hingga 1 dari 100 orang)
- Kecanggungan dan kurang koordinasi (ataksia).
- Penglihatan ganda atau penglihatan kabur.
- Rambut rontok atau menipis yang tidak biasa (*alopecia*).
- Reaksi fotosensitivitas.

Jarang (terjadi pada hingga 1 dari 1.000 orang)
- Reaksi kulit yang mengancam jiwa (*Stevens-Johnson syndrome*) (lihat juga informasi di awal dari bagian 4).
- Sekelompok gejala termasuk: demam, mual, muntah, sakit kepala, leher kaku dan kepekaan berlebihan terhadap cahaya terang. Hal ini mungkin disebabkan oleh peradangan pada selaput yang menutupi otak dan sumsum tulang belakang (meningitis). Gejala-gejala ini biasanya hilang setelah pengobatan dihentikan, tetapi jika gejala terus berlanjut atau memburuk hubungi dokter Anda.
- Gerakan mata yang cepat dan tidak terkendali (nistagmus).
- Mata gatal, disertai dengan keluarnya cairan dan kelopak mata berkerak (konjungtivitis).
- Eritema multiform.

Sangat jarang (terjadi pada hingga 1 dari 10.000 orang)

- Reaksi kulit yang mengancam jiwa (*toxic epidermal necrolysis*) (lihat juga informasi di awal dari *bagian 4*).
- *Drug reaction with eosinophilia and systemic symptoms* (DRESS) (lihat juga informasi di awal dari *bagian 4*).
- Suhu tubuh tinggi (demam) (lihat juga informasi di awal dari *bagian 4*).
- Bengkak di sekitar wajah (edema) atau pembengkakan kelenjar di leher, ketiak atau selangkangan (*lymphadenopathy*) (lihat juga informasi di awal *bagian 4*).
- Perubahan fungsi hati yang akan terlihat pada tes darah atau gagal hati (lihat juga informasi di awal dari *bagian 4*).
- Gangguan pembekuan darah yang serius yang dapat menyebabkan perdarahan atau memar yang tidak terduga (*disseminated intravascular coagulation*) (lihat juga informasi di awal dari *bagian 4*).
- Perubahan yang mungkin terlihat dalam tes darah, termasuk berkurangnya jumlah sel darah merah (anemia), berkurangnya jumlah sel darah putih (leukopenia, neutropenia, agranulositosis), berkurangnya jumlah trombosit (trombositopenia), berkurangnya jumlah semua jenis sel ini (pansitopenia) dan gangguan sumsum tulang disebut anemia *aplastic.*
- Halusinasi (melihat atau mendengar hal-hal yang sebenarnya tidak ada).
- Kebingungan.
- Merasa ‘goyah’ atau tidak stabil saat Anda bergerak.
- Gerakan tubuh yang tidak terkendali (*tics*), kejang otot yang tidak terkendali mempengaruhi mata, kepala dan batang tubuh (*choreoathetosis*) atau gerakan tubuh yang tidak biasa lainnya seperti tersentak, gemetar atau kaku.
- Pada orang yang sudah menderita epilepsi, kejang lebih sering terjadi.
- Pada orang yang sudah menderita penyakit Parkinson, gejala semakin memburuk.
- Reaksi seperti lupus (gejala termasuk: nyeri punggung atau sendi yang kadang bisa disertai demam dan/atau sakit umum).
- *Haemophagocytic lymphohistiocytosis* (HLH) (*lihat bagian 2*: Apa yang perlu Anda ketahui sebelum menggunakan LAMICTAL).
- *Pseudolymphoma.*

Efek samping lainnya
Efek samping lain telah terjadi pada sejumlah kecil orang tetapi frekuensi pastinya tidak diketahui:
- Ada laporan kelainan tulang termasuk osteopenia dan osteoporosis (penipisan tulang) dan patah tulang. Konsultasikan dengan dokter atau apoteker Anda jika Anda menggunakan obat anti epilepsi jangka panjang, memiliki riwayat osteoporosis atau mengonsumsi steroid.
- Kekebalan yang lebih rendah karena menurunkan kadar antibodi yang disebut immunoglobulin dalam darah yang membantu melindungi dari infeksi.

Pelaporan efek samping
Jika efek samping menjadi serius, atau jika Anda melihat terdapat efek samping yang tidak tercantum dalam brosur ini, segera konsultasikan pada dokter atau apoteker Anda.

Laporkan Kejadian Tidak Diinginkan (KTD) ke GSK Indonesia melalui situs web https://gsk.public.reportum.com.

5. Bagaimana cara penyimpanan LAMICTAL

Simpan obat ini jauh dari jangkauan anak-anak.

Jangan menggunakan obat setelah tanggal kedaluwarsa yang tertulis pada kemasan. Tanggal kedaluwarsa merujuk pada tanggal terakhir pada bulan tersebut.

LAMICTAL tidak memerlukan kondisi penyimpanan khusus.

Jangan membuang obat apa pun di air limbah atau limbah rumah tangga. Tanyakan pada apoteker bagaimana membuang obat yang tidak digunakan lagi. Hal ini akan membantu melindungi lingkungan.

6. Isi dari kemasan dan informasi lain

Kandungan pada tablet kunyah/dispersibel LAMICTAL

- Bahan aktif lamotrigine. Tiap tablet kunyah/dispersibel mengandung 5 mg atau 25 mg lamotrigine.
- Komponen lainnya adalah *calcium carbonate, low substituted hydroxypropyl cellulose, aluminium magnesium silicate, sodium starch glycollate, povidone, saccharin sodium, blackcurrant flavour, magnesium stearate.*

Kandungan pada tablet LAMICTAL

- Bahan aktif lamotrigine. Tiap tablet mengandung 50 mg atau 100 mg lamotrigine.
- Komponen lainnya adalah *lactose, microcrystalline cellulose, povidone, sodium starch glycollate, iron oxide yellow (E172), magnesium stearate.*

Pemerian LAMICTAL

- LAMICTAL tablet 50 mg
  Tablet berwarna coklat kekuningan pucat, memiliki banyak sisi, superelips, tanpa garis sepanjang tablet yang ditujukan untuk membantu pembelahan, terdapat label 'GSEE1' di satu sisi, dengan '50' di sisi sebaliknya.
- LAMICTAL tablet 100 mg
  Tablet berwarna coklat kekuningan pucat, memiliki banyak sisi, superelips, tidak ada garis sepanjang tablet yang ditujukan untuk membantu pembelahan, terdapat label 'GSEE5' di satu sisi, dengan '100' di sisi sebaliknya.
- LAMICTAL dispersibel tablet 5 mg
  Tablet berwarna putih sampai putih pucat dengan bau kismis hitam (*blackcurrant*). Tablet memanjang, bikonveks, tanpa garis sepanjang tablet yang ditujukan untuk membantu pembelahan, terdapat label “GSCL2” di satu sisi dan “5” di sisi lain. Tablet mungkin sedikit berbintik-bintik.
- LAMICTAL dispersibel tablet 25 m
  Tablet berwarna putih sampai putih pucat, memiliki banyak sisi, superelips, tanpa garis sepanjang tablet yang ditujukan untuk membantu pembelahan dengan bau kismis hitam (*blackcurrant*). Terdapat label “GSCL5” di satu sisi dan “25” di sisi lain. Tablet mungkin sedikit berbintik-bintik.

HARUS DENGAN RESEP DOKTER

Lamictal Dispersibel Tablet 5 mg, Dus, Botol @ 30 tablet	Reg. No. DKI1433900281A2
Lamictal Dispersibel Tablet 25 mg, Dus, 3 Blister @ 10 tablet	Reg. No. DKI1433900281B1
Lamictal Dispersibel Tablet 25 mg, Dus, 2 Blister @ 15 tablet	Reg. No. DKI1433900281B1
Lamictal Tablet 50 mg, Dus, 2 Blister @ 15 tablet	Reg. No. DKI1833900510A1
Lamictal Tablet 100 mg, Dus, 2 Blister @ 15 tablet	Reg. No. DKI1833900510B1

Diproduksi oleh:
Delpharm Poznań Spółka Akcyjna
Poznań, Polandia.

Diimpor oleh:
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia.

Version number : 04
Reference : GDS54/IPI32
Date of local revision : 10 March 2025