Approved Professional Information for Medicines for Human Use:

RIGADEL

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

RIGADEL 25 mg Tablets

RIGADEL 50 mg Tablets

RIGADEL 100 mg Tablets

RIGADEL 200 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RIGADEL 25 mg Tablets

Each tablet contains 25 mg of lamotrigine.

RIGADEL 50 mg Tablets

Each tablet contains 50 mg of lamotrigine.

RIGADEL 100 mg Tablets

Each tablet contains 100 mg of lamotrigine.

RIGADEL 200 mg Tablets

Each tablet contains 200 mg of lamotrigine.

Contains sugar

Each RIGADEL 25 mg Tablet contains 29,950 mg lactose monohydrate.

Each RIGADEL 50 mg Tablet contains 59,900 mg lactose monohydrate.

Each RIGADEL 100 mg Tablet contains 119,800 mg lactose monohydrate.

Each RIGADEL 200 mg Tablet contains 239,600 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

RIGADEL 25 mg Tablets:

Pale yellow coloured, circular, flat faced bevelled edged uncoated tablets with ‘L 25’ embossing on one side and plain on the other side.

RIGADEL 50 mg Tablets:

Pale yellow coloured, circular, flat faced bevelled edged, uncoated tablets with ‘L50’ embossing on one side and breakline dividing ‘B’ & ‘L’ logo on the other side.

RIGADEL 100 mg Tablets:

Pale yellow coloured, circular, flat faced bevelled edged, uncoated tablets with ‘L100’ embossing on one side and breakline dividing ‘B’ & ‘L’ logo on the other side.

RIGADEL 200 mg Tablets:

Pale yellow coloured, circular, flat faced bevelled edged, uncoated tablets with ‘L200’ embossing on one side and breakline dividing ‘B’ & ‘L’ logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EPILEPSY:

Adults and children over 12 years: RIGADEL is indicated as monotherapy or add-on treatment of partial epilepsy, with or without secondary generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures.

Children* 2 to *12 years: RIGADEL is indicated as add-on treatment of partial epilepsy with or without secondary generalised tonic-clonic seizures, not satisfactorily controlled with other antiepileptic medicines.
Monotherapy in children under 12 years of age is not recommended until such time as adequate information is made available from controlled trials in this particular target population.

Lennox-Gastaut Syndrome: RIGADEL is indicated as add-on treatment for seizures associated with Lennox-Gastaut Syndrome.

BIPOLAR DISORDER (Adults 18 years of age and over):

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

4.2 Posology and method of administration

Posology

It is important to adhere to the recommended dosages especially in combination therapy with valproate where one-tenth of the normal RIGADEL dose is used. Do not exceed the maximum dosage (see section 4.4).

Restarting Therapy: Prescribers should assess the need for escalation to maintenance dose when restarting RIGADEL in patients who have discontinued RIGADEL for any reason, since

the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for RIGADEL (see section 4.4). 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 RIGADEL exceeds five half-lives (see section 5.2), RIGADEL should generally be escalated to the maintenance dose according to the appropriate schedule. It is recommended that RIGADEL not be restarted in patients who have discontinued due to rash associated with prior treatment with RIGADEL.

EPILEPSY:

When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve RIGADEL monotherapy or other AEDs/medications are added-on to treatment regimes containing RIGADEL, consideration should be given to the effect this may have on lamotrigine pharmacokinetics (see section 4.5). To ensure a therapeutic dose is maintained, the weight of a child must be monitored and the dose reviewed as weight changes occur. If a calculated dose of RIGADEL (e.g. for use in children and patients with hepatic impairment) does not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets.

Dosage in epilepsy monotherapy:

Adults and children over 12 years of age: The initial dose in monotherapy is 25 mg once a day for 2 weeks, followed by 50 mg once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 50 mg - 100 mg every 1 – 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 – 200 mg/day given once a day or as two divided doses. Some patients have required 500 mg/day of RIGADEL to achieve the desired response.

Dosage in epilepsy add-on therapy:

Adults and children over 12 years of age: In those patients taking concomitant antiepileptic drugs (AEDs) or other medications (see section 4.5) that induce lamotrigine glucorinidation with/without other AEDs (except valproate), the initial RIGADEL dose is 50 mg once a day for 2 weeks, followed by 100 mg/day given in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 100 mg every 1 – 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 200-400 mg/day given in two divided doses.

In those patients taking sodium valproate with/without any other AED, the initial RIGADEL dose is 25 mg every alternate day for 2 weeks, followed by 25 mg once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 25 – 50 mg every 1 – 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 100 – 200 mg/day given once a day or in two divided doses.

In those patients taking oxcarbazepine 1 200 mg daily, without any other inducers or inhibitors of lamotrigine glucuronidation, the initial RIGADEL dose is 25 mg once a day for 2 weeks, followed by 50 mg once a day for two weeks. Thereafter, the dose should be increased by a maximum of 50 – 100 mg every 1 – 2 weeks until optimal response is achieved or a dose of 200 mg is reached. The usual maintenance dose to achieve an optimal response is 100 – 200 mg/day given once a day or as two divided doses.

Table 1: Recommended treatment regimen for adults 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 1 – 2 weeks
Add-on therapy with valproate regardless of any concomitant medications		12,5 mg (given as 25 mg on 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 1 – 2 weeks
Add-on therapy without valproate	This dosage regimen should be used with phenytoin, carbamazepine, phenobarbitone, primidone, or with other inducers of lamotrigine	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 1 – 2 weeks

	glucuronidation (see section 4.5)			
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	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 1 – 2 weeks
In patients taking AEDs where the pharmacokinetic interaction with lamotrigine is currently not known (see section 4.5), the treatment regimen as recommended for RIGADEL with concurrent valproate should be used.				

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see section 4.4).

Children aged 2 to 12 years: To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed as weight changes occur. If the dose is calculated for children, according to bodyweight, do not equate to whole tablets the dose to be administered is that equal to the lower number of whole tablets.

In those patients taking concomitant AEDs or other medications (see section 4.5) that induce lamotrigine glucuronidation with/without other AEDs (except valproate), the initial RIGADEL dose is 0,6 mg/kg bodymass/day given in two divided doses for 2 weeks, followed by 1,2 mg/kg/day for 2 weeks. Thereafter, the dose should be increased by a maximum of 1,2 mg/kg

every 1 – 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 5 – 15 mg/kg/day given in two divided doses. A maximum daily dose of 400 mg must not be exceeded.

In those patients taking sodium valproate with/without any other AED, the initial RIGADEL dose is 0,15 mg/kg bodymass/day given once a day for 2 weeks, followed by 0,3 mg/kg/day given once a day for 2 weeks. Thereafter, the dose should be increased by a maximum of 0,3 mg/kg every 1 – 2 weeks until the optimal response is achieved. The usual maintenance dose to achieve optimal response is 1 – 5 mg/kg/day given once a day or in two divided doses. A maximum daily dose of 200 mg must not be exceeded.

In patients taking oxcarbazepine without any inducers or inhibitors of lamotrigine glucuronidation, the initial RIGADEL dose is 0,3 mg/kg bodyweight/day given once a day or in two divided doses for 2 weeks, followed by 0,6 mg/kg/day given once a day or in two divided doses for 2 weeks. Thereafter, the dose should be increased by a maximum of 0,6 mg/kg every 1 – 2 weeks until an optimal response is achieved, or a dose of 200 mg is reached. The usual maintenance dose to achieve optimal response is 1 – 10 mg/kg/day given once a day or in two divided doses, with a maximum of 200 mg/day.

Table 2: Recommended treatment regimen for children aged 2 – 12 years (total daily dose in mg/kg bodyweight/day)

Treatment regimen	**Weeks 1 + 2**	**Weeks 3 + 4**	**Maintenance Dose**
Add-on therapy with valproate regardless of any concomitant medications	0,15 mg/kg* (once a day)	0,3 mg/kg (once a day)	0,3 mg/kg increments every 1 – 2 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 section 4.5)	0,6 mg/kg (two divided doses)	1,2 mg/kg (two divided doses)	1,2 mg/kg increments every 1 – 2 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.
	With oxcarbazepine without inducers or inhibitors of lamotrigine glucuronidation	0,3 mg/kg (one or two divided doses)	0,6 mg/kg (one or two divided doses)	0,6 mg/kg increments every 1 – 2 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 section 4.5), the treatment regimen as recommended for RIGADEL with concurrent valproate should be used.				
* If the calculated daily dose in patients taking valproate is 1 – 2 mg, then 2 mg RIGADEL may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 1 mg, then RIGADEL should not be administered.				

The recommended initial dose and subsequent dose escalation should not be exceeded to minimise the risk of skin rash (see section 4.4).
Patients aged 2 – 6 years may require a maintenance dose at the higher end of the recommended range.

Dosage in seizures associated with Lennox-Gastaut syndrome: The doses used for seizures associated with Lennox-Gastaut syndrome correspond to the dosing guidelines outlined above for both adults and children aged 2 – 12 years.

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

BIPOLAR DISORDER:

Because of the risk of rash the initial dose and subsequent dose escalation should not be exceeded (see section 4.4).
RIGADEL 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 RIGADEL to a maintenance

stabilisation dose over 6 weeks (see table below) after which other psychotropic and/or anti-epileptic drugs (AEDs) can be withdrawn, if clinically indicated.

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

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

Treatment Regimen	**Weeks 1 - 2**	**Weeks 3 - 4**	**Week 5**	**Target Stabilisation Dose (Week 6) ****
a) Adjunct therapy with enzyme inhibitors 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 enzyme inducers e.g. carbamazepine and phenobarbitone in patients not taking valproate	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) Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion, or monotherapy with lamotrigine	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 RIGADEL is currently not known, the dose escalation as recommended for RIGADEL with concurrent valproate, should be used.				
**The Target stabilisation dose will alter depending on clinical response.				

a) Adjunct therapy with enzyme inhibitors e.g. valproate: In patients taking enzyme inhibiting concomitant medicines such as valproate the initial RIGADEL dose is 25 mg every alternate day for 2 weeks, followed by 25 mg once a day for 2 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 enzyme inducers e.g. carbamazepine and phenobarbitone in patients NOT taking valproate: In those patients taking enzyme inducing medicines such as carbamazepine or phenobarbitone and NOT taking valproate, the initial RIGADEL dose is 50

mg once a day for 2 weeks, followed by 100 mg/day given in two divided doses for 2 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) Adjunct therapy to medicines with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion, OR monotherapy with RIGADEL: The initial RIGADEL dose in patients taking concomitant medicines with no known / theoretical pharmacokinetic interaction with lamotrigine or in monotherapy, is 25 mg once a day for 2 weeks, followed by 50 mg once a day (or in two divided doses) for 2 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 – 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 below).

Table 4: Maintenance stabilisation total daily dose in BIPOLAR DISORDER following withdrawal of concomitant psychotropic or anti-epileptic drugs (AEDs):

Treatment Regimen	**Week 1**	**Week 2**	**Week 3 onwards***
a) Following withdrawal of enzyme inhibitors e.g. valproate	Double the stabilisation dose, not exceeding 100 mg/week i.e. 100 mg/day target stabilisation dose will be	Maintain this dose (200 mg/day) (two divided doses)	

	increased in week 1 to 200 mg/day		
b) Following withdrawal of enzyme inducers e.g. carbamazepine depending on original dose	400 mg	300 mg	200 mg
	300 mg	225 mg	150 mg
	200 mg	150 mg	100 mg
c) Following withdrawal of the other psychotropic or AED with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion	Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (range 100 – 400 mg)		
NOTE: In patients taking AEDs where the pharmacokinetic interaction with RIGADEL is currently not known, the dose escalation as recommended for RIGADEL with concurrent valproate, should be used.			
* Dose may be increased to 400 mg/day as needed			

a) *Following withdrawal of adjunct therapy with enzyme inhibitors e.g. valproate:* The dose of RIGADEL 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 enzyme inducers e.g. carbamazepine, depending on original maintenance dose:* The dose of RIGADEL should be gradually reduced over 3 weeks as the enzyme inducer is withdrawn.

c) *Following withdrawal of adjunct therapy with other psychotropic or anti-epileptic drugs (AEDs) with no known pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion:* The target dose achieved in the dose escalation programme should be maintained throughout withdrawal of the other medication.

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

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

Table 5: Adjustment of RIGADEL daily dosing in patients with BIPOLAR DISORDER following the addition of other medications:

Treatment Regimen	**Current lamotrigine stabilisation dose (mg/day)**	**Week 1**	**Week 2**	**Week 3 onwards**
a) Addition of enzyme inhibitors e.g. valproate, depending on original dose of RIGADEL	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 enzyme inducers e.g. carbamazepine in patients not taking	200 mg	200 mg	300 mg	400 mg
	150 mg	150 mg	225 mg	300 mg
	100 mg	100 mg	150 mg	200 mg

valproate and depending on original dose of RIGADEL				
c) Addition of other psychotropic or AED with no known clinical pharmacokinetic interaction with lamotrigine e.g. lithium, bupropion	Maintain target dose achieved in dose escalation (200 mg/day) (range 100 – 400 mg)			
NOTE: In patients taking AEDs where the pharmacokinetic interaction with RIGADEL is currently not known, the dose escalation as recommended for RIGADEL with concurrent valproate, should be used.				

Discontinuation of RIGADEL in patients with bipolar disorder: In clinical trials, there was no increase in the incidence, severity or type of adverse experiences following abrupt termination of RIGADEL versus placebo. Therefore, patients may terminate RIGADEL without a step-wise reduction of dose.

Children (less than 18 years of age): Safety and efficacy of RIGADEL in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.

Special populations

Women taking hormonal contraceptives

(a) Starting RIGADEL in patients already taking hormonal contraceptives: Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see section 4.4), no adjustments to the recommended dose escalation guidelines for RIGADEL should be

necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether RIGADEL is added to an inhibitor of lamotrigine glucuronidation e.g. valproate; whether RIGADEL is added to an inducer of lamotrigine glucuronidation e.g. carbamazepine, phenytoin, phenobarbital, primidone or rifampin; or whether RIGADEL is added in the absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone or rifampicin (see Table 1).

(b) Starting hormonal contraceptives in patients already taking maintenance doses of RIGADEL and NOT taking inducers of lamotrigine glucuronidation: The maintenance dose of RIGADEL may need to be increased by as much as two-fold according to the individual clinical response (see section 4.4).

(c) Stopping hormonal contraceptives in patients already taking maintenance doses of RIGADEL and NOT taking inducers of lamotrigine glucuronidation: The maintenance dose of RIGADEL may need to be decreased by as much as 50 % according to the individual clinical response (see section 4.4).

Elderly (over 65 years of age)

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

Hepatic impairment

Initial, escalating 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.

Renal impairment

Caution should be exercised when administering RIGADEL to patients with renal failure. For patients with end-stage renal failure, initial doses of RIGADEL should be based on patient's AED regimen; reduced maintenance doses should be used for patients with significant renal functional impairment.

Paediatric Population

To ensure a therapeutic dose is maintained the weight of a child must be monitored and the dose reviewed if necessary. If the doses calculated for children, according to bodyweight, do not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

Method of administration

RIGADEL is for oral administration.

The tablets should be swallowed whole with a little water, if preferred.

If a calculated dose of RIGADEL (e.g. for use in children and patients with hepatic impairment) does not equate to whole tablets, the dose to be administered is that equal to the lower number of whole tablets.

4.3 Contraindications

RIGADEL is contraindicated in individuals with known hypersensitivity to lamotrigine or to any of the excipients listed in 6.1.

4.4 Special warnings and precautions for use

Cardiac rhythm and conduction abnormalities:

RIGADEL can increase the risk of serious dysrhythmias, which can be life-threatening, in patients with clinically important structural or functional heart disorders. Clinically important

structural and functional heart disorders include heart failure, valvular heart disease, congenital heart disease, conduction system disease, ventricular dysrhythmias, cardiac channelopathies such as Brugada syndrome, clinically important ischemic heart disease, or multiple risk factors for coronary artery disease. The risk of dysrhythmias may increase further if used in combination with other medicines that block sodium channels in the heart.
Dysrhythmogenic ST-T abnormality and typical Brugada ECG pattern has been reported in patients treated with lamotrigine. The use of RIGADEL should be carefully considered in patients with Brugada syndrome.

Skin rash

There have been reports of adverse skin reactions, which have generally occurred within the first eight weeks after initiation of lamotrigine treatment. The majority of rashes are mild and self-limiting, however serious rashes requiring hospitalisation and discontinuation of lamotrigine have also been reported. These have included potentially life-threatening
rashes such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome (HSS) (see section 4.8).
In adults enrolled in studies utilizing the current lamotrigine 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 Stevens-Johnson syndrome (1 in 1000). In clinical trials in patients with bipolar disorder, the incidence of serious rash is approximately 1 in 1000. 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 reaction to lamotrigine treatment 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 lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see section 4.2)
- concomitant use of valproate (see section 4.2).

Caution is also required when treating patients with a history of allergy or rash to other AEDs as the frequency of nonserious rash after treatment with lamotrigine was approximately three times higher in these patients than in those without such history.
All patients (adults and children) who develop a rash should be promptly evaluated and RIGADEL withdrawn immediately unless the rash is clearly not related to lamotrigine treatment. It is recommended that RIGADEL not be restarted in patients who have discontinued due to rash associated with prior treatment with lamotrigine. If the patient has developed SJS, TEN or DRESS with the use of lamotrigine, treatment with lamotrigine must not be re-started in this patient at any time. Rash has also been reported as part of 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, kidney and aseptic meningitis (see section 4.8). The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example 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 RIGADEL discontinued if an alternative aetiology cannot be established.

Aseptic meningitis was reversible on withdrawal of the medicine 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.
There have also been reports of photosensitivity reactions associated with lamotrigine use (see section 4.8). In several cases, the reaction occurred with a high dose (400 mg or more), upon dose escalation or rapid up-titration. If lamotrigine-associated photosensitivity is suspected in a patient showing signs of photosensitivity (such as an exaggerated sunburn), treatment discontinuation should be considered. If continued treatment with lamotrigine is considered clinically justified, the patient should be advised to avoid exposure to sunlight and artificial UV light and take protective measures (e.g. use of protective clothing and sunscreens).

Haemophagocytic lymphohistiocytosis (HLH)

HLH has been reported in patients taking lamotrigine (see section 4.8). HLH is characterised by signs and symptoms, like 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, HLH can be life threatening.

Patients should be informed of the symptoms associated with HLH and should be advised to seek medical attention immediately if they experience these symptoms while on lamotrigine therapy.

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

Clinical worsening and suicide risk

Suicidal ideation and behaviour have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs 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 and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medications for bipolar disorder, including RIGADEL. Therefore, patients receiving RIGADEL 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.
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.

Hormonal contraceptives

Effects of hormonal contraceptives on lamotrigine efficacy

The use of an ethinylestradiol / levonorgestrel (30 µg/150 µg) combination increases the clearance of lamotrigine by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5). A decrease in lamotrigine levels has been associated with loss of seizure

control. 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. When stopping hormonal contraceptives, the clearance of lamotrigine may be halved. Increases in lamotrigine concentrations may be associated with dose-related adverse events. Patients should be monitored with respect to this.

In women not already taking an inducer of lamotrigine glucuronidation and taking a hormonal contraceptive that includes one week of inactive treatment (for example "pill-free week"), gradual transient increases in lamotrigine levels will occur during the week of inactive treatment (see section 4.2). Variations in lamotrigine levels of this order may be associated with adverse effects. Therefore, consideration should be given to using contraception without a pill-free week, as first-line therapy (for example, continuous hormonal contraceptives or non-hormonal methods).

The interaction between other oral contraceptive or HRT treatments and lamotrigine have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters.

Effects of lamotrigine 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 section 4.5). 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 lamotrigine cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern, i.e. breakthrough bleeding.

Dihydrofolate reductase

Lamotrigine has a slight inhibitory effect on dihydrofolic acid reductase, hence there is a possibility of interference with folate metabolism during long-term therapy. However, during

prolonged human dosing, lamotrigine 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 medicines containing lamotrigine

RIGADEL should not be administered to patients currently being treated with any other medicine containing lamotrigine without consulting a doctor.

Precautions relating to epilepsy

As with other AEDs, abrupt withdrawal of RIGADEL may provoke rebound seizures. Unless safety concerns (for example rash) require an abrupt withdrawal, the dose of RIGADEL 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 lamotrigine.

A clinically significant worsening of seizure frequency instead of an improvement may be observed. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

Myoclonic seizures may be worsened by lamotrigine.

There is a suggestion in the data that responses in combination with enzyme inducers is less than in combination with non-enzyme inducing antiepileptic agents. The reason is unclear.

In children taking lamotrigine for the treatment of typical absence seizures, efficacy may not be maintained in all patients.

Excipient lactose

This medicine contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

Children and adolescents below 18 years: 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.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Uridine 5'-diphospho (UDP)-glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Medicine 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 medicines that have been demonstrated to have a clinically relevant impact on lamotrigine concentration are outlined in Table 6. Specific dosing guidance for these medicines is provided in Section 4.2. In addition, this table lists those medicines which have been shown

to have little or no effect on the concentration of lamotrigine. Coadministration of such medicines.

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 medicines on the concentration of lamotrigine

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

* For dosing guidance (see section 4.2) plus for women taking hormonal contraceptives also see Hormonal Contraceptives in section 4.4

Interactions involving antiepileptic drugs (AEDs)

Valproate, which inhibits the glucuronidation of lamotrigine, reduces the metabolism of lamotrigine and increases the mean half-life of lamotrigine nearly two-fold. In patients receiving concomitant therapy with valproate, the appropriate treatment regimen should be used (see section 4.2).

Certain AEDs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce UGTs and, therefore, enhance the metabolism of lamotrigine. In patients receiving concomitant therapy with phenytoin, carbamazepine, phenobarbitone or primidone, the appropriate treatment regimen should be used (see section 4.2).

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 lamotrigine. 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.

There are reports in the literature of decreased lamotrigine levels when lamotrigine was given in combination with oxcarbazepine. However, in a prospective study in healthy adult volunteers using doses of 200 mg lamotrigine and 1200 mg oxcarbazepine, oxcarbazepine did not alter the metabolism of lamotrigine and lamotrigine did not alter the metabolism of oxcarbazepine. Therefore, in patients receiving concomitant therapy with oxcarbazepine, the treatment regimen for lamotrigine adjunctive therapy without valproate and without inducers of lamotrigine glucuronidation should be used (see section 4.2).

In a study of healthy volunteers, coadministration of felbamate (1200 mg twice daily) with lamotrigine (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 lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Potential 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 lamotrigine resulted in a 15 % increase in topiramate concentrations.

In a study of patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (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 AEDs have been reported, controlled studies have shown no evidence that lamotrigine affects the plasma concentrations of

concomitant AEDs. Evidence from in vitro studies indicates that lamotrigine does not displace other AEDs from protein binding sites.

Interactions involving other psychoactive medicines

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 lamotrigine.

Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine 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 lamotrigine 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 lamotrigine was administered alone.

In a study of 18 adult patients with bipolar I disorder, receiving an established regimen of lamotrigine (100 – 400 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 experiments indicated that the formation of lamotrigine's primary metabolite, the 2-N-glucuronide, was minimally inhibited by co-incubation with amitriptyline, bupropion, clonazepam, haloperidol or lorazepam. These experiments also suggested that metabolism of lamotrigine was unlikely to be inhibited by clozapine, fluoxetine, phenelzine, risperidone, sertraline or trazodone. In addition, a study of bufuralol metabolism using human liver

microsome preparations suggested that lamotrigine would not reduce the clearance of medicines metabolised predominantly by CYP2D6.

Interactions involving hormonal contraceptives

Effect of hormonal contraceptives on lamotrigine pharmacokinetics

In a study of 16 female volunteers, dosing with 30 µg ethinylestradiol / 150 µg 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 increased during the course of the week of inactive treatment (including the "pill-free" week), with pre-dose concentrations at the end of the week of inactive treatment being, on average, approximately two-fold higher than during co-therapy (see section 4.4). No adjustments to the recommended dose escalation guidelines for lamotrigine should be necessary solely based on the use of hormonal contraceptives, but the maintenance dose of lamotrigine will need to be increased or decreased in most cases when starting or stopping hormonal contraceptives (see section 4.2).

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 oestradiol 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 section 4.4). The effects of

doses of lamotrigine other than 300 mg/day have not been studied and studies with other female hormonal preparations have not been conducted.

Interactions involving other medicines

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 appropriate treatment regimen should be used (see section 4.2).

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 appropriate treatment regimen should be used (see section 4.2).

In a study in healthy adult volunteers, atazanavir/ritonavir (300 mg/100 mg) administered for 9 days reduced the plasma AUC and C_{max} of lamotrigine (single 100 mg dose) by an average of 32 % and 6 %, respectively. In patients receiving concomitant therapy with atazanavir/ritonavir, the appropriate treatment regimen should be used (see section 4.2).

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 demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of Organic Transporter 2 (OCT 2) at potentially clinically relevant concentrations. These data demonstrate that lamotrigine is an inhibitor of OCT 2, with an IC_{50} value of 53,8 µM. Co-administration of lamotrigine with renally excreted medicines, which are substrates of OCT 2 (e.g. metformin, gabapentin and varenicline), may result in increased plasma levels of these medicines.

The clinical significance of this has not been clearly defined, however care should be taken in patients co-administered with these medicines.

4.6 Fertility, pregnancy and lactation

Safety of RIGADEL in pregnancy and lactation has not been established.

Women of childbearing potential

Specialist advice should be given to women who are of childbearing potential. The antiepileptic treatment should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Pregnancy

There are insufficient data available on the use of RIGADEL in human pregnancy to evaluate its safety. RIGADEL should not be used in pregnancy. 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 RIGADEL therapy should be ensured.

Breastfeeding

There is limited information on the use of RIGADEL in lactation. Preliminary data indicate that it passes into breast milk in concentrations usually of the order of 40 – 60 % of the serum concentration. In a small number of infants known to have been breastfed, the serum concentrations of lamotrigine reached levels at which pharmacological effects may occur.

4.7 Effects on ability to drive and use machines

In clinical trials with lamotrigine adverse events of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how RIGADEL therapy affects them before driving or operating machinery.

4.8 Undesirable effects

a. Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with lamotrigine. Frequency categories are derived from controlled clinical studies [epilepsy monotherapy (identified by†) and bipolar disorder (identified by §)].

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders		Haematological abnormalities[1] including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis Haemophagocytic lymphohistiocytosis (see section 4.4)	Lymphadenopathy[1]

Immune system disorders		Hypersensitivity syndrome[2]	Hypogammaglobulinaemia
Psychiatric disorders	Irritability	Confusion, hallucinations, tics, aggression	Nightmares
Nervous system disorders	Headache[§], somnolence[†§], dizziness[†§], tremor[†], insomnia[†], vertigo, paraesthesia, drowsiness, nystagmus[†], ataxia[†]	Aseptic meningitis (see section 4.4) Unsteadiness, movement disorders, worsening of Parkinson's disease[3], extrapyramidal effects, choreoathetosis[†], increase in seizure frequency, agitation[§]	
Eye disorders	Diplopia[†], blurred vision[†]	Conjunctivitis	
Gastrointestinal disorders	Nausea[†], vomiting[†], diarrhoea[†], dry mouth[§]		
Hepatobiliary disorders		Hepatic failure, hepatic dysfunction[4],	

		increased liver function tests	
Skin and subcutaneous tissue disorders	Skin rash[5†§]	Alopecia, photosensitivity reaction, Stevens–Johnson syndrome[§], toxic epidermal necrolysis, drug reaction with eosinophilia and systemic[2] Symptoms (DRESS)	
Musculoskeletal and connective tissue disorders	Arthralgia[§]	Lupus-like reactions	
Renal and urinary disorders			Tubulointerstitial nephritis, tubulointerstitial nephritis and uveitis syndrome
General disorders and administration site conditions	Tiredness[†], pain[§], back pain[§]		

b. Description of selected adverse reactions

[1] Haematological abnormalities and lymphadenopathy may or may not be associated with the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / hypersensitivity syndrome (see Immune system disorders).

[2] Rash has also been reported as part of this syndrome, also known as DRESS. This condition is associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, facial oedema, and abnormalities of the blood, liver and kidney. The syndrome shows a wide spectrum of clinical severity and may, rarely, lead to disseminated intravascular coagulation and multiorgan failure. It is important to note that early manifestations of hypersensitivity (for example 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 RIGADEL discontinued if an alternative aetiology cannot be established (see section 4.4).

[3] These effects have been reported during other clinical experience.
There have been reports that lamotrigine 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.

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

[5] In clinical trials in adults, skin rashes occurred in up to 8 – 12 % of patients taking lamotrigine and in 5 – 6 % of patients taking placebo. The skin rashes led to the withdrawal of lamotrigine treatment in 2 % of patients. The rash, usually maculopapular in appearance, generally appears within eight weeks of starting treatment and resolves on withdrawal of RIGADEL (see section 4.4). Serious potentially life-threatening skin rashes, including Stevens–Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported.
Although the majority recover on withdrawal of lamotrigine treatment, some patients experience irreversible scarring and there have been rare cases of associated death (see section 4.4).

The overall risk of rash, appears to be strongly associated with:

- high initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine therapy (see section 4.2)
- concomitant use of valproate (see section 4.2).

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with lamotrigine. The mechanism by which lamotrigine affects bone metabolism has not been identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms and signs

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose has 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. Broadening of QRS duration to more than 100 msec may be associated with more severe toxicity.

Treatment

In the event of overdose, the patient should be admitted to hospital and given appropriate supportive therapy. Therapy aimed at decreasing absorption (activated charcoal) should be

performed if indicated. Further management should be as clinically indicated. There is no experience with haemodialysis as treatment of overdose. In six volunteers with kidney failure, 20 % of the lamotrigine was removed from the body during a 4-hour haemodialysis session (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class:

A 2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: Other antiepileptics

ATC Code: N03AX09

The results of pharmacological studies suggest that lamotrigine acts at voltage-sensitive sodium channels to stabilise neuronal membranes and inhibit neurotransmitter release, principally that of glutamate, an excitatory amino acid which is thought to play a key role in the generation of epileptic seizures.

5.2 Pharmacokinetic properties

Absorption

In healthy fasting young adult volunteers, lamotrigine is rapidly and completely absorbed from the gut.

Distribution

The peak plasma concentration occurs 2,5 hours after oral administration. The mean elimination half-life is 29 hours and the pharmacokinetic profile is linear up to 450 mg, the highest single dose tested. The half-life of lamotrigine is affected by concomitant medication, with a mean value of approximately 14 hours when given with enzyme-inducing medicines

such as carbamazepine and phenytoin and increasing to a mean of approximately 70 hours, when co-administered with sodium valproate alone (see section 4.2).

Biotransformation

Following multiple administrations of lamotrigine (150 mg twice daily) to normal volunteers, there is modest induction of its own metabolism, resulting in a 25 % decrease in the elimination half-life at steady state. Lamotrigine is 55 % bound to plasma proteins.

Elimination

Clearance adjusted for bodyweight is higher in children aged 12 years and under than in adults, with the highest values in children under 5 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 medicines such as carbamazepine and phenytoin. The half-life of lamotrigine increases to mean values of approximately 45 to 55 hours when co-administered with sodium valproate alone (see section 4.2).

Linearity/non-linearity

The pharmacokinetic profile is linear up to 450 mg, the highest single dose tested.

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 clinical 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.

Patients with renal impairment

Twelve volunteers with chronic renal failure and another 6 individuals undergoing hemodialysis 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-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on patients' anti-epileptic drug (AED) regimen; reduced maintenance doses should be used in patients with significant renal functional impairment (see section 4.2).

Patients with hepatic impairment

A single-dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as control. 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. Reduced doses should generally be used in patients with grade B or C hepatic impairment (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Ferric oxide yellow

Microcrystalline cellulose

Polyvinyl pyrrolidone

Purified water

Sodium starch glycollate

Purified talc

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool dry place at or below 25 °C. Protect from light.

6.5 Nature and contents of container

Blister pack (PVC film and Aluminium foil) of 1 x 14, 2 x 14, 4 x 14, 6 x 14, 3 x 10, and 6 x 10 tablets.

Bulk pack (White HDPE Jars) of 100, 250, 500 and 1000.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dezzo Trading 392 (Pty) Ltd

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Corner Garrick & Flagtail Street, Extension 8,

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8. REGISTRATION NUMBERS

RIGADEL 25 mg: 57/2.5/0029

RIGADEL 50 mg: 57/2.5/0030

RIGADEL 100 mg: 57/2.5/0031

RIGADEL 200 mg: 57/2.5/0032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 September 2022

10. DATE OF REVISION OF THE TEXT