PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

LAMOTRIGINE 25 MSQ tablets

LAMOTRIGINE 50 MSQ tablets

LAMOTRIGINE 100 MSQ tablets

LAMOTRIGINE 200 MSQ tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LAMOTRIGINE 25 MSQ tablet contains lamotrigine 25 mg.

Contains sugar: 3,125 mg lactose monohydrate per tablet.

Each LAMOTRIGINE 50 MSQ tablet contains lamotrigine 50 mg.

Contains sugar: 6,25 mg lactose monohydrate per tablet.

Each LAMOTRIGINE 100 MSQ tablet contains lamotrigine 100 mg.

Contains sugar: 12,5 mg lactose monohydrate per tablet.

Each LAMOTRIGINE 200 MSQ tablet contains lamotrigine 200 mg.

Contains sugar: 25,0 mg lactose monohydrate per tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

LAMOTRIGINE 25 MSQ

Yellow coloured, capsule shaped, biconvex tablets debossed with '**L**' and '**25**' on either side of the score line on one side and a deep break line on the other side.

LAMOTRIGINE 50 MSQ

Yellow coloured, capsule shaped, biconvex tablets debossed with '**L**' and '**50**' on

either side of the score line on one side and a deep break line on the other side.

LAMOTRIGINE 100 MSQ

Yellow coloured, capsule shaped, biconvex tablets debossed with '**L**' and '**100**' on either side of the score line on one side and a deep break line on the other side.

LAMOTRIGINE 200 MSQ

Yellow coloured, capsule shaped, biconvex tablets debossed with '**L**' and '**200**' on either side of the score line on one side and a deep break line on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EPILEPSY

Adults and children over 12 years

LAMOTRIGINE MSQ 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

LAMOTRIGINE MSQ 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

LAMOTRIGINE MSQ is indicated as add-on treatment for seizures associated with Lennox-Gastaut Syndrome.

BIPOLAR DISORDER

Adults 18 years of age and over

LAMOTRIGINE MSQ 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 LAMOTRIGINE MSQ dose is used. Do not exceed the maximum dosage (see ~~Warnings~~ section 4.4).

General dosing recommendations

Administration: 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 dose (for 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.

Restarting therapy: Prescribers should assess the need for escalation to maintenance dose when restarting LAMOTRIGINE MSQ in patients who have discontinued LAMOTRIGINE MSQ for any reason, since the risk of serious rash is associated with high initial doses and exceeding the recommended dose escalation for LAMOTRIGINE MSQ (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 LAMOTRIGINE MSQ exceeds five half-lives (see section 5.2), LAMOTRIGINE MSQ should generally be escalated to the maintenance dose according to the appropriate schedule. It is recommended that LAMOTRIGINE MSQ not be restarted in patients

who have discontinued due to rash associated with prior treatment with LAMOTRIGINE MSQ.

Epilepsy

When concomitant antiepileptic medicines are withdrawn to achieve LAMOTRIGINE MSQ monotherapy or other AEDs/medicines are added-on to treatment regimens containing lamotrigine as in LAMOTRIGINE MSQ, 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 LAMOTRIGINE MSQ (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

Initial dose in monotherapy is 25 mg once daily for two weeks, followed by 50 mg once daily for two weeks. Thereafter, the dose may be increased by a maximum of 50 mg – 100 mg every 1 - 2 weeks until the optimal response is achieved.

Maintenance dose in monotherapy*:* The usual maintenance dose to achieve optimal response is 100 - 200 mg per day given in one dose or two divided doses. Some patients have required 500 mg/day of LAMOTRIGINE MSQ 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 medicines (AEMs) or other medicines (see section 4.5) that induce lamotrigine glucorinidation with/without other AEMs (except valproate*),* the initial LAMOTRIGINE MSQ dose is 50 mg once a day for two weeks, followed by 100 mg a day, given in two divided ~~into two~~ doses, for two weeks. Thereafter, the dose may be increased be by a maximum of 100 mg every 1 - 2 weeks until the optimal response is achieved. The usual maintenance dose is 200 - 400 mg/day given in two divided doses.

In those patients taking sodium valproate with/without any other AEM, the initial LAMOTRIGINE MSQ dose is 25 mg every alternate day for two weeks, then 25 mg once a day for two weeks. Thereafter, the dose may be increased by a maximum of 25 - 50 mg a day 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 LAMOTRIGINE MSQ 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 and children over 12 years of age

Treatment regime		**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 medicines		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,	50 mg (once a day)	100 mg (two divided doses)	200 - 400 mg (two divided doses) To achieve maintenance,

Treatment regime		**Weeks 1 + 2**	**Weeks 3 + 4**	**Maintenance dose**
	phenobarbitone, primidone, or with other inducers of lamotrigine glucuronidation (see section 4.5).			doses may be increased by 100 mg every 1 - 2 weeks
	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 antiepileptic medicines where the pharmacokinetic interaction with lamotrigine, as in LAMOTRIGINE MSQ is currently not known (see section 4.5), the treatment regimen as recommended for LAMOTRIGINE MSQ 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 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.

In those patients taking concomitant AEMs or other medicines (see section 4.5) that induce lamotrigine glucuronidation with/without other AEMs (except valproate), the initial LAMOTRIGINE MSQ dose is 0,6 mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1,2 mg/kg/day in two divided doses for two 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 AEM, the initial LAMOTRIGINE MSQ dose is 0,15 mg/kg bodyweight/day given once a day for two weeks, followed by 0,3 mg/kg/day given once a day for two weeks. Thereafter the dose should be increased by a maximum of 0,3 mg/kg every 1 to 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 LAMOTRIGINE MSQ 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		**Week 1 + 2**	**Week 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 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	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

Treatment regimen		**Week 1 + 2**	**Week 3 + 4**	**Maintenance dose**
	inducers of lamotrigine glucuronidation (see section 4.5).			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 antiepileptic medicines where the pharmacokinetic interaction with lamotrigine as in LAMOTRIGINE MSQ is currently not known (see section 4.5), the treatment regimen as recommended for LAMOTRIGINE MSQ with concurrent valproate should be used.				
If the calculated daily dose in patients taking valproate is 1 – 2 mg, then 2 mg LAMOTRIGINE MSQ may be taken on alternate days for the first two weeks. If the calculated daily dose is less than 1 mg, then LAMOTRIGINE MSQ 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 dosing guidelines outlined above for both adults and children aged 2 - 12 years apply for the treatment of seizures associated with Lennox-Gastaut syndrome.

Children aged less than 2 years

There is insufficient information on the use of LAMOTRIGINE MSQ 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).

LAMOTRIGINE MSQ 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 LAMOTRIGINE MSQ to a maintenance stabilisation dose over 6 weeks (see table below) after which other psychotropic and/or anti-epileptic medicines can be withdrawn, if clinically indicated.

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

Recommended dose escalation to the maintenance total daily stabilisation dose for adults (over 18 years of age) treated for bipolar disorder:

Treatment regimen	**Week 1 - 2**	**Week 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	25 mg (once a day)	50 mg (once a day or two divided doses)	100 mg (once a day or two divided doses)	200mg (range 100 - 400 mg) (once a day or two

Treatment regimen	Week 1 - 2	Week 3 - 4	Week 5	Target stabilisation dose (Week 6) **
lamotrigine e.g., lithium, bupropion, OR monotherapy with lamotrigine				divided doses)
NOTE: In patients taking AEMs where the pharmacokinetic interaction with LAMOTRIGINE MSQ is currently not known, the dose escalation as recommended for LAMOTRIGINE MSQ 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 LAMOTRIGINE MSQ 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 LAMOTRIGINE MSQ 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, as in LAMOTRIGINE MSQ e.g., lithium, bupropion, OR monotherapy with LAMOTRIGINE MSQ

The initial LAMOTRIGINE MSQ dose in patients taking concomitant medicines with no known/theoretical pharmacokinetic interaction with lamotrigine, as in LAMOTRIGINE MSQ, 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, according to available data, in clinical trials.

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

Maintenance stabilisation total daily dose in bipolar disorder following withdrawal of concomitant psychotropic or anti-epileptic medicines:

Treatment regimen	**Week 1**	**Week 2**	**Week 3 onwards[#]**
a) Following withdrawal of	Double the stabilisation	Maintain this dose (200 mg/day) (two divided doses)	

Treatment regimen	**Week 1**	**Week 2**	**Week 3 onwards[#]**
enzyme inhibitors e.g., valproate	dose, not exceeding 100 mg/week i.e., 100 mg/day target stabilisation dose will be 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 other psychotropic or AEM medicines with no known clinical pharmacokinetic interaction with	Maintain target dose achieved in dose escalation (200 mg/day) (two divided doses) (range 100 - 400 mg)		

Treatment regimen	**Week 1**	**Week 2**	**Week 3 onwards[#]**
lamotrigine e.g., lithium, bupropion			
NOTE: In patients taking AEMs where the pharmacokinetic interaction with LAMOTRIGINE MSQ is currently not known, the dose escalation as recommended for LAMOTRIGINE MSQ 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 LAMOTRIGINE MSQ 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 LAMOTRIGINE MSQ 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 medicines 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 LAMOTRIGINE MSQ daily dosing in patients with bipolar disorder following addition of other medicines

There is no clinical experience in adjusting the lamotrigine, as in LAMOTRIGINE MSQ, daily dose following the addition of other medicines. However, based on data available on medicine interaction studies, the following recommendations can be made (see below):

Adjustment of LAMOTRIGINE MSQ daily dosing in patients with bipolar disorder following the addition of other medications:

<table>
<tr><th>Treatment regimen</th><th>Current lamotrigine stabilisation dose (mg/day)</th><th>Week 1</th><th>Week 2</th><th>Week 3 onwards</th></tr>
<tr><td rowspan="3">a) Addition of enzyme inhibitors e.g., valproate, depending on original dose of LAMOTRIGINE MSQ</td><td>200 mg</td><td>100 mg</td><td colspan="2">Maintain this dose (100 mg/day)</td></tr>
<tr><td>300 mg</td><td>150 mg</td><td colspan="2">Maintain this dose (150 mg/day)</td></tr>
<tr><td>400 mg</td><td>200 mg</td><td colspan="2">Maintain this dose (200 mg/day)</td></tr>
<tr><td>b) Addition of enzyme inducers e.g.,</td><td>200 mg</td><td>200 mg</td><td>300 mg</td><td>400mg</td></tr>
</table>

Treatment regimen	**Current lamotrigine stabilisation dose (mg/day)**	**Week 1**	**Week 2**	**Week 3 onwards**
carbamazepine in patients NOT taking valproate and depending on original dose of LAMOTRIGINE MSQ	150mg	150 mg	225 mg	300 mg
	100 mg	100 mg	150 mg	200 mg
c) Addition of other psychotropic or AEM medicines 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 AEMs where the pharmacokinetic interaction with LAMOTRIGINE MSQ is currently not known, the dose escalation as recommended for LAMOTRIGINE MSQ with concurrent valproate, should be used.				

Discontinuation of LAMOTRIGINE MSQ in patients with bipolar disorder:

Data available shows that there was no increase in the incidence, severity or type of adverse experiences following abrupt termination of lamotrigine, as in LAMOTRIGINE MSQ, versus placebo. Therefore, patients may terminate LAMOTRIGINE MSQ without a stepwise reduction of dose.

Children (younger than 18 years of age)

Safety and efficacy of lamotrigine, as in LAMOTRIGINE MSQ in bipolar disorder has not been evaluated in this age group. Therefore, a dosage recommendation cannot be made.

Special populations

General dosing recommendation for LAMOTRIGINE MSQ in special patient populations

Women taking hormonal contraceptives

a) ***Starting LAMOTRIGINE MSQ in patients already taking hormonal contraceptives***

Although an oral contraceptive has been shown to increase the clearance of lamotrigine (see section 4.4 and 4.5), no adjustments to the recommended dose escalation guidelines for LAMOTRIGINE MSQ should be necessary solely based on the use of hormonal contraceptives. Dose escalation should follow the recommended guidelines based on whether LAMOTRIGINE MSQ is added to an inhibitor of lamotrigine glucuronidation e.g., valproate; whether LAMOTRIGINE MSQ is added to an inducer of lamotrigine glucuronidation e.g., carbamazepine, phenytoin, phenobarbital, primidone, or rifampicin; or whether LAMOTRIGINE MSQ 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 LAMOTRIGINE MSQ and NOT taking inducers of lamotrigine glucuronidation***

The maintenance dose of LAMOTRIGINE MSQ may need to be increased by as much as two-fold according to the individual clinical response (see section 4.4 and 4.5).

(c) Stopping hormonal contraceptives in patients already taking maintenance doses of LAMOTRIGINE MSQ and NOT taking inducers of lamotrigine glucuronidation

The maintenance dose of lamotrigine as in LAMOTRIGINE MSQ may need to be decreased by as much as 50 % according to the individual clinical response (see section 4.4 and 4.5).

Elderly (over 65 years of age)

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

Renal impairment

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to lamotrigine or to any of the excipients of LAMOTRIGINE MSQ (see section 6.1).

4.4 Special warnings and precautions for use

Severe convulsive seizures including *status epilepticus* may lead to rhabdomyolysis, multiorgan dysfunction and disseminated intravascular coagulation, usually with fatal outcome. Similar cases have occurred in association with the use of lamotrigine as in LAMOTRIGINE MSQ.

Patients receiving LAMOTRIGINE MSQ should be closely monitored and changes in hepatic, renal and clotting parameters looked for. Patients should be warned to consult their doctors immediately if rashes or flu-like symptoms associated with hypersensitivity develop, especially within the first month of starting treatment with LAMOTRIGINE MSQ. Withdrawal of therapy should be considered if unexplained rashes, fever, flu-like symptoms, drowsiness or worsening of seizure control occur. Dosage recommendations should not be exceeded to minimise the risk of developing rash requiring withdrawal of therapy. Abrupt withdrawal of LAMOTRIGINE MSQ may provoke rebound seizures. The risk may be reduced by tapering off the withdrawal of LAMOTRIGINE MSQ over a period of two weeks. The weight of a child must be monitored, and the dose reviewed as weight changes occur. If the dose 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.

Skin reactions

Adverse skin reactions have been reported which have generally occurred within the first 8 weeks of starting lamotrigine, as in LAMOTRIGINE MSQ. Although the majority of rashes usually resolve when LAMOTRIGINE MSQ is discontinued,

irreversible scarring and cases of associated death have been reported. A mild rash may subside even with continuation of LAMOTRIGINE MSQ therapy; however, close monitoring is essential. Serious and potentially life-threatening skin rashes including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); also known as hypersensitivity syndrome (HSS) have been reported especially in children and in patients (adults and children) using valproate (see section 4.8). Isolated cases have been reported after prolonged treatment (6 months). The estimated incidence of serious skin rashes in adults is 1 in 1 000. The risk is higher in children than in adults. Some children may require hospitalisation because of the seriousness of skin rashes.

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

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

• High initial doses of LAMOTRIGINE MSQ and exceeding the recommended dose escalation of LAMOTRIGINE MSQ (see section 4.2).

• Concomitant use of valproate, which increases the mean half-life of LAMOTRIGINE MSQ nearly two- fold (see section 4.2 and 5.2).

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

As it cannot be predicted reliably which rashes will prove to be life-threatening, all patients (adults and children) who develop a rash should be promptly evaluated and LAMOTRIGINE MSQ withdrawn immediately unless the rash is clearly not

medicine related. It is recommended that LAMOTRIGINE MSQ not be restarted in patients who have discontinued due to rash associated with prior treatment with LAMOTRIGINE MSQ. If the patient has developed SJS, TEN or DRESS with the use of lamotrigine, treatment with LAMOTRIGINE MSQ must not be re-started in this patient at any time.

Rash has also been reported as part of a hypersensitivity syndrome associated with a variable pattern of systemic symptoms including fever, lymphadenopathy, pruritus, facial oedema, abnormalities of the blood, liver, kidney and aseptic meningitis (see section 4.8). The syndrome has shown a wide spectrum of clinical severity and may lead to disseminated intravascular coagulation and multiorgan failure. It is important 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 LAMOTRIGINE MSQ therapy discontinued if an alternative aetiology cannot be immediately 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, as in LAMOTRIGINE MSQ.

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, as in

LAMOTRIGINE MSQ 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, as in LAMOTRIGINE MSQ (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, as in LAMOTRIGINE MSQ 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 AEMs in several indications, and data available 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, as in LAMOTRIGINE MSQ.

In patients with bipolar disorder, worsening of depressive symptoms and/or the emergence of suicidality may occur whether or not they are taking medicines for bipolar disorder, including LAMOTRIGINE MSQ. Therefore, patients receiving LAMOTRIGINE MSQ 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 behavior 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, inpatients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behavior, 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 MSQ efficacy

Data shows that an ethinyl estradiol/levonorgestrel (30 µg/150 µg) combination has been demonstrated to increase the clearance of lamotrigine as in LAMOTRIGINE MSQ by approximately two-fold resulting in decreased lamotrigine levels (see section 4.5). Following titration, higher maintenance doses of lamotrigine (by as much as two-fold) may be needed to attain an optimum 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 medication (e.g., 'pill-free week'), gradual transient increases in lamotrigine levels will occur during the week of inactive medicine. These increases will be greater when LAMOTRIGINE MSQ dose increases are made in the days before or during the week of inactive

contraceptive medicine. Cases of breakthrough convulsions have been reported in women also using hormonal contraceptives. For dosing instructions see 'General Dosing Recommendations for LAMOTRIGINE MSQ in Special Patient Populations', section 4.2.

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 MSQ on hormonal contraceptive efficacy

Data available has shown that when lamotrigine, as in LAMOTRIGINE MSQ, and a hormonal contraceptive (ethinyl estradiol/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. Cases of unplanned pregnancy, metro/menorrhagia, breakthrough bleeding and amenorrhoea have been reported. 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 (see section 4.6). LAMOTRIGINE MSQ should be used with caution with other folate antagonists.

Renal failure

Data available shows that in single dose studies in subjects with end stage renal

failure, plasma concentrations of lamotrigine were not significantly altered. However, there is accumulation of the glucuronide metabolite; caution should therefore be exercised in treating patients with renal failure.

Patients taking other medicines containing lamotrigine

Lamotrigine should not be administered to patients currently being treated with any other medicine containing lamotrigine without consulting a medical practitioner.

Brugada-type ECG

Arrhythmogenic ST-T abnormality and typical Brugada ECG pattern has been reported in patients treated with lamotrigine. The use of LAMOTRIGINE MSQ should be carefully considered in patients with Brugada syndrome.

Excipient warnings

LAMOTRIGINE MSQ contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take LAMOTRIGINE MSQ.

LAMOTRIGINE MSQ contains lactose monohydrate, which may have an effect on the glycaemic control of patients with diabetes mellitus.

LAMOTRIGINE MSQ 25 mg, 50 mg, 100 mg and 200 mg tablets contains not more than 0,16, 0,32, 0,64 and 1,28 mg of sodium per tablet, respectively. This amounts to less than 1 mmol sodium (23 mg) per tablet and thus essentially ‘sodium free’.

4.5 Interaction with other medicines and other forms of interaction

Uridine 5'-diphospho (UDP) glucuronyl transferases (UGTs) have been identified as the enzymes responsible for metabolism of lamotrigine. Medicines 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.

Effects of other medicines on glucuronidation of lamotrigine as in LAMOTRIGINE MSQ

Medicines that significantly induce glucuronidation of lamotrigine (such as phenytoin, carbamazepine, phenobarbitone, primidone, rifampicin, lopinavir/ritonavir, atazanavir/ritonavir, ethinyl oestradiol/levonorgestrel combination (other oral contraceptive and HRT treatments have not been studied, though they may similarly affect lamotrigine pharmacokinetic parameters) and primidone, enhance the metabolism of LAMOTRIGINE MSQ leading to an increased clearance and subsequent reduction of the elimination half-life of LAMOTRIGINE MSQ.

There is no evidence that lamotrigine causes clinically significant induction or inhibition of cytochrome P450 enzymes.

Interactions involving antiepileptic medicines (AEMs)

Concomitant use of valproate, which inhibits the glucuronidation of lamotrigine, significantly reduces the metabolism of lamotrigine and increases the mean half-life and plasma concentrations of LAMOTRIGINE MSQ. Plasma concentrations of valproic acid may decrease slightly when LAMOTRIGINE MSQ is added (see section 5.20).

Certain AEMs (such as phenytoin, carbamazepine, phenobarbitone and primidone) which induce cytochrome P450 enzymes also induce the metabolism glucuronidation of lamotrigine 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 LAMOTRIGINE MSQ. These events usually resolve when the dose of carbamazepine is reduced.

No evidence has shown that LAMOTRIGINE MSQ affects the plasma concentration of other concomitant antiepileptic medicine ~~agents~~. LAMOTRIGINE MSQ does not displace other antiepileptic medicine ~~agents~~ from protein binding sites.

Interactions involving other psychotropic medicines

Data available of *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. 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

Data available shows that 30 µg ethinyl oestradiol/150 µg levonorgestrel in a combined oral contraceptive pill caused an approximately two-fold increase in lamotrigine oral clearance, resulting in a reduction in lamotrigine AUC and $C_{max.}$

Breakthrough seizures have been reported in women using contraceptives.

Effect of lamotrigine on hormonal contraceptive pharmacokinetics

LAMOTRIGINE MSQ does not seem to affect plasma concentrations of ethinyl oestradiol following the administration of the combined oral contraceptive pill. 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). However, any change in the menstrual bleeding pattern should be investigated.

Interactions involving other medicines

There is no evidence that LAMOTRIGINE MSQ causes clinically significant induction or inhibition of hepatic oxidative medicine ~~drug~~ -metabolising enzymes. However, it has been reported that, 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 MSQ and concurrent glucuronidation inducers should be used (see section 4.2).

LAMOTRIGINE MSQ may induce its own metabolism, but the effect is modest and unlikely to have significant clinical consequences.

4.6 Fertility, pregnancy and lactation

The safety of LAMOTRIGINE MSQ, in pregnancy and lactation has not been established.

Pregnancy

There are insufficient data available on the use of lamotrigine as in LAMOTRIGINE MSQ in human pregnancy to evaluate its safety. LAMOTRIGINE MSQ 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 LAMOTRIGINE MSQ therapy should be ensured.

Breastfeeding

There is limited information on the use of lamotrigine as in LAMOTRIGINE MSQ

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.

Fertility

Animal experiments did not reveal impairment of fertility by lamotrigine.

4.7 Effects on ability to drive and use machines

Adverse events of a neurological character such as dizziness and diplopia have been reported. Therefore, patients should see how LAMOTRIGINE MSQ therapy affects them before driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The undesirable effects for epilepsy and bipolar disorder indications are based on available data from controlled clinical studies and other clinical experience and are listed in the table below.

b. Tabulated summary of adverse reactions

All known ADRs are listed by system organ class and frequency: more frequent, frequent, less frequent or frequency unknown. Frequency categories are derived from controlled clinical studies (epilepsy monotherapy (identified by†) and bipolar disorder (identified by§)). Where frequency categories differ between clinical trial data from epilepsy and bipolar disorder the most conservative frequency is shown. However, where no controlled clinical trial data are available, frequency categories have been obtained from other clinical experience.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Haematological abnormalities[1] including neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia, agranulocytosis, haemophagocytic lymphohistiocytosis (see section 4.4)
	Frequency unknown	Lymphadenopathy[1]
Immune system disorders	Less frequent	Hypersensitivity syndrome[2]
	Frequency unknown	Hypogammaglobulinaemia
Psychiatric disorders	Frequent	Aggression, irritability
	Less frequent	Confusion, hallucinations, tics
	Frequency unknown	Nightmares
Nervous system disorders	Frequent	Headache[§], somnolence[†§], dizziness[†§], tremor[†], insomnia[†] agitation[§]
	Less frequent	Ataxia[†], nystagmus[†], aseptic meningitis (see section 4.4), unsteadiness, movement disorders, worsening of

System organ class	Frequency	Adverse reactions
		Parkinson's disease[3], extrapyramidal effects, choreoathetosis†, increase in seizure frequency
Eye disorders	Less frequent	Diplopia†, blurred vision†, conjunctivitis
Gastrointestinal disorders	Frequent	Nausea†, vomiting†, diarrhoea†, dry mouth§
Hepato-biliary disorders	Less frequent	Hepatic failure, hepatic dysfunction[4], increased liver function tests
Skin and subcutaneous tissue disorders	Frequent	Skin rash[5†§]
	Less frequent	Alopecia, photosensitivity reaction, Stevens–Johnson Syndrome§, toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic[2] Symptoms
Musculoskeletal, connective tissue and bone disorders	Frequent	Arthralgia§
	Less frequent	Lupus-like reactions
Renal and urinary disorders	Frequency unknown	Tubulointerstitial nephritis, tubulointerstitial nephritis and uveitis syndrome

System organ class	Frequency	Adverse reactions
General disorders and administration site conditions	Frequent	Tiredness[†], pain[§], back pain[§]

c. 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 section 4.4).

[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 lamotrigine 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 lamotrigine (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;
- concomitant use of valproate.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem 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 10-20 times the maximum therapeutic dose has been reported. Overdose has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma

Treatment

In the event of overdosage, the patient should be admitted to hospital and given appropriate supportive therapy. Gastric lavage should be performed if indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: other antiepileptics, ATC code: N03AX09.

Lamotrigine blocks voltage-sensitive sodium channels, thereby stabilising neuronal membranes and inhibiting neurotransmitter release, principally that of glutamate, an excitatory amino acid which is thought to play a major role in the generation of epileptic seizures.

In contrast, the mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established, although interaction with voltage gated sodium channels is likely to be important.

5.2 Pharmacokinetic properties

Absorption

Lamotrigine is well and completely absorbed from the gut. The absorption is unaffected by food. Peak plasma concentrations occur approximately 2,5 hours after oral administration of lamotrigine.

Distribution

Lamotrigine is moderately (55 %) bound to plasma proteins. The volume of distribution is 0,92 to 1,22 L/kg.

Biotransformation

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

Following multiple administration of lamotrigine (150 mg twice daily) there is a modest induction of its own metabolism, resulting in a 25 % decrease in the elimination half-life at steady state. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEMs, and data suggest that interactions between lamotrigine and medicines metabolised by cytochrome P_{450} enzymes are unlikely to occur.

Elimination

The apparent plasma clearance in healthy subjects is approximately 30 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 lamotrigine-related material is excreted in faeces. Clearance and half-life are independent of dose. The apparent plasma half-life in healthy subjects is estimated to be approximately 33 hours (range 14 to 103 hours). The half-life of lamotrigine is affected by concomitant use of enzyme-inducing medicines such as phenytoin, carbamazepine, phenobarbital or primidone with a mean value of approximately 14 hours. The half-life of lamotrigine increases to approximately ~~59~~ 70 hours when co-administered with valproic acid alone (see ~~s~~ection 4.2).

Linearity/non-linearity

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

Special patient population

Paediatric population

Clearance adjusted for body ~~mass~~ weight is higher in children aged 12 years and under 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 medicines such as carbamazepine and phenytoin and increasing to mean values of 45 to 55 hours when co-administered with valproate alone (see section 4.2).

Elderly

Data available from 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.

Patients with renal impairment

Data available shows that in volunteers with chronic renal failure and individuals undergoing haemodialysis which were each given a single 100 mg dose of lamotrigine, the 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 the patient's

concomitant medicines; reduced maintenance doses may be effective for patients with significant renal functional impairment (see sections 4.2 and 4.4).

Patients with hepatic impairment

Data available from a study which was performed in subjects with various degrees of hepatic impairment and healthy subjects as control, shows that 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 and 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Ferric oxide yellow (E172)

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Purified talc

Sodium starch glycollate (Type A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C in the original package, protected from moisture.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

The tablets are packed in transparent PVdC coated PVC blister strips.

Pack size: Cardboard cartons containing 10, 30 or 60 tablets.

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

MSQ Pharma (Pty) Ltd.

Soetdoring Office Park, First Floor

7 Protea Street

Doringkloof

Centurion

0157

8 REGISTRATION NUMBERS

LAMOTRIGINE 25 MSQ: 40/2.5/0036

LAMOTRIGINE 50 MSQ: 40/2.5/0037

LAMOTRIGINE 100 MSQ: 40/2.5/0038

LAMOTRIGINE 200 MSQ: 40/2.5/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 February 2019

10 DATE OF REVISION OF THE TEXT

11 January 2023