

## LAMOTRIGINE - SAFE PRESCRIBING - DOES THE DOSE FIT

- ▶ START LOW AND GO SLOW TO AVOID SEVERE ADVERSE EFFECTS
- ▶ REGULAR BLOOD TESTING IS NOT NECESSARY
- ▶ REDUCE DOSE WHEN IN COMBINATION WITH SODIUM VALPROATE
- ▶ DOSE ADJUSTMENT IS REQUIRED WITH COMBINED ORAL CONTRACEPTIVES
- ▶ ROUTINELY ASSESS FOR ANXIETY, DEPRESSION AND SUICIDALITY

Lamotrigine is an antiepileptic medicine, which can also be used to prevent depressive episodes of bipolar disorder.

Lamotrigine can also be useful for rapid cycling of mood or mixed episodes of bipolar disorder, usually in combination with other medicines.<sup>1</sup>

Compared to other commonly used antiepileptic medicines such as phenytoin, carbamazepine and sodium valproate, lamotrigine has few cognitive adverse effects and does not cause osteoporosis or affect bodyweight. For these reasons, it is a considered useful option for older adults.<sup>2</sup>

### START LOW AND GO SLOW TO AVOID SEVERE ADVERSE EFFECTS

When starting lamotrigine it is advisable to start low and go slow.<sup>3</sup> High initial doses or rapid dose escalation increases the risk of a rash and potentially severe adverse effects.<sup>4</sup>

#### Skin reactions

Adverse skin reactions are most likely to occur within the first 8 weeks of starting lamotrigine.<sup>5</sup> Although often mild and self-limiting, skin reactions can progress to severe and potentially fatal conditions, including Stevens Johnson syndrome and toxic epidermal necrolysis.<sup>4</sup>

Inform everyone who is prescribed lamotrigine to seek medical advice immediately at the first sign of a rash, skin reaction or indication of hypersensitivity such as fever, especially if it occurs within the first 8 weeks of treatment.<sup>1</sup> The risk of severity is increased with existing autoimmune disorders, including rheumatoid arthritis and lupus erythematosus, and viruses such as Epstein Barr and HIV.<sup>6</sup>

Serious skin rash has been reported in 1 in 500 adults and 1 in 100-300 children who are prescribed lamotrigine for epilepsy, and 1 in 1000 people with bipolar disorder.<sup>4</sup> If a rash develops, discontinue lamotrigine unless the rash is clearly not drug-related.<sup>7</sup> If lamotrigine is being used for epilepsy,

abrupt withdrawal should be managed in consultation with a specialist to reduce the risk of rebound seizures.<sup>3</sup> If lamotrigine is being used for bipolar disorder (with no history of seizures), lamotrigine may be withdrawn without a step-wise reduction of dose.<sup>4</sup>

#### Anticonvulsant Hypersensitivity Syndrome

Lamotrigine has been associated with the rare but potentially severe anticonvulsant hypersensitivity syndrome (AHS). This usually presents as a high spiking fever, rash and/or hepatitis. It does not appear to be dose-related; it is a form of allergic hypersensitivity. Other possible symptoms of AHS include periorbital and facial oedema, blistering, lymphadenopathy and haematological abnormalities.<sup>8</sup> If any of the above symptoms occur, advise patients to seek medical advice immediately and discontinue lamotrigine as above. Take special care with children, the initial presentation of AHS can be mistaken for an infection.

**Note:** If lamotrigine has been stopped for 5 days or more, re-titrate the dose to avoid serious skin reactions.<sup>5</sup> See the data sheet for specific information.<sup>4</sup>

### REGULAR BLOOD TESTING IS NOT NECESSARY

Routine monitoring of serum lamotrigine and liver function is not considered necessary. Instead, advise everyone prescribed lamotrigine about the potential of any fever or rash escalating to a serious condition, and to report these warning signs immediately.<sup>3</sup> Rarely, elevated transaminases can occur (in less than 1 in 1000 patients). Usually this is when lamotrigine is prescribed with other medicines that adversely affect the liver such as valproic acid.<sup>9</sup> Hepatic dysfunction usually occurs in association with hypersensitivity reactions, so if there are abnormal blood levels, check for other signs of hypersensitivity.

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Reduce initial and maintenance doses of lamotrigine for patients with moderate to severe hepatic impairment.<sup>4</sup>

**Note:** Dizziness, blurred vision and headache are common when initiating lamotrigine. Typically these effects are mild to moderate and resolve within the first few weeks of treatment. The incidence is increased if the dose is escalated too quickly, or if other medicines are prescribed that affect the metabolism of lamotrigine. If these adverse effects occur and carbamazepine is also prescribed, the dose of carbamazepine may need to be reduced.<sup>3</sup>

### REDUCE DOSE WHEN IN COMBINATION WITH SODIUM VALPROATE

Sodium valproate **inhibits** the metabolism of lamotrigine, increasing its toxicity and the risk of toxic epidermal necrolysis and Stevens Johnson syndrome. The risk is further increased if the recommended starting dose or the rate of dose escalation of lamotrigine is exceeded.<sup>10</sup> If the patient is taking both medicines, adhere to the dosing guidelines in the New Zealand Formulary<sup>5</sup> when starting or stopping lamotrigine or sodium valproate.

Other antiepileptic medicines such as phenytoin, carbamazepine, phenobarbitone and primidone, **induce** the metabolism of lamotrigine and can lead to subtherapeutic levels. Adhere closely to dosing guidelines in the datasheet to ensure therapeutic effect is achieved without risking toxicity.<sup>4</sup>

### ROUTINELY ASSESS FOR ANXIETY, DEPRESSION AND SUICIDALITY

The combined oral contraceptive (COC) ethinylestradiol/levonorgestrel **induces** the metabolism of lamotrigine. If starting COCs after the maintenance dose of lamotrigine has been established, the dose of lamotrigine will need to be increased, possibly as much as two-fold. Always increase doses of lamotrigine gradually; see the data sheet for specific information.<sup>4</sup>

Conversely if stopping a COC and lamotrigine is at the maintenance dose, the dose of lamotrigine will need to be gradually reduced, by up to 50%.<sup>4</sup>

Check lamotrigine serum levels before and after starting COCs, and adjust the dose as per clinical response of seizure control and serum levels.<sup>11</sup> There is currently no evidence to suggest that progestogen-only contraceptive methods affect lamotrigine.<sup>11</sup>

There is a theoretical interaction with lamotrigine and hormone replacement therapy which may reduce the plasma levels of lamotrigine. The dose of lamotrigine may need to be increased as appropriate.<sup>5</sup>

**Note:** If hormonal contraceptives are already being taken, and lamotrigine is being initiated, no adjustments are necessary; adhere to the recommended dose escalation guideline in the datasheet.<sup>4</sup>

### Pregnancy

Lamotrigine is currently classified as a category D;<sup>5</sup> effective contraception is recommended when lamotrigine is prescribed to females of childbearing age.<sup>11</sup> One pregnancy registry has received increased reports of oral clefts when lamotrigine is taken during the first trimester in doses over 200mg per day, and when the clefts were not caused by any known syndrome.<sup>12</sup> More evidence is emerging about the safety of lamotrigine during pregnancy. Other reported data has not shown evidence of increased teratogenic risk, with rates of major malformations well within the expected baseline rates.<sup>12</sup>

#### Medications in pregnancy classifications<sup>13</sup>

##### Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Adapted from Australian categorisation system for prescribing medicines in pregnancy.

Lamotrigine is known to deplete folate levels, so women who are planning to become pregnant or who are pregnant while taking lamotrigine should take folic acid 5mg daily preferably for four weeks before conception, and for the first 12 weeks of pregnancy<sup>14,15</sup> to offset the folate depletion from lamotrigine.<sup>16</sup>

Due to physiological changes during pregnancy, blood levels of lamotrigine have been shown to decrease, so the therapeutic effect of lamotrigine will need to be closely monitored.<sup>4</sup> During pregnancy and after birth, dose adjustments should be made on a clinical basis<sup>5</sup> depending on the results of plasma-drug monitoring, therapeutic and adverse effects.

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### Breastfeeding

The potential benefits of breastfeeding should be weighed against the potential risk of adverse effects occurring in the infant.<sup>4</sup> Lamotrigine passes into breastmilk in variable concentrations; in some infants, serum concentrations reach levels at which pharmacological effects occur.<sup>4</sup> Monitor breastfed infants for sedation, feeding difficulties, adequate weight gain and developmental milestones. If suspected adverse reactions develop, check serum-drug concentration of the infant.<sup>14</sup>

**Note:** Withdrawal effects may occur in infants if a mother suddenly stops breastfeeding.<sup>14</sup>

### ROUTINELY ASSESS FOR ANXIETY, DEPRESSION AND SUICIDALITY

An increased risk of anxiety, depression and suicidality has been associated with the use of anticonvulsants. Everyone prescribed these medicines should routinely be assessed for these symptoms,<sup>3</sup> and advised to seek medical advice should they emerge.<sup>3</sup>

There is also evidence that people diagnosed with epilepsy and bipolar disorder have an elevated risk for suicidality.<sup>3</sup>

**Note:** Lamotrigine is not indicated for children aged under 18 years with bipolar disorder,<sup>4</sup> but it is indicated from the age of 2 years for children with epilepsy.

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For further information on other high-risk medicines visit our website at: [www.saferx.co.nz](http://www.saferx.co.nz)

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